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Dopamine receptors in emesis: Molecular mechanisms and potential therapeutic function

Louiza Belkacemi, Nissar A. Darmani*

Department of Basic Medical Sciences, College of Osteopathic Medicine of the Pacific, Western University of Health Sciences, Pomona, CA, 91766, USA

Abstract

Dopamine is a member of the catecholamine family and is associated with multiple physiological functions. Together with its five receptor subtypes, dopamine is closely linked to neurological disorders such as schizophrenia, Parkinson's disease, depression, attention deficit-hyperactivity, and restless leg syndrome. Unfortunately, several dopamine receptor-based agonists used to treat some of these diseases cause nausea and vomiting as impending side-effects. The high degree of cross interactions of dopamine receptor ligands with many other targets including G-protein coupled receptors, transporters, enzymes, and ion-channels, add to the complexity of discovering new targets for the treatment of nausea and vomiting. Using activation status of signaling cascades as mechanism-based biomarkers to foresee drug sensitivity combined with the development of dopamine receptor-based biased agonists may hold great promise and seems as the next step in drug development for the treatment of such multifactorial diseases. In this review, we update the present knowledge on dopamine and dopamine receptors and their potential roles in nausea and vomiting. The pre- and clinical evidence provided in this review supports the implication of both dopamine and dopamine receptor agonists in the incidence of emesis. Besides the conventional dopaminergic antiemetic drugs, potential novel antiemetic targeting emetic protein signaling cascades may offer superior selectivity profile and potency.

Keywords

Parkinson's disease; Dopamine subtypes; Intracellular emetic signals; Biased GPCRs signaling; Phenothiazines; Benzamides

1. Introduction

Dopamine is an endogenous monoamine catecholamine involved in multiple physiological functions [1]. Dopamine acts on both central (CNS) and peripheral nervous systems. In the CNS, dopamine operates as a neurotransmitter and signals through multiple distinct pathways to regulate locomotion, cognition, emotion, and neuroendocrine secretion [2,3]. Outside the CNS, dopamine functions primarily as a local chemical messenger. Indeed,

*Corresponding author at: Department of Basic Medical Sciences, College of Osteopathic Medicine of the Pacific, Western University of Health Sciences, 309 E. Second Street, Pomona, CA, 91766-1854, USA. ndarmani@westernu.edu (N.A. Darmani).

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dopamine acts as a modulator of cardiovascular function, catecholamine release, hormone secretion, vascular tone, renal function, and gastrointestinal motility. Deficits or surfeits in dopamine tissue levels results in diverse and severe pathological conditions ranging from schizophrenia, Parkinson's disease, depression, attention deficit–hyperactivity, to restless leg syndrome to name a few. Several dopamine-based agonists developed for the treatment of some of these diseases evoke nausea and vomiting (emesis) as common and distressing adverse-effects. The use of dopamine agonist therapy can also lead to other severe side-effects including impulse control disorders characterized by pathological gambling, compulsive eating, hypersexuality, and compulsive buying. These symptoms have been reported in up to 17% of Parkinson's disease and restless leg syndrome patients who continually use dopamine receptor agonists [4]. The most effective way to lessen these side-effects is to reduce or discontinue the therapy, which can lead to dopamine agonist syndrome in a subset of patients. The symptoms of dopamine agonist syndrome not only include anxiety, panic attacks, dysphoria, depression, suicidal ideation, drug cravings, but also nausea and vomiting [5].

Nausea and vomiting are important protective defense mechanisms by which humans and animals avoid ingestion and/or digestion of potentially toxic substances. Specifically, vomiting is the act of forceful expulsion of gastrointestinal contents through the mouth. However, severe and chronic vomiting can become detrimental due to significant loss of fluid and ion imbalance as is the case during exposure to cancer chemotherapeutic drugs such as cisplatin [6]. The act of vomiting is usually preceded by retching, where the gastrointestinal tract contents are forced into the esophagus, without the vomitus being expelled. On the other hand, nausea is an unpleasant painless subjective feeling that one will imminently vomit. Nausea and vomiting are often thought to exist on a temporal continuum; however, this is not always the case. There are situations when severe nausea may be present without emesis, and less frequently, where emesis may be present without preceding nausea. Most patients state that nausea is more common, more disabling, feels worse and lasts longer than vomiting. While significant knowledge exists on the neurotransmitter and anatomical basis of vomiting [7], nausea is the neglected symptom and its anatomical neurochemistry remains to be fully defined.

Functional pathophysiology of nausea and vomiting indicate that these processes are controlled by a balance between the gastrointestinal enteric nervous system and the CNS [7] as detailed below and in Fig. 1. Emetogens such as lipid soluble dopamine D₂/D₃ receptor agonists can directly act in the gastrointestinal tract and/or by stimulating the brainstem emetic nuclei [7]. The brainstem cluster of medullary nuclei involved in vomiting are the area postrema, the nucleus of the solitary tract, and the dorsal motor nucleus of the vagus, which are collectively named as the dorsal vagal complex. A more ventrolaterally localized group of cells forming the central pattern generator coordinates the act of vomiting. The peripheral emetic loci include the sentinel epithelial enterochromaffin cells present in the mucosa of gastrointestinal tract as well as the vagus and splanchnic nerves, and other intestinal tissues and nerves. Vagal afferent and efferent nerves mainly transfer information between the gastrointestinal tract and the brainstem at the dorsal vagal complex/central pattern generator sites. The different compartments of the emetic reflex arc are detailed later in Fig. 1.

The actions of dopamine including vomiting are mediated by cell membrane-bound dopamine receptors. There are five different but closely related heterotrimeric G protein-coupled dopamine receptors [8–10], divided into two major dopamine receptors families: D₁-like and D₂-like classes of receptors [11,12]. The dopamine D₁-like receptors include dopamine D₁ and D₅ subtypes, whereas dopamine D₂-like receptors include dopamine D₂, D₃, and D₄ subtypes. Behavioral evidence from ferrets, dogs, and least shrews (*Cryptotis parva*) have convincingly shown that dopamine D₂ and D₃ receptors are associated with an emetic response [13,14]. Conversely, dopamine D₁/D₅, or D₄ receptor-selective agonists lack emetic effects [14]. Despite the pivotal role of the different dopamine D₂-like receptors in vomiting and the continued preclinical research, their corresponding downstream intracellular biochemical emetic signals, are at best scantily defined or remain unknown.

In this review, we focus on dopamine and dopamine receptors and their potential roles in emesis. We describe: 1) dopamine synthesis, storage, and release, 2) dopamine receptors basic structural and genetic organization, distribution, function in the brain and the periphery, and their signal transduction mechanisms, and finally 3) we discuss experimental and clinical evidence for dopamine receptors' agonists-mediated emesis together with dopamine antagonist-based antiemetic drugs.

2. Dopamine synthesis, storage, and release

Dopamine is synthesized in the cytoplasm from the non-essential amino acid L-tyrosine. A structural based summary of dopamine biosynthesis and breakdown is illustrated in Fig. 2. In brief, tyrosine is converted to L-3,4-dihydroxyphenylalanine (levodopa, L-DOPA) by the tyrosine hydroxylase enzyme using tetrahydrobiopterin, oxygen (O₂), and iron (Fe²⁺) as cofactors in both the CNS and in a non-neuronal dopaminergic system within the gastrointestinal tract. In neurons, L-DOPA is quickly decarboxylated to dopamine by aromatic L-amino acid decarboxylase (AADC) enzyme [15]. This oxidation reaction is a rate-limiting step in the production of both dopamine and other catecholamines. In noradrenergic neurons, L-DOPA is converted by the β -hydrolase enzyme into norepinephrine (NE) with O₂ and L-ascorbic acid as cofactors. In turn, NE can be converted into epinephrine by phenylethanolamine N-methyltransferase (PMNT) with S-adenosyl-L-methionine as the cofactor [16,17].

Once formed, dopamine is transferred into secretory vesicles for storage. Following nerve cell stimulation, the vesicles containing dopamine merge with the cytoplasmic membrane to deliver dopamine into the synaptic cleft by exocytosis. In the synaptic cleft, dopamine binds to postsynaptic dopaminergic receptors and or presynaptic dopaminergic D₂ autoreceptors. Auto-receptors are found at both somatodendritic and axonal sites where they regulate the firing patterns of dopamine neurons and control the timing and amount of dopamine released from their terminals in target regions [18]. Most of the free dopamine is moved back into presynaptic neurons by a dopamine active transporter, where it is either recycled back into vesicles for reuse or broken down by monoamine oxidase (MAO) enzymes into inactive metabolites. Notably, MAO-A is found in the gastrointestinal tract, whereas MAO-B is primarily located in the brain. Both isoforms can metabolize dopamine to dihydroxyphenyl acetic acid (DOPAC) in the presence of aldehyde dehydrogenase (ALDH). Any remaining

extracellular dopamine either diffuses out of the presynaptic cleft or is broken down by catechol-o-methyltransferase (COMT). COMT is expressed in both the brain and peripheral tissues. Together with MAO, COMT converts dopamine to homovanillic acid (HVA) (Fig. 2), which has no recognized biological activity. Dopamine exerts its physiological effects by binding to and activating cell surface dopamine receptor subtypes.

3. Molecular properties of dopamine receptors

Similarities and differences in gene structure, amino acid composition, and signaling cascades of the dopamine receptors are detailed in the sections below:

3.1. Gene structure and amino acid composition

The genetic structure of dopamine D₁- and D₂-like classes of receptors are differentiated by the presence or the absence of introns in their coding sequences [19]. The genetic organization of the dopamine D₂-like receptors provides the foundation for receptor splice transcript variants. For instance, alternative splicing of an 87-base-pair exon between introns 4 and 5 of the dopamine D₂ receptor yields two major dopamine D₂ receptor variants; dopamine D₂S (D₂-short) and dopamine D₂L (D₂-long) [20,21] carrying distinctive anatomical, physiological, and pharmacological properties. Splice variants for dopamine D₃ and D₄ receptors have been described but are poorly characterized [22,23]. Dopamine D₃ receptor can be split at the third cytoplasmic loop into two fragments (dopamine D₃ trunk and D₃ tail), and the mixture of the two fragments retains the binding and functional activity of the wild type receptor. The dopamine D₄ receptors have three variants dopamine D_{4.2}, D_{4.4} and D₄ receptors [24]. The pharmacological characteristics of dopamine D₄ receptors resemble that of the dopamine D₂ and D₃ receptors. The atypical neuroleptic drug clozapine has a higher affinity for dopamine D₄ than for dopamine D₂ and D₃ receptors [25], which suggests the existence of important characteristics that may separate dopamine D₄ receptor from the other receptors.

Dopamine D₁- and D₂-like class receptors display considerable amino acid sequence conservation within their transmembrane domains [26] and members of each class share a high level of homology in their transmembrane domains. For example, dopamine D₁ and D₅ receptors share an 80% identity in their transmembrane domains. Dopamine D₂ and D₃ receptors have a 75% identity in their transmembrane domains, and dopamine D₂ and D₄ receptors share a 53% identity [8]. Site-directed mutagenesis for catecholamine receptors [27–29], and protein modeling with the adrenergic α_2 -, β_2 - and dopamine D₂ receptors [30,31], indicate that dopamine agonist binding site is likely located within the hydrophobic transmembrane domains.

3.2. Dopamine signaling

Dopamine signals through its receptors to induce and regulate a myriad of cellular responses as well as dopamine-associated behaviors and functions [19,32]. Signaling cascades have provided a basis for the understanding of intracellular mechanisms implicated in dopamine-related pathologies. The role of these pathways is well studied in neurodegenerative disease

but poorly explored in emesis. In this section, we describe the potential intracellular signaling pathways associated with emetogenic dopamine D_{2/3} receptors.

3.2.1. cAMP/PKA signaling—Dopamine receptors have signaling systems that contribute to the definition of each class of receptors, though differences within a class have been reported. For instance, the non-emetic dopamine D₁-like receptors are generally coupled to G_s alpha proteins (G_{as}/olf or G_{as}/o proteins = adenylyl cyclase stimulator) and adenylyl cyclase to yield higher levels of the second messenger cyclic adenosine monophosphate or cyclic AMP (cAMP), which in turn stimulates the activity of protein kinase A (PKA). Consequently, specific proteins are phosphorylated by PKA [33]. The phosphorylated and activated substrates include dopamine cAMP-regulated phosphoprotein, MW 32 kDa (DARPP-32). When DARPP-32 is phosphorylated on Thr³⁴, it inhibits protein phosphatase 1 (PP1). The inhibition of PP1 results in the phosphorylation and the activation of many downstream physiological effectors, including various neurotransmitter receptors, ion channels and pumps, and transcription factors leading to evoked cellular effects (Fig. 3A). Conversely, dopamine D₂-like receptors, which are coupled to pertussis toxin (PTX)-sensitive Gi/Go proteins (G_{ai}/o = adenylyl cyclase inhibitor) block adenylyl cyclase and lower the intracellular concentration of cAMP [34], resulting in lower PKA activity [8,35,36] (Fig. 2A). Dopamine D₂-like receptors also activate the protein phosphatase calcineurin, which dephosphorylates DARPP-32 at Thr³⁴.

In terms of behavior, the cAMP/PKA signaling pathway in the CNS is well-characterized and has a pivotal role for different physiological responses that are valuable for cell survival, synaptic plasticity, and gene expression [37,38]. The emetic role of cAMP in the PKA pathway has been demonstrated by microinjection of cAMP analogs (e.g., 8-bromo cAMP) and forskolin (an activator of adenylyl cyclase that increases endogenous of cAMP) in the brainstem AP emetic zone, which elevates the electrical activity of local neurons and stimulates vomiting in dogs [38]. Likewise, the administration of 8-chloro cAMP to cancer patients produces nausea and vomiting [39]. The use of phosphodiesterase inhibitors (such as rolipram) boosts cAMP tissue levels, which trigger excessive nausea and vomiting in vomit competent animals and humans [40]. Our laboratory has found a direct association between increased PKA phosphorylation with peak vomit frequency during immediate and delayed phases of vomiting caused by either cisplatin or cyclophosphamide in the least shrew [41–43]. It is important to note that since dopamine D₂-like receptor activation results in decreased cAMP production, vomiting is improbable to occur as a direct effect of dopamine D₂-like stimulation via the cAMP/PKA signaling cascade. We also expect stimulation of cAMP by dopamine D₁/D₅ receptor-selective agonists and subsequent PKA increase is unlikely to elicit an emetic response since dopamine D₁-like receptors are devoid of emetic properties [14].

3.2.2. ERK signaling—Extracellular signal-regulated kinases 1 and 2 (ERK_{1/2} or p44^{ERK} and p42^{ERK}) are part of the Ras-MEK-ERK signaling cascade which belongs to the mitogen-activated protein kinases (MAPKs), a highly conserved family of serine/threonine protein kinases [44]. Evidence support ERK_{1/2} activation through dopamine receptors [45,46]. Indeed, primary mesencephalic neuronal cells from wild-type (WT) mice treated

with the dopamine D₂ receptor agonist quinpirole, results in an increase in the number of TH-positive neurons, which coincide with ERK activation in the same neurons [47]. Dopamine D₂ receptor-mediated ERK activation has also been observed in a variety of other cell lines, including in HEK-293, fibroblast-like COS-7, and C6 glioma cells [48,49]. The mechanisms by which the dopamine D₂ receptor stimulates ERKs have not been fully clarified [50]. However, it is well established that the $\beta\gamma$ subunits of G-protein downstream of tyrosine kinase receptors (TKRs) and the small G-protein of the proto-oncogene protein P21 (Retrovirus-associated DNA sequences (Ras)) have been implicated in dopamine D₂ receptor activation of ERK [48,49,51] (Fig. 3B). Dopamine D₂ receptors can activate ERK [48] by the typical Ras-associated signaling pathway i.e., Ras/Raf (rapidly accelerated fibrosarcoma)/MEK₁. In this cascade, stimulated Ras binds Raf kinase and carries it to plasma membranes for activation through tyrosine phosphorylation [50]. The Raf kinase phosphorylates and stimulates MEK, which activates ERK [48] (Fig. 3B). Furthermore, ERK activation by G protein-coupled receptors (GPCRs) can be mediated by arrestins (Arrs) [52]. Arrs are a small family of proteins that are important for regulating signal transduction of GPCRs [53,54]. Dopamine D₁ receptors can regulate protein complex formed of β -Arr₂/ERK and MEK and induce ERK activation. Indeed, in transfected cells, β -Arr₂ can support the formation of a MAPK complex composed of β -Arr₂ and the MAPK pathway kinases Raf, MEK, and ERK in response to GPCRs activation [55] resulting in activation of ERK [56]. In dopamine D₂ receptors signaling, the receptors- β -Arr₂ complex can stimulate ERK, but dopamine D₃ receptors cannot except for specific conditions. In fact, using the same experimental conditions, dopamine D₃ receptors could still activate ERK in HEK-293 and COS-7 cell lines when G α_o was co-expressed but not G α_i . Meanwhile, dopamine D₂ receptors can mediate ERK activation by both isoforms G α_i/o proteins and by dopamine D₂ receptors- β -Arr complex [57]. Upon stimulation, activated ERK enters the cell nucleus to modulate its downstream targets and ultimately behavior [58–62].

In terms of behavior, dopamine receptors are frequently associated with the activation of ERK signaling. This is consistent with a study showing that psychostimulants such as amphetamine augment levels of dopamine, locomotor hyperactivity, and activation of ERK in mice [63]. Other effects associated with ERK signaling include: memory formation, survival, and adaption [64,65]. Yet, some studies suggest that activation of the ERK signaling cascade may induce a cytotoxic neuronal response to oxidative stress [66,67], implying that ERK signaling may have an alternate function mediating neurotoxic actions. Previous work from our laboratory has implicated the phosphorylation of ERK_{1/2} in the induction of emesis in the brainstem following stimulation of serotonergic 5-hydroxytryptamine 3 receptor (5-HT₃R), which is in line with ERK potentiation of a cytotoxic neural stress response [68]. Also, stimulation of phosphatidylinositol-3-kinase (PI3K)-ERK and protein kinase C (PKC)-ERK signaling pathways by the selective substance P neurokinin type 1 receptor (NK₁R) agonist GR73632, yields an emetic response [69]. Additionally, Ca²⁺ mobilizers such as the selective L-type Ca²⁺ (LTCC) agonist FPL44176, and the sarcoplasmic/endoplasmic reticulum Ca²⁺-ATPase (SERCA) inhibitor thapsigargin, are potent emetogens [70, 71]. They respectively evoke vomiting through extracellular and intracellular Ca²⁺ mobilization via phosphorylation of ERK_{1/2} in the least shrew brainstem [71]. Since a role of dopamine D₂-like receptors in ERK phosphorylation

during emesis has yet to be established, we speculate that these receptors may promote ERK phosphorylation and subsequent vomiting through either of the above ERK signaling pathways or by other pathways yet to be discovered. Dopamine D₁ receptors activate ERK_{1/2} as well, but this activation is unlikely to result in vomiting since dopamine D₁ class of dopamine receptors is devoid of emetic properties.

3.2.3. Akt/GSK-3 signaling—GSK-3 (glycogen synthase kinase-3) and Akt/PKB (thymoma viral protooncogene, also known as protein kinase B) are serine-threonine kinases that participate in the Akt/GSK-3 signaling cascade. GSK-3 is a downstream target for Akt protein, which can phosphorylate GSK-3 and suppresses its activity. GSK-3 is encoded by two known genes, GSK-3 α and GSK-3 β . Dopamine can exert part of its actions by modulating the activity of Akt/GSK-3 [72] acting through various mechanisms, two of which have an opposite effect on the activity of these two kinases (Fig. 3C). In the first mechanism, Akt protein activation and subsequent deactivation of GSK-3 by respective phosphorylation occur after the stimulation of the dopamine D₂-like receptors [73–76]. In the second mechanism, the opposite occurs; stimulation of dopamine D₂ receptors leads to a regulated deactivation of Akt by the protein phosphatase 2A (PP₂A), which is known to have a role in mediating Akt inactivation in other biological systems [77]. The inactivation of Akt and the ensuing formation of an Akt, β -Arr₂, and PP₂A signaling complex facilitates the inactivation of Akt by the phosphatase [78], which consequently leads to a reduced phosphorylation and increased activation of GSK-3 α and GSK-3 β that, in turn, regulate dopamine-associated behaviors [78–80] (Fig. 3C).

The importance of Akt/GSK-3 signaling for dopamine-related behaviors is apparent from the pioneering findings which uncovered the role of this pathway in dopamine receptor signaling. Pharmacological and genetic manipulations that elevate or reduce dopaminergic activity can cause profound effects on locomotor activity in mice and significant alterations in the phosphorylation of Akt and GSK-3 [79]. For instance, pharmacological or genetic inhibition of GSK-3 activity prevents locomotor hyperactivity associated with excessive dopaminergic tone in dopamine transporter knockout or amphetamine-treated mice [79,81]. Mice overexpressing GSK-3 β show noticeable locomotor hyperactivity as well [82]. Activation of Akt/GSK-3 signaling by dopamine receptors has also been extensively discussed in cell survival and neuroprotection against oxidative stress, which may indirectly be related to emesis [83–85]. Indeed, Akt which is a downstream effector of PI3K, and the antiapoptotic protein Bcl₂ (B-cell CLL/lymphoma 2) were activated by the dopamine D₂-like receptor agonist bromocriptine in samples from primary cultures obtained from the cerebral cortex of fetal rats (17–19 days of gestation) [83]. These findings imply that dopamine D₂ receptor activation has a vital role in neuroprotection against cytotoxicity with the upregulation of Bcl₂ expression located upstream of Akt protein in the PI3K/Akt/GSK-3 cascade is, at least partially, associated with this effect [83]. It has also been suggested that neurodegeneration may result from dopaminergic agonists due to side-effects of retching and vomiting that are known for high levels of oxidative stress [86] and elevated free radical production [87]. Specific activation of dopamine D₃ receptors boosts the Akt activity associated increase in dendritic arborization in dopaminergic neurons from mouse embryos [88]. Given that reactive oxygen species (ROS) regulation and inhibition can be controlled

by the Akt upstream of PI3K protein [89], the role of these proteins in neurodegenerative diseases associated with emesis requires further assessment. Since dopaminergic drugs have other molecular targets and alternative mechanisms such as an action on serotonin receptors [90–92], these additional mechanisms could also contribute to the effect of these drugs on Akt/GSK-3 signaling including in vomiting but a reliable link to emesis has still to be made. More recently preliminary findings from our laboratory indicate that GSK-3 inhibitors such as AR-A014418 and SB216763 protect shrews from vomiting caused by the nonselective dopamine D₂ receptor agonist apomorphine and the more selective dopamine D₂ receptor agonist quinpirole [93] are an initial indication of the direct involvement of Akt/GSK-3 signaling in the mechanism of the induced-emesis.

3.2.4. Phospholipases signaling—Phospholipases (PL) are a diverse group of enzymes that catalyze the hydrolysis of membrane-forming phospholipids. Phospholipase A (PLA), phospholipase C (PLC), and phospholipase D (PLD) form the major groups among which PLC and PLD are the most studied in correlation with dopamine receptors signaling.

Several investigators have shown that dopamine and dopamine D₁-like receptor agonists can stimulate PLC-phosphoinositide hydrolysis in mammalian tissues [94]. These findings have been reproduced in rat [95, 96] and mouse brains, [97], postmortem human brain [98,99], and fresh monkey brain [100]. Interestingly, two studies indicate dopamine and dopamine D₂ receptor agonists inhibit phosphoinositide hydrolysis in striatal slice preparations [101, 102]. However, Undieh [103] and his group were unable to replicate the findings in the absence of kynurenine, scopolamine, and glutathione, all of which were reported to be relevant for showing a dopamine or quinpirole blockade effect [102]. These agents have unpredictable effects on signaling events [100, 104], as in the case of glutathione. Thus, it remains unclear if dopamine D₂ receptor stimulation, on its own, can prevent basal or heterologous agonist-stimulated phosphoinositide hydrolysis. The mechanism by which PLC can participate in phosphatidylinositol 4,5-bisphosphate (PIP₂) metabolism signaling pathways in a calcium (Ca²⁺)-dependent-manner includes several steps [103]. Specifically, dopamine receptors can couple to Gαq to activate PLC leading to the hydrolysis of PIP₂ into two-second messengers; 1,2-diacylglycerol (DAG) and inositol-1,4,5-trisphosphate (IP₃) [105]. As a very hydrophobic molecule, the DAG remains associated with the cytoplasmic membrane, where it activates PKC. Being a water-soluble messenger, the IP₃ travels through the cytosol to the endoplasmic reticulum (ER) membrane where it stimulates Ca²⁺ channel IP₃ receptors (IP₃R) with subsequent release of intracellular stored Ca²⁺ into the cytosol [105–107]. The released Ca²⁺ regulates Ca²⁺-dependent activity of proteins including Ca²⁺/calmodulin-dependent kinase II (CaMKII) and protein phosphatase 2B (calcineurin). The essential components of these interconnected cascades are illustrated in Fig. 3D. Interestingly, not all dopamine receptors can activate Ca²⁺ release since transfected cells expressing dopamine D₁ receptors do not have any effect on intracellular Ca²⁺, whereas the expression of dopamine D₅ receptors transfected in the same cells caused substantial Ca²⁺ mobilization after stimulation. These observations imply that either dopamine D₅ receptors are the major receptors in this signaling cascade *in vivo*, or the dopamine D₁ receptors need to interact with other proteins to mobilize Ca²⁺, which is consistent with PLC involvement in receptors heterodimerization. In fact, co-activation of dopamine D₁- and D₂-like receptors

causes activation of PLC likely through a $G\alpha_q$ -mediated mechanism [108], with a subsequent increase in DAG and IP_3 . The activation of $G\alpha_q$ /PLC signaling requires both dopamine D_1 and D_2 receptors since dopamine D_1 or D_2 receptor antagonists or genetic deletion of either dopamine D_1 or D_2 receptors prevents the effect [109]. Besides heterodimerization with dopamine D_1 receptors, dopamine D_2 receptors alone can evoke Ca^{2+} mobilization. Although the $G\alpha_i/o$ subunits of the G-proteins, which are traditionally associated with dopamine D_2 receptor signal transduction, have not been directly connected with the increase of intracellular Ca^{2+} , the PTX-sensitive signaling pathways have been associated with the activation of Ca^{2+} signals. In such pathways, $G\beta\gamma$ dimers of PTX-sensitive G-proteins stimulate PLC directly (reviewed in Ref. [110]) or by changing the $G\alpha_q$ pathway, which in turn activates PLC leading to Ca^{2+} signaling [111]. Whether these dopamine D_2 receptors mediate PLC pathways activation in the dorsal vagal complex or gastrointestinal tract have not been explored and requires further consideration.

Behavioral studies show that the activation of the dopamine D_1 -like receptor/ $G\alpha_q$ /PLC signaling cascade is involved in vacuous jaw movements and intense grooming [104,112] that could be important during the incidence of emesis. The activation of Ca^{2+} /CaMKII, a product of PLC pathway, is thought to be a crucial mediator of learning and memory [113]. On the other hand, dysregulation of CaMKII is associated with Alzheimer's disease, Angelman syndrome, and heart arrhythmia to name a few [113]. Our laboratory has found that the activation of the Ca^{2+} /CaMKII cascade promotes vomiting in the least shrew through: 1) activation of substance P neurokinin NK1 receptor, and 2) thapsigargin-evoked Ca^{2+} /CaMKII signaling cascade involving substance P release [70]. The potential existence of dopamine D_2 -like receptor/PLC/CaMKII pathways mediated emesis has yet to be described.

PLD is a lipid-modifying enzyme that catalyzes the conversion of phosphatidylcholine into phosphatidate and choline. A wide variety of neurotransmitters [114] activates PLD through stimulation of GPCRs via mechanisms not completely understood. The importance of the GPCRs in dopamine receptors mediated activation of PLD has been shown in various studies [115]. Among the GPCRs, dopamine D_2 [116] and D_3 receptor [117] stimulation of PLD [116,118], is not mediated by $G\alpha_i/o$ since the activation is insensitive to PTX [116]. It has been suggested that the stimulation of PLD activity by dopamine D_2 receptors is associated with the presence of a PKC ϵ isoform.

PLDs have been implicated in the pathophysiology of various diseases: cancer, Alzheimer's disease, and Parkinson's disease [119]. Hence, several PLD inhibitors have been developed for the treatment of some of these diseases among which halopemide, NOPT (N-[2-(4-oxo-1-phenyl-1,3,8-triazaspiro[4,5]dec-8-yl)ethyl]-2-naphthalenecarboxamide [120], and NFOT (N-[2-[1-(3-Fluorophenyl)-4-oxo-1,3,8-triazaspiro[4,5]dec-8-yl]ethyl]-2-naphthalenecarboxamide) have been developed specifically for the inhibition of PLD2 [121,122]. These inhibitors suppress PLD2 activity through various pathways preventing phosphatidic acid production and biological processes mediated by the expression of PLD [122]. Certain inhibitors affect the activity of both PLD1 and PLD2, including Fifi (5-fluoro-2-indolyl-des-chlorohalopemide), ML-299 (4-bromo-N-[(1S)-2-[1-(3-fluorophenyl)-4-oxo-1,3,8-triazaspiro[4.5]dec-8-yl]-1-methylethyl]-benzamide), VU-0155056, and

VU-0285655–1 [123,124]. Whether these inhibitors would induce vomiting in humans or in vomit competent animals remains unknown.

3.2.5. Ca^{2+} channel signaling—Ionic Ca^{2+} is a highly flexible intracellular messenger, which modulates complex cellular processes including cell activation and neurotransmission. The loss of Ca^{2+} homeostasis is associated with many neurological diseases and neuropsychiatric disorders such as Parkinson's, Alzheimer's, and schizophrenia [125]. It is also considered as a possible unifying signal in emesis [126]. Levels of Ca^{2+} concentration in the cell depend on the homeostasis between Ca^{2+} influx and its extrusion from the cell. In resting cells, the cytosolic concentration of Ca^{2+} can be as low as 50–150 nM. The transcellular Ca^{2+} transport mechanism has been described in nerve cells [127, 128]. Typically, the intracellular rise in Ca^{2+} concentration triggers neurotransmitter release. This elevation in Ca^{2+} is attributed to intracellular Ca^{2+} mobilization, which consists of extracellular Ca^{2+} influx and/or Ca^{2+} discharge from intracellular pools [70,129]. Two transport mechanisms are responsible for the entry of Ca^{2+} into the cell [128]. In the passive paracellular pathway, Ca^{2+} enters via tight junctions located between epithelial cells, whereas transepithelially Ca^{2+} enters via active transport. The extracellular Ca^{2+} influx into the cell for transmitter release is carried out by several Ca^{2+} permeable channels coexisting in the plasma membrane [130]. The latter proceeds through a well-controlled sequence of three events: 1) an apical Ca^{2+} entry involving channels such as voltage-dependent Ca^{2+} channels (VDCCs including L-type, N-type, P/Q type, and R-type sometimes classified as intermediate voltage-activated (IVA) channels [131,132], and members of the transient receptor potential (TRP) gene family, then 2) a cytosolic diffusion of Ca^{2+} bound to calbindins (CaBPs), and finally 3) a basolateral extrusion of Ca^{2+} through plasma membrane Ca^{2+} -ATPase (PMCA) and to a lesser extent by $\text{Na}^{+}/\text{Ca}^{2+}$ exchanger (NCX) [133,134]. When intracellular Ca^{2+} homeostasis is uncontrolled, emesis can occur. The voltage-gated L-type Ca^{2+} channels (LTCCs), the transient receptor potential vanilloid type 1 (TRPV1) channel and the sarcoplasmic and endoplasmic reticulum (SER) Ca^{2+} -ATPase (SERCA) pump are central to emesis, will be discussed in the subsequent sections.

LTCCs are activated by membrane depolarization and operate as the principal route of Ca^{2+} entry in electrically excitable cells such as neurons and muscle [135,136]. Recently, our laboratory has found direct evidence of Ca^{2+} mobilization as a critical factor in the mediation of emesis. These studies indicate that intraperitoneal administration of the selective LTCC agonist FPL64176 causes vomiting in the least shrew in a dose-dependent manner [130,137]. Pretreatment with corresponding LTCC antagonists amlodipine (0.5–10 mg/kg) or nifedipine (2.5–10 mg/kg), not only attenuate in a dose-dependent and potent manner FPL64176-evoked vomiting, but also suppress vomiting caused by a variety of other emetogens including those caused following intraperitoneal (i.p.) administration of dopamine $\text{D}_{2/3}$ receptor agonists such as apomorphine (2 mg/kg) or quinpirole (2 mg/kg) [130,137]. These findings indicate that the LTCC agonists may trigger an influx of Ca^{2+} into cells via LTCC opening (Fig. 3D), which then prompts a Ca^{2+} signaling cascade leading to emesis, whereas selective antagonists of LTCCs prevent the extracellular Ca^{2+} influx and the ensuing emesis. The mechanism by which LTCC antagonists prevent emesis in the presence of dopamine $\text{D}_{2/3}$ receptors agonists warrant further investigation.

TRPV1 is a nonselective cation channel with a preference for Ca^{2+} . The presence of TRPV1 on neural membranes as well as in the membrane of intracellular organelles (e.g., mitochondria, ER) [138,139], substantiates a role for this receptor in intracellular Ca^{2+} mobilization and consequent vomiting. The expression of TRPV1 in the brainstem nuclei (area postrema, nucleus of the solitary tract, and dorsal motor nucleus of the vagus) and gastrointestinal tract vomit circuits, further supports a functional role for this receptor in emesis [140,141]. TRPV1 is activated by numerous agonists from natural sources including the pungent component of chili peppers, capsaicin (8-methyl-*N*-vanillyl-6-nonenamide) and its ultrapotent analog resiniferatoxin from the plant genus *Euphorbia* [142]. An initial dose-dependent bell-shaped pro-emetic effect (10–1000 $\mu\text{g/kg}$) was found for resiniferatoxin in ferrets and house musk shrews. Furthermore, a 100 $\mu\text{g/kg}$ (s.c.) resiniferatoxin dose was shown to protect these species from vomiting evoked by various centrally and peripherally acting emetogens including cisplatin. In the least shrew, resiniferatoxin also evokes a dose-dependent and bell-shaped profile of vomiting, whose maximal pro-emetic effects occurred at its 18 $\mu\text{g/kg}$ dose, whereas doses below 5 $\mu\text{g/kg}$ had no significant emetic effect [143]. Recently, our laboratory has demonstrated that ultra-low doses of resiniferatoxin (0, 0.01, 0.025, 0.05, and 0.5 $\mu\text{g/kg}$) suppress vomiting evoked by apomorphine (2 mg/kg, i.p.) with complete protection occurring at its 0.5 $\mu\text{g/kg}$ (s.c.) dose [144]. Resiniferatoxin was protective against vomiting evoked by the more potent and more selective dopamine D_2 receptor agonist quinpirole, with maximal efficacy at its 5 $\mu\text{g/kg}$ dose as well. Capsazepine, a synthetic antagonist of capsaicin [145], was the first reported competitive antagonist of the TRPV1 receptor. Capsazepine blocks the painful sensation of heat caused by capsaicin, an resiniferatoxin analog, known to activate TRPV1.

Some insight into TRPV1 signaling associated with dopamine and dopamine receptors activation were provided by Chakraborty group [146] who investigated the effect of dopamine and dopamine receptors on the activation of capsaicin. They found that dopamine and SKF 81, 297 (an agonist at dopamine D_1/D_5 receptors), but not quinpirole (an agonist at dopamine D_2 receptors), decrease the activity of TRPV1 channels in dorsal root ganglion neurons. The authors suggested that modulation of TRPV1 channels by dopamine in nociceptive neurons may represent a way for dopamine to modulate incoming noxious stimuli. They further argued against a direct implication of PKC or PKA proteins [146]. However, Naittou and his team [147] have shown that dopamine D_2 receptor antagonists prevent capsaicin-evoked colorectal motility which contrasts with the latter report and supports the notion that phosphorylation by PKC sensitizes TRPV1 channels by increasing the channel open probability [148], while phosphorylation by PKA may reverse the desensitization of TRPV1 channels induced by repeated administration of the agonist [149]. Remarkably, capsaicin activation of TRPV1 on astrocytes yields endogenous ciliary neurotrophic factor (CNTF) in vivo, which prevents the degeneration of dopamine neurons by acting through CNTF receptor alpha (CNTFR α) on dopamine neurons in animal models of Parkinson's disease. This endogenous neuroprotective system (TRPV1 and CNTF on astrocytes, and CNTFR α on dopamine neurons) could be exploited as a novel beneficial therapeutic target for the treatment of Parkinson's disease [150]. These findings on TRPV1 may provide a platform that links dopamine D_2 receptors to pathways involved in vomiting and neuroprotection.

Excess of intracellular Ca^{2+} concentration is counterbalanced by the SERCA pump, which transports and sequesters free surplus cytosolic Ca^{2+} into the lumen of sarcoplasmic/endoplasmic reticulum (SER) for storage [151,152] to help maintain internal cell homeostasis. Intracellular Ca^{2+} release from the SER store into the cytoplasm is achieved via two Ca^{2+} release channels: i) IP_3Rs which are activated by metabotropic receptor-dependent IP_3 production [153], and ii) ryanodine receptors (RyRs) activated by Ca^{2+} via Ca^{2+} -induced Ca^{2+} release mechanism, and by a change in membrane voltage [154,155]. Recently, our laboratory has found that the i.p. injection of thapsigargin (0.1 10 mg/kg), a specific and potent inhibitor of SERCA pumps, causes vomiting in the least shrew suggesting that the increase in the cytosolic level of free Ca^{2+} in emetic loci result from SERCA inhibition and subsequent depletion of corresponding SER Ca^{2+} pool stores, leading to an influx of extracellular Ca^{2+} [70]. The evoked vomiting may also be due to SERCA inhibition and luminal ER Ca^{2+} release through RyRs and IP_3Rs in the brainstem. The thapsigargin-induced increase in cytosolic Ca^{2+} resulted in CaMKII activation in the brainstem emetic nuclei. How dopamine D_2 -like receptors can evoke vomiting though remains unknown and warrant further exploration. It is possible that dopamine D_2 receptors couple to $\text{G}\alpha_q$ to activate PLC and stimulate Ca^{2+} release. Indeed, previous work from our laboratory has shown that GR736322 induced-activation of substance P neurokinin NK1R can stimulate intracellular Ca^{2+} release from SER stores via $\text{G}\alpha_q$ -mediated PLC pathway which elicits extracellular Ca^{2+} influx through LTCC and evokes emesis (Fig. 3D). Interestingly, Patel and his group [151] have demonstrated that SERCA participates in dopamine release using fast-scan cyclic voltammetry to monitor stimulated extracellular dopamine concentration ($[\text{DA}]_o$) in midbrain slices. These investigators found that SERCA inhibition by cyclopiazonic acid lowers evoked $[\text{DA}]_o$ release in the substantia nigra pars compacta, which implies a functional role for ER Ca^{2+} stores in somatodendritic dopamine release. We speculate that SERCA may indirectly contribute to emesis through the release of dopamine. In fact, thapsigargin has been shown to cause vomiting via the activation of Ca^{2+} -CaMKII-ERK1/2 cascade, involved in an evoked increase in substance P content in the least shrew brainstem emetic loci, and the evoked emesis occurred through substance P-induced activation of corresponding neurokinin NK_1 receptors [70].

Collectively, these findings suggest a pivotal role for dopamine and dopamine D_2 receptors in cell signaling cascades in both physiological and pathological states. Further knowledge of the pathways activated/deactivated by dopamine would likely contribute to the identification of crucial specific alterations associated with the pathologic conditions and side-effects of dopamine-related treatments. The use of experimental animal models and the design of drugs capable of selectively altering these pathways should contribute to our understanding of the role of signaling cascades in eliciting emesis.

4. Distribution of dopamine and dopamine receptors in the emetic reflex arc

4.1. Emetic reflex: anatomical components and distribution, and potential function of dopamine and dopamine receptors

4.1.1. Dorsal vagal complex—The key known players of the emetic reflex arc include the dorsal vagal complex, the central pattern generator, the enteric nervous system, the gastrointestinal tract, and the vagus nerve (Fig. 1). The dorsal vagal complex comprises the area postrema, the nucleus of the solitary tract, and the dorsal motor nucleus of the vagus in the brainstem of both non-emetic (e.g., mice and rats) as well as vomit-competent species such as humans and animals (e.g., ferrets, house musk, and least shrews). The area postrema, which is pharmacologically defined as the chemoreceptive trigger zone, is a circumventricular organ with both fenestrated capillaries and active transport systems, which allow blood-borne chemicals absorbed by the gastrointestinal tract or secreted from the gastrointestinal mucosa (e.g., substance P) to bypass the brain-blood barrier and stimulate the dorsal vagal complex to induce vomiting [156,157] (Fig. 1). Likewise, the nucleus of the solitary tract contains large numbers of fenestrated capillaries and lacks a brain-blood barrier and thus permit neurons in both areas access to blood-borne circulating elements including brain-blood barrier penetrating emetogens. The area postrema/chemoreceptive trigger zone and nucleus of the solitary tract have high concentrations of emetic receptors for serotonin 5-HT₃, dopamine D_{2/3}, substance P, neurokinin NK₁, muscarinic, histamine H₁, and opioid (μ), among others [7]. The nucleus of the solitary tract receives emesis-related information both from the central nervous system (area postrema and cerebral cortex), as well as the peripheral emetic loci such as the gastrointestinal tract conveyed by vagal afferents and integrate these signals which eventually result in vomiting. Following the integration of emesis associated central and peripheral signals, the nucleus of the solitary tract neurons project the integrated emetic signals to the dorsal motor nucleus of the vagus (Fig. 1). The dorsal motor nucleus of the vagus sends emetic signals via motor vagal efferent pathways to the gastrointestinal tract and modulates vomiting [7,158,159]. It also sends efferent signals to the enteric nervous system as well as the central pattern generator (described below) that coordinate peristaltic activity and its reversal during emesis [7] (Fig. 1).

Dopamine has been consistently found in the area postrema, nucleus of the solitary tract, and dorsal motor nucleus of the vagus nuclei [160, 161]. Although only 10% of neurons in the nucleus of the solitary tract appear to be dopaminergic, the application of dopamine into the nucleus of the solitary tract resulted in 64% of these being stimulated by dopamine [162]. Vagally correlated catecholaminergic neurons in the dorsal motor nucleus of the vagus are also dopaminergic and display tyrosine hydroxylase immunoreactivity. The dorsal vagal complex harbors a high density of emetogenic dopamine D₂-like receptors (dopamine D₂ and D₃), which are substantially represented in the dorsal vagal complex of the mammalian medulla [163]. Most dopamine D₂ receptors are in the intermediate and medial sub-nuclei of the area postrema, nucleus of the solitary tract, and dorsal motor nucleus of the vagus. Conversely, dopamine D₃ receptors are homogenously expressed in area postrema, nucleus of the solitary tract, and dorsal motor nucleus of the vagus. Dopamine D₄ receptors are almost exclusively found in the intermediate and medial sub-nuclei of the nucleus of the

solitary tract, and the dorsal motor nucleus of the vagus [163]. Contrary to dopamine D₂-like receptors, D₁-like dopaminergic receptors have low expression across the emetic loci.

4.1.2. Gastrointestinal tract and enteric nervous system—Like the dorsal vagal complex, the gastrointestinal tract is central for the act of vomiting. Enterochromaffin cells residing alongside the epithelium lining the lumen of the digestive tract act as custodian cells in the intestinal mucosa [7] and play a crucial role in gastrointestinal tract regulation, especially intestinal motility and secretion [164] (Fig. 1). Since enteric afferent and efferent nerves do not protrude into the intestinal lumen, enterochromaffin cells act as a form of sensory transduction. Interestingly, the presence of dopamine has been found in gastric mucosa of cats and rabbits [165]. Besides contributing to the vomiting reflex, dopamine modulates several other vital functions in the gastrointestinal tract [166] such as fluid absorption [167], motility [7, 168], blood flow [169], and cytoprotection [170] to name a few. These broad and essential dopamine functions are consistent with mesenteric organs producing nearly half of the dopamine formed in the body [166]. Contrary to some beliefs that suggest tyrosine hydroxylase is found solely in catecholaminergic neurons in the brain, sympathetic nerves, and chromaffin tissue; various molecular biology techniques (RT-PCR, in situ hybridization, and immunohistochemistry) have revealed the presence of dopamine, dopamine receptors, and tyrosine hydroxylase in non-neuronal cells within the basal granulated cells of the mucosal epithelium along the entire extent of the small intestine of gerbils [171, 172], in the denervated rat and human gastric mucosal and parietal cells [173]. Furthermore, the mammalian gut has several populations of amine-containing neurons, which would likely contribute to the control of gastrointestinal motility. These populations include noradrenergic neurons of extrinsic sympathetic origin, which contain dopamine as a metabolic intermediate in the formation of norepinephrine. Although the physiological effects of dopamine in the gut can be mediated through α - or β -adrenoreceptor activation, a dopaminergic receptor-specific response has also been found [174]. In fact, dopaminergic receptors are present in several areas of the gastrointestinal tract [175,176]. Specifically, dopamine D₁-D₅ receptor mRNAs and respective proteins have been observed in rats, mice, and human gastric, duodenal, ileal, and colonic mucosa [173,177,178]. Additionally, dopamine D₁ and D₂ receptors are widely distributed in the cholinergic and catecholaminergic neurons in the dorsal motor nucleus of the vagus of rats, where it has been suggested that they may play a vital role in the regulation of dopamine on the activity of cholinergic and catecholaminergic neurons [179]. This is consistent with the critical role of dorsal motor nucleus of the vagus in the regulation of gastrointestinal tract [180] as the dorsal motor nucleus of the vagus motoneurons project to various parts of the gastrointestinal tract including stomach, lower esophageal sphincter, duodenum, and jejunum. During vomiting, dopamine evokes biphasic effects on the lower esophageal sphincter, with relaxation (a dopamine D₂ receptors-mediated effect) followed by a marked contraction via dopamine D₁ receptors in mammals [181,182]. Intriguingly, transcripts encoding D₄ were confined to the mucosal layer, whereas dopamine D₁, D₃, and D₅ were expressed both in nerve-containing layers of the gut and in the mucosa. The authors argued that transcripts encoding D₄ restriction to the mucosa line with the probability that the enteric D₄ was non-neuronal while both neurons and non-neuronal cells possibly expressed dopamine D₁, D₃, and D₅ in the gut [178]. Recently, dopamine D₄ ligands with improved

selectivity for dopamine D₄ receptors against not only dopamine D_{1-3,5} receptors but also other biogenic amine targets have emerged [183]. In fact, the dopamine D₄ receptor is in the spotlight as a novel target for both addiction and Parkinson's disease, as well as other emerging diseases [183]; however, no direct link to emesis has been found for this receptor yet [14].

Like the dorsal vagal complex and the gastrointestinal tract, the enteric nervous system is pivotal for the act of emesis. Enterochromaffin cells modulate neuron signaling in the enteric nervous system via the secretion of the neurotransmitter serotonin and peptides, which are vital for the act of vomiting [184–186]. Once the transmitters are released, they directly act on the corresponding receptors present in the enteric nervous system plexi since enteric nervous system has the ability to regulate enteric behavior in the absence of CNS input [187]. Distinctively, the enteric plexuses harbor intrinsic primary afferent neurons and interneurons that enable the enteric nervous system to independently mediate integrative responses to local stimuli [188]. The enteric nervous system communicates with the CNS via the parasympathetic (e.g., via the vagus nerve described below) and the sympathetic nervous systems (e.g., via the prevertebral ganglia) [189]. Hence, several of the emetic neurotransmitters secreted by the enteric nervous system are also found in the CNS [190] including 5-HT [191] and substance P [7,192]. There is no direct evidence supporting the existence of dopamine in the enteric nervous system. Although segments of the gastrointestinal tract of mice contains dopamine [193]; it has been difficult to determine whether enteric dopamine is an integral part of intrinsic neurons or because dopamine is the precursor of norepinephrine in the sympathetic innervation [188]. Indirect evidence supporting the existence of enteric dopaminergic neurons in the enteric nervous system are found in: i) pigs [194], ii) the enteric dopamine transporter-immunoreactive nerves [195], iii) transgenic mice lacking dopamine active transporter indicated that the mouse colon may usually contain inhibitory dopaminergic neurons [196], iv) dopamine-containing neurons in the myenteric plexus of the gastrointestinal tract of mice [197], and v) humans ganglion-containing layers of the gut in Parkinson's disease, which affects dopaminergic neurons [197]. Our laboratory has found that dopamine D₂-like receptor-selective agonists mediated-vomiting increases the expression of c-fos protein in the enteric nervous system of the least shrew [198].

4.1.3. Vagal afferents and efferents—The brain connects with the gut via the vagus nerve. It facilitates autonomic information transfer from the gastrointestinal tract to the CNS and *vice versa* [199,200] (Fig. 1). Specifically, the vagal afferent nerves relay a considerable amount of sensory information from thoracic and abdominal organs to the CNS circuits regulating gastric function. The cell bodies of origin for this afferent sensory pathway are in the nodosal ganglion near the jugular vein. Independent of their functions or modalities, all vagal afferent neurons use glutamate as the primary neurotransmitter to transfer information to the nucleus of the solitary tract. Neurons of the nucleus of the solitary tract implicated in the gastrointestinal tract regulation, innervate the adjacent dorsal motor nucleus of the vagus. The dorsal motor nucleus of the vagus has pre-ganglionic parasympathetic motoneurons that transmit the precise integrated neuronal response back to the upper gastrointestinal tract via the efferent vagus nerve (reviewed in [159]). Efferent vagus nerve transmits the integrated

and coordinated output response to the peripheral organs. Activity within vagal efferent pathways during emetic reflexes results in a large retropulsive wave of intestinal motility accompanied by gastric contraction. It is important to note that nodose ganglionic vagal afferents have dopamine mRNA markers and dopamine D₂ receptors [201]. In the rat nucleus of the solitary tract, the bulk of dopamine D₂ receptors seem to localize post-synaptically with respect to vagal terminals and are located either on ascending glossopharyngeal terminals, descending terminals from higher brain regions, or on neuronal cell bodies within the nucleus of the solitary tract [201]. It is suggested that dopamine D₂ receptors are synthesized in nodose perikarya and axoplasmically transported to the central nerve terminals in the medial sub-nucleus of the nucleus of the solitary tract [201]. There is a close relationship between the state of the peripheral vagus nerve activity and the function of the dopamine system in the brain. In the rat brain structures, chronic impairment of the function of the vagus nerve leads to the inhibition of dopaminergic but not serotonergic neurons [202].

4.1.4. Vomiting coordinator site: the central pattern generator—Regardless of how emesis is initiated, the motor act of vomiting is coordinated by the central pattern generator previously known as the vomiting center [203] (Fig. 1). The central pattern generator is located in the ventrolateral medulla in the area of the nucleus ambiguus (or retrofacial nucleus in the brainstem), which instigates a coordinated stimulation of appropriate motor nuclei [204–206]. Cerebral, vestibular, area postrema, and gut afferent inputs for nausea and vomiting converge on the nucleus of the solitary tract, which seems to be the logical candidate as a potential final common pathway integrated by central pattern generator for vomiting [207]. This is supported by data showing c-fos immunoreactivity was increased in the central pattern generator in response to pseudo-stimuli induced by vagal afferent stimulation. Interestingly, nodose neurons from the nodose ganglion propel considerably branched afferent fibers in both ascending and descending directions leading to the same neurons innervating a segment within the enteric nervous system and the medulla. In the medulla, branches of vagal afferents innervate the central pattern generator area and possibly the dorsal vagal complex [208,209]. Modulatory inputs are essential components of central pattern generator function: neuromodulators set the parameters of central pattern generator neurons and synapses to render the networks functional. Central pattern generator networks have provided a unique opportunity to study opposing actions of neuromodulators such as dopamine at the level of a single identified neuron or synapse. At several sites, dopamine evokes responses that oppose its overall actions on pyloric neurons and synapses. For example, dopamine hyperpolarizes and silences one neuron, but simultaneously enhances its hyperpolarization-activated inward current, which would depolarize the neuron to resume firing. Dopamine increases spike frequency in several neurons but enhances a slowly activating potassium current that would reduce spike frequency. Dopamine can also activate opposing effects at a single synapse. For instance, it can enhance transmitter release from the pre-synaptic terminal by increasing calcium currents but reduce post-synaptic responsiveness to the released transmitter. How these phenomena play out during emesis are still unexplored [210]. However, it is well known that central pattern generator activities of neural structures produce a complex patterned response, resulting in the action of vomiting [211] (Fig. 1).

Collectively, these findings support the existence of dopamine and dopamine D₂-like receptors throughout the emetic reflex arc, as well as a dopaminergic transmission through brainstem-gastrointestinal-vagal circuits during the process of vomiting.

5. Pharmacological evidence for dopamine-mediated emesis and treatment

Dopaminergic agonists act directly on dopamine receptors mimicking endogenous dopamine [212]. There are two subclasses of dopamine receptors agonists: non-ergoline-derived (non-ergots) and ergoline-(structural skeleton is the alkaloid ergoline; ergots) agonists both of which target dopamine D₂-like receptors (Table 1). In this section, we describe pre- and clinical evidence associated with the activation of emetogenic dopamine D₂-like receptors. We also list dopamine receptor antagonists used with varying degrees of success for suppression of vomiting (Tables 2–4).

5.1. Preclinical studies revealing the role of dopamine and dopamine receptors in vomiting

Experimental studies investigating dopamine and dopamine receptor agonists sites of action, dose-dependency, binding affinity, and potency across species are described in the subsequent sections.

The discovery of the emetic sites of action of dopamine started nearly seven decades ago with a set of pioneering experiments by Wang and Borison using apomorphine [213]. These investigators posed the possibility that the site of emetic action of apomorphine, orally or intravenously injected, was in the brainstem, because they found the ablation of the area postrema/chemoreceptive trigger zone prevented the induced emesis in dogs, whereas vagotomy and abdominal sympathectomy did not alter the response. These findings were later corroborated by new evidence demonstrating that 50 µg/animal intracerebroventricular (i.c. v) or 0.1 mg/kg intravenous (i.v.) injections of the nonselective dopamine D_{2/5}-HT₃ receptor antagonist metoclopramide in dogs blocked the vomiting produced by subcutaneously injected apomorphine, while vagotomy in combination with splanchnectomy did not [214]. Another report revealed that the CNS penetrable D₂ receptor preferring antagonist sulpiride was more effective when injected via i.v. versus the i.c.v. route against vomiting caused by i.v. administration of apomorphine. But, when apomorphine was administered via i.c.v., sulpiride was similarly effective in preventing vomiting independent of its route of injection [214]. If the drug does not penetrate or barely crosses the blood-brain barrier, the peripheral effects will prevail and conversely in the case of extensive penetration in the brain. Since dopamine is a polar molecule, it cannot enter or leave the brain easily. Thus, the above discussed results indicate that systemic release of endogenous dopamine stimulates peripheral emetic dopamine D₂ receptors in the area postrema zone on the blood side of the brain-blood barrier, whereas endogenous dopamine within the brain activates emetic dopamine D₂ receptors on the cerebrospinal fluid side of the brain-blood barrier. This concept was further validated by four additional studies showing that: 1) surgical disruption of blood flow in the area postrema zone abolished the emetic response to i.c.v. apomorphine, but only transiently interfered with emesis evoked by i.v. apomorphine [214], 2) the

prevention of peripheral conversion of L-DOPA to dopamine by carbidopa (a peripheral decarboxylase inhibitor) simultaneously decreased blood dopamine concentration and emesis despite the increase in brain dopamine levels, but vomiting was often not entirely stopped in dogs [215]. Moreover, in the least shrew carbidopa (0, 10, 20 and 40 mg/kg, i.p.) pretreatment dose-dependently and nearly completely prevented vomiting caused by several different doses of L-DOPA (50, 100 and 150 mg/kg, i.p.). In addition, the peripherally acting dopamine D₂ receptor antagonist domperidone can only partially decrease apomorphine-induced vomiting in dogs in doses up to 40 mg/kg, whereas the CNS permeable dopamine D₂ receptor antagonist risperidone fully prevented the emesis at just 10 mg/kg [216], and finally, 4) peripheral injection of direct-acting and selective dopamine D_{2/3} receptor agonists trigger emesis and induces c-fos expression in the nucleus of the solitary tract and dorsal motor nucleus of the vagus but not in the area postrema zone of the least shrew [198]. This is consistent with dopamine causing emesis by acting on dopamine D_{2/3} receptors localized to neurons whose dendrites stretch out the nucleus of the solitary tract into the area postrema. Further support for a site of action in the nucleus of the solitary tract comes from studies in ferrets showing that thermocautery lesions of the area postrema abolished the emetic response to loperamide [217]. It has been proposed that loperamide induced emesis by acting on opiate receptors located on the dendrites of neurons projecting from the nucleus of the solitary tract into the area postrema [218, 219].

Dopamine D₂-like receptor agonists evoke vomiting in a dose-dependent manner in emetic-competent species. Indeed, our laboratory has shown that quinpirole dose-dependently increases both the number of shrews vomiting and the mean frequency of emesis which were comparable to that of apomorphine [220]. Dopamine D₃ receptor involvement in vomiting was substantiated by data demonstrating that dopamine D₃-like agonists such as 7-OH-DPAT (7-hydroxy-2-(di-*N*-propylamino) tetralin) dose-dependently increased the number of shrews vomiting and potentiated the mean vomit frequency [13,220]. Interestingly, combinations of different doses of dopamine D₂ and D₃ preferring antagonists more potently prevented vomiting caused by various dopamine D₂ and D₃ preferring agonists. One of these combinations is U99194A (a dopamine D₃ receptor preferring antagonist) with sulpiride (a dopamine D₂ receptor preferring antagonist) (2 or 4 mg/kg each), which blocked quinpirole-induced vomiting frequency and significantly reduced the number of shrews vomiting, relative to each antagonist tested alone at the same doses. This synergism suggests that quinpirole probably causes emesis via the activation of both dopamine D₂ and D₃ receptor sites [221].

Another important parameter in dopamine D₂-like receptor agonists-mediated vomiting is its binding affinity for the receptor. In preclinical investigations, the inhibition constant (K_i) is the parameter of prime interest. This parameter demonstrates the capacity of a dopamine receptor agonist to displace a selective ligand for a receptor subtype from the receptor; the smaller the value, the higher the affinity of the agonist for the receptor subtype and hence, theoretically, the efficacy of the drug [222]. Dopamine activates dopamine D₁ to D₅ receptors with varying affinities ranging from nanomolar to micromolar range. In general, different subtypes of dopamine receptors vary significantly in their sensitivity to dopamine agonists and antagonists [223,224]. For example, non-ergot agonists such as apomorphine display high affinity for dopaminergic D₂, D₃, D₅, and D₄ receptors and, to a lesser extent,

for dopamine D₁ receptor subtypes [216]. Another non-ergot agonist, pramipexole, a dopamine D₃ receptor preferring agonist which binds to these receptors in low doses [225,226] (receptors affinities are summarized in Table 1). Depending on binding conditions, pramipexole affinity to dopamine D₃- *versus* dopamine D₂-receptors was reported to be 6–95 times higher [225,227]. Ropinirole binding affinity is similar to that of pramipexole, except that it does not have an affinity for α_2 -adrenergic receptors [228] (Table 1). The ergot agonists cabergoline has the highest affinities for dopamine D₂ receptor (K_i = 0.61 nM) [222] (Table 1) while pergolide has a high affinity for the dopamine D₂ receptors and moderate affinity for the dopamine D₁ receptors [229] (Table 1). Affinities of cabergoline (K_i = 1.27 nM), lisuride (K_i = 1.08 nM), and pergolide (K_i = 0.86 nM) for the dopamine D₃ receptor subtype were comparable to that of pramipexole with negligible affinity for dopamine D₁ receptor family or 5-HT receptors [222]. It has been suggested that the chemical structure of dopamine agonists may account for their greater selectivity for dopamine D₂-like family of receptors [230].

Dopamine receptor agonist potency has also been determined in several species. For example, apomorphine's (a non-selective dopamine receptor agonist) emetic potency varies across species with the following ED₅₀ potency order: dog > human > ferret, cat = pigeon. Also, 7-(OH) DPAT (a dopamine D₃ receptor preferring agonist) is a more potent emetogenic agent in dogs [231] and ferrets [14], when compared to the least shrew [220]. Based on the results obtained from the three species, the ED₅₀ potency order is: 7-(OH) DPAT < apomorphine < quinpirole. On the other hand, it has been well-established that agonists of dopamine D₁-like and D₄ receptors have no emetic effect in ferrets and dogs. Dopamine D₁/D₅ agonists like SKF1297 and SKF38393 do not induce emesis in ferrets [13], dogs [231], or least shrews [220]. Moreover, their corresponding antagonists do not block apomorphine-evoked vomiting [231].

In sum, findings from animal models have established that dopamine D₂ and/or D₃ receptors are important players in dopamine-induced emesis in vomit-competent species. In contrast, dopamine D₁-like and D₄ receptors are devoid of emetic response. Furthermore, the specificity of the site of the antiemetic action of an antagonist on peripheral or central dopamine D₂/D₃ receptors depends primarily on its pharmacokinetic properties.

5.2. Clinical applications of dopamine receptor agonists and consequent emesis

The dopaminergic system has been implicated in Parkinson's disease, drug addiction, depression, psychotic depression, ADHD, bipolar disorder, and schizophrenia. Some of the conditions are dominantly marked by low dopamine levels (hypodopaminergia) like in Parkinson's disease, pituitary tumors (prolactinomas), and restless leg syndrome [232], whereas others exhibit increased dopamine levels (hyperdopaminergia) as in schizophrenia [233]. However, many dopamine-related diseases are complex and feature both ends of the spectrum, frequently associated with pathogenetic implications of other neurotransmitters. The dopaminergic system is considered a major target for drug design applied in the treatment of neurological diseases. The sections below and Table 1 discuss established agonists and new therapies for patients with neurological diseases.

5.2.1. Dopamine and dopamine receptor agonists use for the treatments of neuropsychiatric conditions—

The discovery of dopamine and the account of an analytical method for its measurement were trailed by a study of markedly depleted levels of dopamine in the basal ganglia of individuals dying from Parkinson's disease [234]. Unlike dopamine, L-DOPA, a naturally occurring amino acid converted into dopamine in the brain and periphery is used clinically in the management of Parkinson's disease as it crosses the brain-blood barrier. One of the most common issues in patients treated with L-DOPA is the delayed onset of response following the ingestion of the drug. Indeed, a delay in reaching an "on" state or a full response failure accounted for more than 60% of daily "off" time (no active drug given) among 327 patients with advanced Parkinson's disease [235]. Moreover, L-DOPA therapy is frequently associated with motor complications leading to the addition of carbidopa, a peripheral decarboxylase inhibitor, to enhance the therapeutic benefit of this indirect-acting dopamine receptor agonist. Therefore, several psychotropic non-ergot and ergot direct-acting agonists were introduced as an adjunct to L-DOPA treatment in patients exhibiting fluctuating motor responses and dyskinesias associated with its chronic use [236,237]. The addition of agonists to these patients' regimes allows around a 20%–30% reduction in the dose of L-DOPA in practice and leads to improvement in the disabling complications. Dopamine agonists have also been successfully used as monotherapy in de novo patients with the intention of delaying treatment with L-DOPA and subsequently deferring the onset of complications [238]. Apomorphine for example is widely accepted as a suitable therapeutic alternative for Parkinson's disease [239]. It has also been applied in a variety of other treatments ranging from addiction (i.e., to heroin, alcohol, or cigarettes) to erectile dysfunction [240]. A potential important neuroprotective role for apomorphine in the treatment of Alzheimer's disease has also been implied since this drug lowers neural cell death [240]. In the 1990s, two other non-ergot dopamine receptors agonists, pramipexole and ropinirole (description in Table 1), were approved in the United States for use in Parkinson's disease and restless leg syndrome patients [222]. These drugs have been favored by many clinicians for various reasons, involving a more stable motor response, an improved side-effect profile, and a more desirable dosing schedule [240]. Notably, the early oral ergot derivatives of dopamine agonists encompassing bromocriptine, pergolide, lisuride, and the long-acting cabergoline (described in Table 1) [212], are among the most used clinically drugs nowadays. Moreover, bromocriptine is used as an adjunct to L-DOPA therapy in patients experiencing a worsening response to L-DOPA or who suffer fluctuations in response to the drug. Other patients who may benefit from bromocriptine therapy include those with limited clinical response to L-DOPA due to an inability to tolerate higher doses.

5.2.2. Dopamine D_{2/3} receptor agonist-mediated emesis—Despite the beneficial actions of dopamine receptor agonists in patients with CNS disorders, nausea and vomiting are subsequent debilitating side-effects that cannot be ignored. Chiefly, emesis may be due to the direct action of dopaminergic D_{2/3} receptor agonists or neuroleptic withdrawal syndrome [241] in patients. As detailed in the previous section, L-DOPA-mediated vomiting can be explained by its ability to have both central and peripheral effects. Usually, L-DOPA is combined with carbidopa to prevent it from being converted into dopamine pre-maturely in the bloodstream, allowing more of it to get into the brain. Dopaminergic agonists including non-ergot derivatives (e.g., apomorphine, piribedil, quinagolide, ropinirole, and

pramipexole), ergot derivatives (e.g., bromocriptine, lisuride, pergolide, and cabergoline), or other drugs used to treat neurological disorders can also cross the brain-blood barrier and evoke emesis. This is reflected in a meta-analysis of randomized controlled trials evaluating the efficacy of long-acting non-ergot dopamine agonists vs. placebo in Parkinson's disease. The results demonstrated that the long-acting non-ergot agonists were associated with a higher risk of nausea and vomiting [242]. One systematic review using PUBMED, EMBASE, and clinical trial databases to find placebo-controlled clinical trials of non-ergot ropinirole for restless leg syndrome revealed that ropinirole use led to a higher risk of nausea and vomiting at nearly 50% of all adverse events reported [243]. The authors of the study suggested that as restless leg syndrome was more widely recognized and treated; the prevalence of ropinirole-induced nausea and vomiting could grow substantially, and thus this drug use should be considered as a cause of chronic nausea and vomiting. As with many non-ergot dopamine agonists (Table 1), apomorphine's common initial side-effects are nausea and vomiting [244]. Indeed, in placebo-controlled trials used for US registration, nausea occurred in almost a third (31%) of patients and led to treatment discontinuation in 3% of patients. Vomiting was reported in 11% of patients and led to discontinuation in 2% of patients [245–247]. Notably, nausea and vomiting are more frequently found in intermittent injections than with continuous infusion therapy in apomorphine-treated patients [248]. Perhaps this could be attributed to a down-regulation of medullary dopamine receptor sensitivity (i.e., tolerance) with the continuous dopaminergic stimulation. The peripheral dopaminergic effects of apomorphine are usually well controlled by the co-administration of an appropriate antiemetic until tolerance emerges (typically 3–6 weeks after initiation of apomorphine therapy). Although, patients who inject apomorphine less than 4 times per day are plausible exceptions to this rule since they have been shown to be more prone to nausea and might require antiemetic prophylaxis for a longer period [234]. Emesis has also been reported during the utilization of ergot-derived dopamine agonists such as bromocriptine. Moreover, clinical research indicates that the partial agonist aripiprazole (described in Table 1) can cause nausea or vomiting in some patients.

Despite the benefits of conventional agonists, there has been a significant decrease in the development of new psychiatric drugs around the world, because of the multiple etiologies related to these diseases. New promising therapies based on biased GPCRs signaling being developed and are described in the following section.

5.2.3. Potential use of biased GPCRs signaling for the treatment of neurological disorders—Remarkable advances have been made in signaling cascades that are linked with the risks of neurological diseases. Normally, activation of GPCRs engages broad networks of signaling pathways, which for most receptors are mediated by both G-proteins and β -Arrestins. Distinctive biological responses are frequently associated with these diverse pathways. D₂-like receptor agonists such as those used to treat schizophrenia and the receptor antagonists activate or prevent the whole signaling network of the receptor. In contrast, “biased” receptor agonists selectively involve some signaling pathways but evade, or even deactivate, other signals mediated by the same receptor. By stabilizing a particular receptor conformation(s) that preferentially stimulate one specific signaling pathway, these biased receptor agonists allow a more targeted modulation of cell function

and treatment of disease [249]. Biased ligands selectivity is expected to control biological functions of GPCRs and Arrs in a more precise way, thus yielding new drug molecules with superior efficacy and/or reduced side-effects [250]. Indeed, the introduction of biased receptor agonists has led to the finding of encouraging drug candidates in clinical development like the G-protein-biased μ opioid receptor biased agonist oliceridine (also known as TRV130). Oliceridine causes robust G-protein signaling, with strength and efficacy comparable to morphine, but with far less β -Arr₂ recruitment and receptor internalization. It also demonstrates fewer undesirable effects than morphine. Biased dopamine D₂ receptor- β -Arr₂ ligands, UNC9975, UN0006, and UNC9994 have been discovered during the exploration of multiple regions of aripiprazole [251] (described in Table 1). It was found depending on the cell type, aripiprazole (Table 1) may act as a partial receptor agonist at dopamine D₂-Gi/o, and/or a dopamine D₂ receptor- β -Arr₂ pathway [252]. However, these compounds have dopamine D₂ receptor- β -Arr₂ agonistic/antagonistic activity in various cellular assays but show minimal dopamine D₂ receptor-Gi/o agonist activity [251,253]. They also have inhibitory effects on amphetamine-induced hyperlocomotion via the β -Arr₂-mediated pathway with less motoric side-effect in mice. Thus, perhaps aripiprazole-derived compounds could spare nausea and vomiting symptoms, compared to their parent drug aripiprazole. However, this will require further investigation.

5.3. Antiemetic use of dopamine receptor antagonists

Emesis can lead to several complications (e.g., water and electrolytes loss and tear of esophageal mucosa) especially if it recurs over a period of hours or days. This prompted a rationale for the development of antiemetic drugs that can prevent the binding of dopamine to dopamine D_{2/3} receptor subtypes [254]. Based on the initial findings in animal models, clinical studies have further refined the effectiveness of dopamine receptor-based antiemetics. The dopamine receptor antiemetics prevent vomiting by blocking either the area postrema / chemoreceptive trigger zone or peripheral stimulation of the dorsal vagal complex. Although serotonin 5-HT₃R antagonists became the drug of choice to treat chemotherapy-induced emesis, dopamine receptor antagonists especially dopamine D₂-like receptors antagonists remain effective drugs of choice in other emetic conditions associated with uremia, radiation sickness, and viral gastroenteritis. Contrary to dopamine D₂ receptor antagonism, partial dopamine D₂ receptor agonism (Table 1) is thought to concurrently decrease dopamine activity in overactive dopamine systems and increase its activity in parts of the brain where dopaminergic activity is inadequate. There are three classes of commonly prescribed dopamine receptor antagonists:

5.3.1. Phenothiazines—Phenothiazines are organic compounds related to the thiazine-class of heterocyclic compounds. Phenothiazines are grouped into three groups based on the substituents on nitrogen: (i) aliphatic analogs, which harbor acyclic groups; (ii) piperidines, which contain piperidine-derived groups; (iii) piperazine, which contains piperazine-derived substituents [255,256]. The first neuroleptic phenothiazine prototype; chlorpromazine was discovered in 1950, had many pharmacological effects including; anti-dopaminergic, antihistaminic, antiserotonin, anti-muscarinic, and antiemetic [257,258]. Since the discovery of the importance of chlorpromazine in the treatment of vomiting, numerous phenothiazine derivatives have been tested in search of a compound with a more increased antiemetic

potency (Table 2). Currently, phenothiazines are considered as general purpose antiemetics and used against vomiting evoked by uremia, radiation-sickness, viral gastroenteritis, postoperative nausea and vomiting as well as prophylaxis in patients receiving chemotherapy with low emetogenic potential or as salvage antiemetic in patients who have breakthrough emesis. The most significant antiemetic phenothiazines together with their properties are illustrated in Table 2.

5.3.2. Butyrophenones—These compounds have a functional ketone group and are often clinically used to treat various psychiatric diseases. They may be utilized for the prevention of post-operative nausea and vomiting as well. The dual use of butyrophenones is exemplified by neuroleptic drugs like haloperidol, the most widely used classical antipsychotic drug in this class, is a key tranquilizing drug, with substantial antiemetic activity due to its dopamine D₂ receptor antagonist properties [259]. Unfortunately, side-effects [260] such as drowsiness, dysphoria, delayed discharge, extrapyramidal reactions, restlessness, and anxiety after discharge have led to the refusal to use these drugs in the outpatient setting. Another dopamine D₂ receptor antagonist of this class is domperidone that is utilized in functional dyspepsia [261,262], and as a prokinetic and as an antiemetic agent [263]. Unlike haloperidol, domperidone does not produce any adverse neurological symptoms since it has minimal penetration through the brain-blood barrier. Thus, domperidone offers an excellent safety profile for long-term administration orally in the suggested doses [263]. Structures and properties of the commonly used antiemetic butyrophenones are depicted in Table 3.

5.3.3. Benzamides—Benzamides are amide of benzoic acid or any of its byproducts; some of its derivatives are pharmaceuticals. Although nowadays benzamides have largely been replaced by 5-HT₃-antagonists, they are still used in post-chemotherapy nausea and vomiting as an adjunct agent for delayed emesis. Benzamide analogs screening revealed that metoclopramide is one of the most effective drug in blocking vomiting [264]. Metoclopramide has been used clinically for the suppression of moderate-to-severe chemotherapy nausea and vomiting. High doses of metoclopramide have been combined with dexamethasone as antiemetic for highly emetogenic chemotherapy. It is also an advantageous antiemetic for Parkinson's disease patients for whom it was used to prevent L-DOPA-induced emesis [7]. Metoclopramide exerts its antiemetic activity on central [265,266], and peripheral systems [267]. Besides its ability to block dopaminergic receptors, metoclopramide blocks serotonin 5-HT₃ receptors, increases lower esophageal sphincter tone, and enhances gastric and small bowel motility [268]. Another important active substance from this group of benzamides is sulpiride, which is utilized not only as an antiemetic but also as antipsychotic agent. Sulpiride acts primarily as a dopamine D₂-preferring antagonist and lacks effects on norepinephrine, acetylcholine, serotonin, histamine, or gamma-aminobutyric acid (GABA) receptors. The low risk of unfavorable side-effects like extrapyramidal symptoms and torsade de pointes, has restored interest in dopamine D₂ receptor class antagonists [269]. Amisulpride is another such agent that has high and selective affinity for both dopamine D₂ and D₃ receptors and shows evidence of dose-dependent activity at preventing acute chemotherapy nausea and vomiting, especially, nausea [270]. This is consistent with results obtained in a recent randomized trial reporting

that 17% of patients treated with amisulpride alone had no emesis and 67% had insignificant nausea [271]. When amisulpride was combined with ondansetron (5-HT₃-receptor antagonist), the efficacy among 83% of the patients treated was increased, relative to ondansetron treatment alone. Since drugs such as 5-HT₃ or NK₁R antagonists are less effective against nausea, the use of amisulpride may prove to be more appropriate. More on common anti-emetic benzamides and their properties are shown in Table 4.

Collectively, these findings underline the availability of several dopamine D₂ receptor antagonists with versatile pharmacological activities as they can be both antiemetic and antipsychotic.

6. Conclusion

Dopamine is involved in a variety of critical physiological functions and as such, it is not surprising that several human disorders have been associated with dopaminergic dysfunctions. Agents that activate the dopamine D₂-like family of receptors elicit vomiting in humans and other vomit competent species. Dopamine D₂-like receptor antagonists are the oldest and most frequently utilized antiemetic agents in chemotherapy-induced nausea and vomiting, especially when serotonin antagonists have failed. However, dopamine antagonists tend to be at best intermediate in antiemetic effectiveness. Some progress has been made in revealing the intracellular signaling pathways that underlie the actions of dopamine accounting for its effect on vomiting. In particular, preliminary findings from our laboratory have pointed to potential development of new potent broad-spectrum classes of antiemetics targeting PI3K intracellular signals and their interaction with the downstream Akt/GSK-3 signaling [93,272]. Based upon these results, potential antiemetic drugs could be developed clinically. Together with partial agonists such as aripiprazole, these novel antiemetic targets may contribute to the development of antidopaminergic agents that will provide selective, long-lasting effects, with an optimal safety profile.

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Abbreviations:

AADC
aromatic L-amino acid decarboxylase

Akt/PKB
thymoma viral proto-oncogene

ALDH
aldehyde dehydrogenase

Arr
Arrestin

Ca²⁺

calcium

CaMKIICa²⁺/calmodulin-dependent kinase II**cAMP**

cyclic adenosine monophosphate

CNS

central nervous system

CNTF

ciliary neurotrophic factor

COMT

catechol-o-methyltransferase

DAG

1,2-diacylglycerol

DARPP-32

dopamine and cyclic AMP-regulated phosphoprotein, 32 kDa

DOPAC

3,4-dihydroxyphenylacetic acid

ER

endoplasmic reticulum

ERK_{1/2} or p44^{ERK} and p42^{ERK}

extracellular signal-regulated kinase 1 and 2

GABA

gamma aminobutyric acid

GPCRs

G protein-coupled receptors

GRKs

G-protein-coupled receptor kinases

GSK-3

glycogen synthase kinase-3

HIAA

hydroxy indole acetic acid

5-HT₃R

5-hydroxytryptamine 3 receptor

HVA

homovanillic acid

IP₃

inositol triphosphate

IP₃RIP₃ receptor**L-DOPA**

L-3,4-dihydroxyphenylalanine

LTCC

L-type calcium channel

MAO

monoamine oxidase

MAPK

mitogen-activated protein kinase

MEK

mitogen-activated protein kinase (also known as MAP2K, MEK, MAPKK)

mTOR

mammalian target of rapamycin

NE

norepinephrine

NK₁R

neurokinin type 1 receptor

6-OHDA

6-hydroxydopamine

PDGF

platelet-derived growth factor

PDK

phosphoinositide-dependent kinase

PI3K

phosphatidylinositol 3-kinase or phosphoinositide 3 kinase

PIP₂

phosphatidylinositol 4, 5-diphosphate

PIP₃

phosphatidylinositol 3,4,5-trisphosphate

PKA

protein kinase A

PKC

protein kinase C

PL

Phospholipase

PLC β phospholipase C isoform β **PMNT**

phenylethanolamine N-methyltransferase

PP1, PP2A, or PP2B

protein phosphatase 1, 2A or 2B

Raf

rapidly accelerated fibrosarcoma

Ras

retrovirus-associated DNA sequences

ROS

reactive oxygen species

RyR

ryanodine receptors

SER

sarcoplasmic and endoplasmic reticulum

SERCAsarcoplasmic and endoplasmic reticulum Ca^{2+} ATPase**Th³⁴**

phosphorylation of protein at threonine 34 site

TKRs

tyrosine kinase receptors

TRVP1

transient receptor potential vanilloid type 1

References

- [1]. Sotnikova TD, Beaulieu JM, Espinoza S, Masri B, Zhang X, Salahpour A, et al. The dopamine metabolite 3-methoxytyramine is a neuromodulator, PLoS One 5 (10) (2010), e13452. [PubMed: 20976142]

- [2]. Jaber M, Robinson SW, Missale C, Caron MG, Dopamine receptors and brain function, *Neuropharmacology* 35 (11) (1996) 1503–1519. [PubMed: 9025098]
- [3]. Centonze D, Grande C, Saulle E, Martin AB, Gubellini P, Pavon N, et al. Distinct roles of D1 and D5 dopamine receptors in motor activity and striatal synaptic plasticity, *J. Neurosci* 23 (24) (2003) 8506–8512. [PubMed: 13679419]
- [4]. Shimo Y, Nakajima A, Hattori N, Dopamine agonist withdrawal syndrome in a patient with restless legs syndrome without impulse control disorder or drug abuse, *Neurol. Sci* 36 (6) (2015) 1021–1023. [PubMed: 25362251]
- [5]. Dorfman BJ, Nirenberg MJ, Dopamine agonist withdrawal syndrome in a patient with restless legs syndrome, *Parkinsonism Relat. Disord* 19 (2) (2013) 269–270. [PubMed: 22749683]
- [6]. Darmani NA, Mechanisms of broad-spectrum antiemetic efficacy of cannabinoids against chemotherapy-induced acute and delayed vomiting, *Pharmaceuticals (Basel)* 3 (9) (2010) 2930–2955. [PubMed: 27713384]
- [7]. Darmani NA, Ray AP, Evidence for a re-evaluation of the neurochemical and anatomical bases of chemotherapy-induced vomiting, *Chem. Rev* 109 (7) (2009) 3158–3199. [PubMed: 19522506]
- [8]. Missale C, Nash SR, Robinson SW, Jaber M, Caron MG, Dopamine receptors: from structure to function, *Physiol. Rev* 78 (1) (1998) 189–225. [PubMed: 9457173]
- [9]. Gainetdinov RR, Premont RT, Bohn LM, Lefkowitz RJ, Caron MG, Desensitization of G protein-coupled receptors and neuronal functions, *Annu. Rev. Neurosci* 27 (2004) 107–144. [PubMed: 15217328]
- [10]. Vassilatis DK, Hohmann JG, Zeng H, Li F, Ranchalis JE, Mortrud MT, et al. The G protein-coupled receptor repertoires of human and mouse, *Proc. Natl. Acad. Sci. U. S. A* 100 (8) (2003) 4903–4908. [PubMed: 12679517]
- [11]. Andersen PH, Gingrich JA, Bates MD, Dearry A, Falardeau P, Senogles SE, et al. Dopamine receptor subtypes: beyond the D1/D2 classification, *Trends Pharmacol. Sci* 11 (6) (1990) 231–236. [PubMed: 2200181]
- [12]. Bouvier C, Salon JA, Johnson RA, Civelli O, Dopaminergic activity measured in D1- and D2-transfected fibroblasts by silicon-microphysiometry, *J. Recept. Res* 13 (1–4) (1993) 559–571. [PubMed: 8450504]
- [13]. Yoshikawa T, Yoshida N, Hosoki K, Involvement of dopamine D3 receptors in the area postrema in R(+)-7-OH-DPAT-induced emesis in the ferret, *Eur. J. Pharmacol* 301 (1–3) (1996) 143–149. [PubMed: 8773458]
- [14]. Osinski MA, Uchic ME, Seifert T, Shaughnessy TK, Miller LN, Nakane M, et al. Dopamine D2, but not D4, receptor agonists are emetogenic in ferrets, *Pharmacol. Biochem. Behav* 81 (1) (2005) 211–219. [PubMed: 15894081]
- [15]. Christenson JG, Dairman W, Udenfriend S, Preparation and properties of a homogeneous aromatic L-amino acid decarboxylase from hog kidney, *Arch. Biochem. Biophys* 141 (1) (1970) 356–367. [PubMed: 4991409]
- [16]. Udenfriend S, Wyngaarden JB, Precursors of adrenal epinephrine and norepinephrine in vivo, *Biochim. Biophys. Acta* 20 (1) (1956) 48–52. [PubMed: 13315348]
- [17]. Weinshilboum RM, Thoa NB, Johnson DG, Kopin IJ, Axelrod J, Proportional release of norepinephrine and dopamine- β -hydroxylase from sympathetic nerves, *Science* 174 (4016) (1971) 1349–1351. [PubMed: 5135722]
- [18]. Ford CP, The role of D2-autoreceptors in regulating dopamine neuron activity and transmission, *Neuroscience* 282 (2014) 13–22. [PubMed: 24463000]
- [19]. Gingrich JA, Caron MG, Recent advances in the molecular biology of dopamine receptors, *Annu. Rev. Neurosci* 16 (1993) 299–321. [PubMed: 8460895]
- [20]. Giros B, Sokoloff P, Martres MP, Riou JF, Emorine LJ, Schwartz JC, Alternative splicing directs the expression of two D2 dopamine receptor isoforms, *Nature* 342 (6252) (1989) 923–926. [PubMed: 2531847]
- [21]. Monsma FJ Jr., L.D. McVittie, C.R. Gerfen, L.C. Mahan, D.R. Sibley, Multiple D2 dopamine receptors produced by alternative RNA splicing, *Nature* 342 (6252) (1989) 926–929. [PubMed: 2480527]

- [22]. Giros B, Martres MP, Pilon C, Sokoloff P, Schwartz JC, Shorter variants of the D3 dopamine receptor produced through various patterns of alternative splicing, *Biochem. Biophys. Res. Commun* 176 (3) (1991) 1584–1592. [PubMed: 2039532]
- [23]. Van Tol HH, Bunzow JR, Guan HC, Sunahara RK, Seeman P, Niznik HB, et al. Cloning of the gene for a human dopamine D4 receptor with high affinity for the antipsychotic clozapine, *Nature* 350 (6319) (1991) 610–614. [PubMed: 1840645]
- [24]. Seeman P, Van Tol HH, Dopamine receptor pharmacology, *Trends Pharmacol. Sci* 15 (7) (1994) 264–270. [PubMed: 7940991]
- [25]. Sanyal S, Van Tol HH, Review the role of dopamine D4 receptors in schizophrenia and antipsychotic action, *J. Psychiatr. Res* 31 (2) (1997) 219–232. [PubMed: 9278187]
- [26]. Probst WC, Snyder LA, Schuster DI, Brosius J, Sealfon SC, Sequence alignment of the G-protein coupled receptor superfamily, *DNA Cell Biol* 11 (1) (1992) 1–20. [PubMed: 1310857]
- [27]. Kjelsberg MA, Cotecchia S, Ostrowski J, Caron MG, Lefkowitz RJ, Constitutive activation of the alpha 1B-adrenergic receptor by all amino acid substitutions at a single site. Evidence for a region which constrains receptor activation, *J. Biol. Chem* 267 (3) (1992) 1430–1433. [PubMed: 1346134]
- [28]. Strader CD, Sigal IS, Candelore MR, Rands E, Hill WS, Dixon RA, Conserved aspartic acid residues 79 and 113 of the beta-adrenergic receptor have different roles in receptor function, *J. Biol. Chem* 263 (21) (1988) 10267–10271. [PubMed: 2899076]
- [29]. Strader CD, Candelore MR, Hill WS, Sigal IS, Dixon RA, Identification of two serine residues involved in agonist activation of the beta-adrenergic receptor, *J. Biol. Chem* 264 (23) (1989) 13572–13578. [PubMed: 2547766]
- [30]. Hibert MF, Trumpp-Kallmeyer S, Hoflack J, Bruinvels A, This is not a G protein-coupled receptor, *Trends Pharmacol. Sci* 14 (1) (1993) 7–12. [PubMed: 8095116]
- [31]. Trumpp-Kallmeyer S, Hoflack J, Bruinvels A, Hibert M, Modeling of G-protein-coupled receptors: application to dopamine, adrenaline, serotonin, acetylcholine, and mammalian opsin receptors, *J. Med. Chem* 35 (19) (1992) 3448–3462. [PubMed: 1328638]
- [32]. Beaulieu JM, Espinoza S, Gainetdinov RR, Dopamine receptors – IUPHAR review 13, *Br. J. Pharmacol* 172 (1) (2015) 1–23. [PubMed: 25671228]
- [33]. Brown KM, Lee LC, Findlay JE, Day JP, Baillie GS, Cyclic AMP-specific phosphodiesterase, PDE8A1, is activated by protein kinase A-mediated phosphorylation, *FEBS Lett* 586 (11) (2012) 1631–1637. [PubMed: 22673573]
- [34]. Sidhu A, Niznik HB, Coupling of dopamine receptor subtypes to multiple and diverse G proteins, *Int. J. Dev. Neurosci* 18 (7) (2000) 669–677. [PubMed: 10978845]
- [35]. Kebabian JW, Petzold GL, Greengard P, Dopamine-sensitive adenylate cyclase in caudate nucleus of rat brain, and its similarity to the “dopamine receptor”, *Proc. Natl. Acad. Sci. U. S. A* 69 (8) (1972) 2145–2149. [PubMed: 4403305]
- [36]. Kebabian JW, Calne DB, Multiple receptors for dopamine, *Nature* 277 (5692) (1979) 93–96. [PubMed: 215920]
- [37]. Borrelli E, Montmayeur JP, Foulkes NS, Sassone-Corsi P, Signal transduction and gene control: the cAMP pathway, *Crit. Rev. Oncog* 3 (4) (1992) 321–338. [PubMed: 1329990]
- [38]. Nestler EJ, Gould E, Manji H, Buncan M, Duman RS, Greshenfeld HK, et al. Preclinical models: status of basic research in depression, *Biol. Psychiatry* 52 (6) (2002) 503–528. [PubMed: 12361666]
- [39]. Racke K, Reimann A, Schworer H, Kilbinger H, Regulation of 5-HT release from enterochromaffin cells, *Behav. Brain Res* 73 (1–2) (1996) 83–87. [PubMed: 8788482]
- [40]. Mori F, Perez-Torres S, De Caro R, Porzionato A, Macchi V, Beleta J, et al. The human area postrema and other nuclei related to the emetic reflex express cAMP phosphodiesterases 4B and 4D, *J. Chem. Neuroanat* 40 (1) (2010) 36–42. [PubMed: 20347962]
- [41]. Darmani NA, Zhong W, Chebolu S, Mercadante F, Differential and additive suppressive effects of 5-HT3 (palonosetron)- and NK1 (netupitant)-receptor antagonists on cisplatin-induced vomiting and ERK1/2, PKA and PKC activation, *Pharmacol. Biochem. Behav* 131 (2015) 104–111. [PubMed: 25687374]

- [42]. Darmani NA, Dey D, Chebolu S, Amos B, Kandpal R, Alkam T, Cisplatin causes over-expression of tachykinin NK(1) receptors and increases ERK1/2- and PKA- phosphorylation during peak immediate- and delayed-phase emesis in the least shrew (*Cryptotis parva*) brainstem, *Eur. J. Pharmacol* 698 (1–3) (2013) 161–169. [PubMed: 23001014]
- [43]. Alkam T, Chebolu S, Darmani NA, Cyclophosphamide causes activation of protein kinase A (PKA) in the brainstem of vomiting least shrews (*Cryptotis parva*), *Eur. J. Pharmacol* 722 (2014) 156–164. [PubMed: 24513510]
- [44]. Naor Z, Benard O, Seger R, Activation of MAPK cascades by G-protein-coupled receptors: the case of gonadotropin-releasing hormone receptor, *Trends Endocrinol. Metab* 11 (3) (2000) 91–99. [PubMed: 10707049]
- [45]. Conrad PW, Millhorn DE, Beitner-Johnson D, Novel regulation of p38gamma by dopamine D2 receptors during hypoxia, *Cell. Signal* 12 (7) (2000) 463–467. [PubMed: 10989281]
- [46]. Beom S, Cheong D, Torres G, Caron MG, Kim KM, Comparative studies of molecular mechanisms of dopamine D2 and D3 receptors for the activation of extracellular signal-regulated kinase, *J. Biol. Chem* 279 (27) (2004) 28304–28314. [PubMed: 15102843]
- [47]. Kim SY, Choi KC, Chang MS, Kim MH, Kim SY, Na YS, et al. The dopamine D2 receptor regulates the development of dopaminergic neurons via extracellular signal-regulated kinase and Nurr1 activation, *J. Neurosci* 26 (17) (2006) 4567–4576. [PubMed: 16641236]
- [48]. Luo Y, Kokkonen GC, Wang X, Neve KA, Roth GS, D2 dopamine receptors stimulate mitogenesis through pertussis toxin-sensitive G proteins and Ras-involved ERK and SAP/JNK pathways in rat C6-D2L glioma cells, *J. Neurochem* 71 (3) (1998) 980–990. [PubMed: 9721723]
- [49]. Welsh GI, Hall DA, Warnes A, Strange PG, Proud CG, Activation of microtubule-associated protein kinase (Erk) and p70 S6 kinase by D2 dopamine receptors, *J. Neurochem* 70 (5) (1998) 2139–2146. [PubMed: 9572301]
- [50]. Wang C, Buck DC, Yang R, Macey TA, Neve KA, Dopamine D2 receptor stimulation of mitogen-activated protein kinases mediated by cell type-dependent transactivation of receptor tyrosine kinases, *J. Neurochem* 93 (4) (2005) 899–909. [PubMed: 15857393]
- [51]. Huff RM, Signal transduction pathways modulated by the D2 subfamily of dopamine receptors, *Cell. Signal* 8 (6) (1996) 453–459. [PubMed: 8958449]
- [52]. Wei H, Ahn S, Shenoy SK, Karnik SS, Hunyady L, Luttrell LM, et al. Independent beta-arrestin 2 and G protein-mediated pathways for angiotensin II activation of extracellular signal-regulated kinases 1 and 2, *Proc. Natl. Acad. Sci. U. S. A* 100 (19) (2003) 10782–10787. [PubMed: 12949261]
- [53]. Moore CA, Milano SK, Benovic JL, Regulation of receptor trafficking by GRKs and arrestins, *Annu. Rev. Physiol* 69 (2007) 451–482. [PubMed: 17037978]
- [54]. Lefkowitz RJ, Shenoy SK, Transduction of receptor signals by beta-arrestins, *Science* 308 (5721) (2005) 512–517. [PubMed: 15845844]
- [55]. Shenoy SK, Lefkowitz RJ, Angiotensin II-stimulated signaling through G proteins and beta-arrestin, *Sci. STKE* 2005 (311) (2005) cm14. [PubMed: 16304060]
- [56]. Luttrell LM, Gesty-Palmer D, Beyond desensitization: physiological relevance of arrestin-dependent signaling, *Pharmacol. Rev* 62 (2) (2010) 305–330. [PubMed: 20427692]
- [57]. Jin M, Min C, Zheng M, Cho DI, Cheong SJ, Kurose H, et al. Multiple signaling routes involved in the regulation of adenylyl cyclase and extracellular regulated kinase by dopamine D(2) and D(3) receptors, *Pharmacol. Res* 67 (1) (2013) 31–41. [PubMed: 23059541]
- [58]. Valjent E, Corvol JC, Pages C, Besson MJ, Maldonado R, Caboche J, Involvement of the extracellular signal-regulated kinase cascade for cocaine-rewarding properties, *J. Neurosci* 20 (23) (2000) 8701–8709. [PubMed: 11102476]
- [59]. Choe ES, McGinty JF, Cyclic AMP and mitogen-activated protein kinases are required for glutamate-dependent cyclic AMP response element binding protein and Elk-1 phosphorylation in the dorsal striatum in vivo, *J. Neurochem* 76 (2) (2001) 401–412. [PubMed: 11208903]
- [60]. Mattson BJ, Bossert JM, Simmons DE, Nozaki N, Nagarkar D, Kreuter JD, et al. Cocaine-induced CREB phosphorylation in nucleus accumbens of cocaine-sensitized rats is enabled by enhanced activation of extracellular signal-related kinase, but not protein kinase A, *J. Neurochem* 95 (5) (2005) 1481–1494. [PubMed: 16219028]

- [61]. Lu L, Koya E, Zhai H, Hope BT, Shaham Y, Role of ERK in cocaine addiction, *Trends Neurosci* 29 (12) (2006) 695–703. [PubMed: 17084911]
- [62]. Zhang J, Zhang L, Jiao H, Zhang Q, Zhang D, Lou D, et al. c-Fos facilitates the acquisition and extinction of cocaine-induced persistent changes, *J. Neurosci* 26 (51) (2006) 13287–13296. [PubMed: 17182779]
- [63]. Girault JA, Valjent E, Caboche J, Herve D, ERK2: a logical AND gate critical for drug-induced plasticity? *Curr. Opin. Pharmacol* 7 (1) (2007) 77–85. [PubMed: 17085074]
- [64]. Xia Z, Dickens M, Raingeaud J, Davis RJ, Greenberg ME, Opposing effects of ERK and JNK-p38 MAP kinases on apoptosis, *Science* 270 (5240) (1995) 1326–1331. [PubMed: 7481820]
- [65]. Atkins CM, Selcher JC, Petraitis JJ, Trzaskos JM, Sweatt JD, The MAPK cascade is required for mammalian associative learning, *Nat. Neurosci* 1 (7) (1998) 602–609. [PubMed: 10196568]
- [66]. Alessandrini A, Namura S, Moskowitz MA, Bonventre JV, MEK1 protein kinase inhibition protects against damage resulting from focal cerebral ischemia, *Proc. Natl. Acad. Sci. U. S. A* 96 (22) (1999) 12866–12869. [PubMed: 10536014]
- [67]. Kulich SM, Chu CT, Role of reactive oxygen species in extracellular signal-regulated protein kinase phosphorylation and 6-hydroxydopamine cytotoxicity, *J. Biosci* 28 (1) (2003) 83–89. [PubMed: 12682429]
- [68]. Zhong W, Hutchinson TE, Chebolu S, Darmani NA, Serotonin 5-HT₃ receptor-mediated vomiting occurs via the activation of Ca²⁺/CaMKII-dependent ERK1/2 signaling in the least shrew (*Cryptotis parva*), *PLoS One* 9 (8) (2014), e104718. [PubMed: 25121483]
- [69]. Zhong W, Chebolu S, Darmani NA, Intracellular emetic signaling cascades by which the selective neurokinin type 1 receptor (NK1R) agonist GR73632 evokes vomiting in the least shrew (*Cryptotis parva*), *Neurochem. Int* 122 (2019) 106–119. [PubMed: 30453005]
- [70]. Zhong W, Chebolu S, Darmani NA, Thapsigargin-induced activation of Ca(2+)-CaMKII-ERK in brainstem contributes to substance P release and induction of emesis in the least shrew, *Neuropharmacology* 103 (2016) 195–210. [PubMed: 26631534]
- [71]. Zhong W, Chebolu S, Darmani NA, Intracellular emetic signaling evoked by the L-type Ca(2+) channel agonist FPL64176 in the least shrew (*Cryptotis parva*), *Eur. J. Pharmacol* 834 (2018) 157–168. [PubMed: 29966616]
- [72]. Beaulieu JM, Gainetdinov RR, Caron MG, Akt/GSK3 signaling in the action of psychotropic drugs, *Annu. Rev. Pharmacol. Toxicol* 49 (2009) 327–347. [PubMed: 18928402]
- [73]. Bami-Cherrier K, Valjent E, Garcia M, Pages C, Hipkind RA, Caboche J, Dopamine induces a PI3-kinase-independent activation of Akt in striatal neurons: a new route to cAMP response element-binding protein phosphorylation, *J. Neurosci* 22 (20) (2002) 8911–8921. [PubMed: 12388598]
- [74]. Svenningsson P, Tzavara ET, Carruthers R, Rachleff I, Wattler S, Nehls M, et al. Diverse psychotomimetics act through a common signaling pathway, *Science* 302 (5649) (2003) 1412–1415. [PubMed: 14631045]
- [75]. Mannoury la Cour C, Salles MJ, Pasteau V, Millan MJ, Signaling pathways leading to phosphorylation of Akt and GSK-3 β by activation of cloned human and rat cerebral D(2) and D(3) receptors, *Mol. Pharmacol* 79 (1) (2011) 91–105. [PubMed: 20952497]
- [76]. Rau TF, Kothiwala A, Zhang L, Ulatowski S, Jacobson S, Brooks DM, et al. Low dose methamphetamine mediates neuroprotection through a PI3K-AKT pathway, *Neuropharmacology* 61 (4) (2011) 677–686. [PubMed: 21635908]
- [77]. Ugi S, Imamura T, Maegawa H, Egawa K, Yoshizaki T, Shi K, et al. Protein phosphatase 2A negatively regulates insulin's metabolic signaling pathway by inhibiting Akt (protein kinase B) activity in 3T3-L1 adipocytes, *Mol. Cell. Biol* 24 (19) (2004) 8778–8789. [PubMed: 15367694]
- [78]. Beaulieu JM, Sotnikova TD, Marion S, Lefkowitz RJ, Gainetdinov RR, Caron MG, An Akt/beta-arrestin 2/PP2A signaling complex mediates dopaminergic neurotransmission and behavior, *Cell* 122 (2) (2005) 261–273. [PubMed: 16051150]
- [79]. Beaulieu JM, Sotnikova TD, Yao WD, Kockeritz L, Woodgett JR, Gainetdinov RR, et al. Lithium antagonizes dopamine-dependent behaviors mediated by an AKT/glycogen synthase kinase 3 signaling cascade, *Proc. Natl. Acad. Sci. U. S. A* 101 (14) (2004) 5099–5104. [PubMed: 15044694]

- [80]. Lovestone S, Killick R, Di Forti M, Murray R, Schizophrenia as a GSK-3 dysregulation disorder, *Trends Neurosci* 30 (4) (2007) 142–149. [PubMed: 17324475]
- [81]. Gould TD, O'Donnell KC, Picchini AM, Manji HK, Strain differences in lithium attenuation of d- amphetamine-induced hyperlocomotion: a mouse model for the genetics of clinical response to lithium, *Neuropsychopharmacology* 32 (6) (2007) 1321–1333. [PubMed: 17151598]
- [82]. Prickaerts J, Moechars D, Cryns K, Lenaerts I, van Craenendonck H, Goris I, et al. Transgenic mice overexpressing glycogen synthase kinase 3 β : a putative model of hyperactivity and mania, *J. Neurosci* 26 (35) (2006) 9022–9029. [PubMed: 16943560]
- [83]. Kihara T, Shimohama S, Sawada H, Honda K, Nakamizo T, Kanki R, et al. Protective effect of dopamine D2 agonists in cortical neurons via the phosphatidylinositol 3 kinase cascade, *J. Neurosci. Res* 70 (3) (2002) 274–282. [PubMed: 12391586]
- [84]. Lim JA, Woo JH, Kim HS, Phosphoinositide 3-kinase/Akt signalling is responsible for the differential susceptibility of myoblasts and myotubes to menadione-induced oxidative stress, *Free Radic. Res* 42 (9) (2008) 798–806. [PubMed: 19051078]
- [85]. Nair VD, Olanow CW, Differential modulation of Akt/glycogen synthase kinase-3 β pathway regulates apoptotic and cytoprotective signaling responses, *J. Biol. Chem* 283 (22) (2008) 15469–15478. [PubMed: 18387957]
- [86]. Verit FF, Erel O, Sav M, Celik N, Cadirci D, Oxidative stress is associated with clinical severity of nausea and vomiting of pregnancy, *Am. J. Perinatol* 24 (9) (2007) 545–548. [PubMed: 17893839]
- [87]. Fathi H, Ebrahimzadeh MA, Ziar A, Mohammadi H, Oxidative damage induced by retching; antiemetic and neuroprotective role of *Sambucus ebulus* L, *Cell Biol. Toxicol* 31 (4–5) (2015) 231–239. [PubMed: 26493312]
- [88]. Collo G, Bono F, Cavalleri L, Plebani L, Merlo Pich E, Millan MJ, et al. Pre-synaptic dopamine D(3) receptor mediates cocaine-induced structural plasticity in mesencephalic dopaminergic neurons via ERK and Akt pathways, *J. Neurochem* 120 (5) (2012) 765–778. [PubMed: 22145570]
- [89]. Ma Y, Zhao P, Zhu J, Yan C, Li L, Zhang H, et al. Naioxintong protects primary neurons from oxygen-glucose deprivation/reoxygenation induced injury through PI3K-Akt signaling pathway, *Evid. Complement. Alternat. Med* 2016 (2016), 5815946.
- [90]. Beaulieu JM, Not only lithium: regulation of glycogen synthase kinase-3 by antipsychotics and serotonergic drugs, *Int. J. Neuropsychopharmacol* 10 (1) (2007) 3–6. [PubMed: 16784549]
- [91]. Li X, Rosborough KM, Friedman AB, Zhu W, Roth KA, Regulation of mouse brain glycogen synthase kinase-3 by atypical antipsychotics, *Int. J. Neuropsychopharmacol* 10 (1) (2007) 7–19. [PubMed: 16672106]
- [92]. Beaulieu JM, Zhang X, Rodriguiz RM, Sotnikova TD, Cools MJ, Wetsel WC, et al. Role of GSK3 β in behavioral abnormalities induced by serotonin deficiency, *Proc. Natl. Acad. Sci. U. S. A* 105 (4) (2008) 1333–1338. [PubMed: 18212115]
- [93]. Zhong W, Darmani NA, The pivotal role of glycogen synthase kinase 3 (GSK-3) in vomiting evoked by specific emetogens in the least shrew (*Cryptotis parva*), *Neurochem. Int* 132 (2019), 104603. [PubMed: 31738972]
- [94]. Rosengarten H, Friedhoff AJ, A phosphoinositide-linked dopamine D1 receptor mediates repetitive jaw movements in rats, *Biol. Psychiatry* 44 (11) (1998) 1178–1184. [PubMed: 9836022]
- [95]. Alexander GE, Crutcher MD, Functional architecture of basal ganglia circuits: neural substrates of parallel processing, *Trends Neurosci* 13 (7) (1990) 266–271. [PubMed: 1695401]
- [96]. Arias-Montano JA, Aceves J, Young JM, Carbachol-induced phosphoinositide metabolism in slices of rat substantia nigra pars reticulata, *Brain Res. Mol. Brain Res* 19 (3) (1993) 233–236. [PubMed: 8412567]
- [97]. Friedman E, Jin LQ, Cai GP, Hollon TR, Drago J, Sibley DR, et al. D1-like dopaminergic activation of phosphoinositide hydrolysis is independent of D1A dopamine receptors: evidence from D1A knockout mice, *Mol. Pharmacol* 51 (1) (1997) 6–11. [PubMed: 9016340]
- [98]. Wallace MA, Claro E, Transmembrane signaling through phospholipase C in human cortical membranes, *Neurochem. Res* 18 (2) (1993) 139–145. [PubMed: 8386329]

- [99]. Pacheco MA, Joje RS, Comparison of [3H]phosphatidylinositol and [3H] phosphatidylinositol 4,5-bisphosphate hydrolysis in postmortem human brain membranes and characterization of stimulation by dopamine D1 receptors, *J. Neurochem* 69 (2) (1997) 639–644. [PubMed: 9231722]
- [100]. Panchalingam S, Undie AS, SKF83959 exhibits biochemical agonism by stimulating [(35)S]GTP gamma S binding and phosphoinositide hydrolysis in rat and monkey brain, *Neuropharmacology* 40 (6) (2001) 826–837. [PubMed: 11369036]
- [101]. Pizzi M, D'Agostini F, Da Prada M, Spano PF, Haefely WE, Dopamine D2 receptor stimulation decreases the inositol trisphosphate level of rat striatal slices, *Eur. J. Pharmacol* 136 (2) (1987) 263–264. [PubMed: 2954833]
- [102]. Pizzi M, Da Prada M, Valerio A, Memo M, Spano PF, Haefely WE, Dopamine D2 receptor stimulation inhibits inositol phosphate generating system in rat striatal slices, *Brain Res* 456 (2) (1988) 235–240. [PubMed: 2974746]
- [103]. Undieh AS, Pharmacology of signaling induced by dopamine D(1)-like receptor activation, *Pharmacol. Ther* 128 (1) (2010) 37–60. [PubMed: 20547182]
- [104]. Undie AS, Berki AC, Beardsley K, Dopaminergic behaviors and signal transduction mediated through adenylate cyclase and phospholipase C pathways, *Neuropharmacology* 39 (1) (2000) 75–87. [PubMed: 10665821]
- [105]. Berridge MJ, Inositol trisphosphate and diacylglycerol as second messengers, *Biochem. J* 220 (2) (1984) 345–360. [PubMed: 6146314]
- [106]. Berridge MJ, Irvine RF, Inositol trisphosphate, a novel second messenger in cellular signal transduction, *Nature* 312 (5992) (1984) 315–321. [PubMed: 6095092]
- [107]. Kania E, Roest G, Vervliet T, Parys JB, Bultynck G, IP3 receptor-mediated calcium signaling and its role in autophagy in cancer, *Front. Oncol* 7 (2017) 140. [PubMed: 28725634]
- [108]. Grisshammer R, Hermans E, Functional coupling with Galpha(q) and Galpha(i1) protein subunits promotes high-affinity agonist binding to the neurotensin receptor NTS-1 expressed in *Escherichia coli*, *FEBS Lett* 493 (2–3) (2001) 101–105. [PubMed: 11287004]
- [109]. Rashid AJ, So CH, Kong MM, Furtak T, El-Ghundi M, Cheng R, O'Dowd BF, et al. D1-D2 dopamine receptor heterooligomers with unique pharmacology are coupled to rapid activation of Gq/11 in the striatum, *Proc. Natl. Acad. Sci. U. S. A* 104 (2) (2007) 654–659. [PubMed: 17194762]
- [110]. Rhee SG, Regulation of phosphoinositide-specific phospholipase C, *Annu. Rev. Biochem* 70 (2001) 281–312. [PubMed: 11395409]
- [111]. Charles AC, Mostovskaya N, Asas K, Evans CJ, Dankovich ML, Hales TG, Coexpression of delta-opioid receptors with micro receptors in GH3 cells changes the functional response to micro agonists from inhibitory to excitatory, *Mol. Pharmacol* 63 (1) (2003) 89–95. [PubMed: 12488540]
- [112]. Deveney AM, Waddington JL, Pharmacological characterization of behavioural responses to SK&F 83959 in relation to 'D1-like' dopamine receptors not linked to adenylyl cyclase, *Br. J. Pharmacol* 116 (3) (1995) 2120–2126. [PubMed: 8640354]
- [113]. Yamauchi T, Neuronal Ca2+/calmodulin-dependent protein kinase II—discovery, progress in a quarter of a century, and perspective: implication for learning and memory, *Biol. Pharm. Bull* 28 (8) (2005) 1342–1354. [PubMed: 16079472]
- [114]. Cho JH, Han JS, Phospholipase D and its essential role in cancer, *Mol. Cells* 40 (11) (2017) 805–813. [PubMed: 29145720]
- [115]. Exton JH, Phospholipase D: enzymology, mechanisms of regulation, and function, *Physiol. Rev* 77 (2) (1997) 303–320. [PubMed: 9114816]
- [116]. Senogles SE, The D2s dopamine receptor stimulates phospholipase D activity: a novel signaling pathway for dopamine, *Mol. Pharmacol* 58 (2) (2000) 455–462. [PubMed: 10908315]
- [117]. Everett PB, Senogles SE, D3 dopamine receptor activates phospholipase D through a pertussis toxin-insensitive pathway, *Neurosci. Lett* 371 (1) (2004) 34–39. [PubMed: 15500962]
- [118]. Mitchell R, McCulloch D, Lutz E, Johnson M, MacKenzie C, Fennell M, et al. Rhodopsin-family receptors associate with small G proteins to activate phospholipase D, *Nature* 392 (6674) (1998) 411–414. [PubMed: 9537328]

- [119]. Bae EJ, Lee HJ, Jang YH, Michael S, Masliah E, Min DS, Lee SJ, Phospholipase D1 regulates autophagic flux and clearance of alpha-synuclein aggregates, *Cell Death Differ* 21 (7) (2014) 1132–1141. [PubMed: 24632948]
- [120]. Lewis JA, Scott SA, Lavieri R, Buck JR, Selvy PE, Stoops SL, et al. Design and synthesis of isoform-selective phospholipase D (PLD) inhibitors. Part I: impact of alternative halogenated privileged structures for PLD1 specificity, *Bioorg. Med. Chem. Lett* 19 (7) (2009) 1916–1920. [PubMed: 19268584]
- [121]. Lavieri RR, Scott SA, Selvy PE, Kim K, Jadhav S, Morrison RD, et al. Design, synthesis, and biological evaluation of halogenated N-(2-(4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]decan-8-yl)ethyl)benzamides: discovery of an isoform-selective small molecule phospholipase D2 inhibitor, *J. Med. Chem* 53 (18) (2010) 6706–6719. [PubMed: 20735042]
- [122]. Su W, Chen Q, Frohman MA, Targeting phospholipase D with small-molecule inhibitors as a potential therapeutic approach for cancer metastasis, *Future Oncol* 5 (9) (2009) 1477–1486. [PubMed: 19903073]
- [123]. Lavieri R, Scott SA, Lewis JA, Selvy PE, Armstrong MD, Alex Brown H, et al. Design and synthesis of isoform-selective phospholipase D (PLD) inhibitors. Part II. Identification of the 1,3,8-triazaspiro[4,5] decan-4-one privileged structure that engenders PLD2 selectivity, *Bioorg. Med. Chem. Lett* 19 (8) (2009) 2240–2243. [PubMed: 19299128]
- [124]. Scott SA, Selvy PE, Buck JR, Cho HP, Criswell TL, Thomas AL, et al. Design of isoform-selective phospholipase D inhibitors that modulate cancer cell invasiveness, *Nat. Chem. Biol* 5 (2) (2009) 108–117. [PubMed: 19136975]
- [125]. Fregeau MO, Carrier M, Guillemette G, Mechanism of dopamine D2 receptor-induced Ca(2+) release in PC-12 cells, *Cell. Signal* 25 (12) (2013) 2871–2877. [PubMed: 24055909]
- [126]. Zhong W, Picca AJ, Lee AS, Darmani NA, Ca(2+) signaling and emesis: Recent progress and new perspectives, *Auton. Neurosci* 202 (2017) 18–27. [PubMed: 27473611]
- [127]. McRory JE, Santi CM, Hamming KS, Mezeyova J, Sutton KG, Baillie DL, et al. Molecular and functional characterization of a family of rat brain T-type calcium channels, *J. Biol. Chem* 276 (6) (2001) 3999–4011. [PubMed: 11073957]
- [128]. Peng JB, Brown EM, Hediger MA, Apical entry channels in calcium-transporting epithelia, *News Physiol. Sci* 18 (2003) 158–163. [PubMed: 12869616]
- [129]. Wu J, Dougherty JJ, Nichols RA, Dopamine receptor regulation of Ca2+ levels in individual isolated nerve terminals from rat striatum: comparison of presynaptic D1-like and D2-like receptors, *J. Neurochem* 98 (2) (2006) 481–494. [PubMed: 16805841]
- [130]. Darmani NA, Zhong W, Chebolu S, Vaezi M, Alkam T, Broad-spectrum antiemetic potential of the L-type calcium channel antagonist nifedipine and evidence for its additive antiemetic interaction with the 5-HT(3) receptor antagonist palonosetron in the least shrew (*Cryptotis parva*), *Eur. J. Pharmacol* 722 (2014) 2–12. [PubMed: 24513517]
- [131]. Yamakage M, Namiki A, Calcium channels—basic aspects of their structure, function and gene encoding; anesthetic action on the channels—a review, *Can. J. Anaesth* 49 (2) (2002) 151–164. [PubMed: 11823393]
- [132]. Stea A, Soong TW, Snutch TP, Determinants of PKC-dependent modulation of a family of neuronal calcium channels, *Neuron* 15 (4) (1995) 929–940. [PubMed: 7576641]
- [133]. Bindels RJ, Calcium handling by the mammalian kidney, *J. Exp. Biol* 184 (1993) 89–104. [PubMed: 8270857]
- [134]. Friedman PA, Gesek FA, Stimulation of calcium transport by amiloride in mouse distal convoluted tubule cells, *Kidney Int* 48 (5) (1995) 1427–1434. [PubMed: 8544399]
- [135]. Suzuki Y, Yoshimaru T, Inoue T, Ra C, Ca v 1.2 L-type Ca2+ channel protects mast cells against activation- induced cell death by preventing mitochondrial integrity disruption, *Mol. Immunol* 46 (11–12) (2009) 2370–2380. [PubMed: 19447492]
- [136]. Yoshimaru T, Suzuki Y, Inoue T, Ra C, L-type Ca2+ channels in mast cells: activation by membrane depolarization and distinct roles in regulating mediator release from store-operated Ca2+ channels, *Mol. Immunol* 46 (7) (2009) 1267–1277. [PubMed: 19128833]

- [137]. Zhong W, Chebolu S, Darmani NA, Broad-spectrum antiemetic efficacy of the L-type calcium channel blocker amlodipine in the least shrew (*Cryptotis parva*), *Pharmacol. Biochem. Behav* 120 (2014) 124–132. [PubMed: 24631485]
- [138]. Gallego-Sandin S, Rodriguez-Garcia A, Alonso MT, Garcia-Sancho J, The endoplasmic reticulum of dorsal root ganglion neurons contains functional TRPV1 channels, *J. Biol. Chem* 284 (47) (2009) 32591–32601. [PubMed: 19778904]
- [139]. Zhao R, Tsang SY, Versatile roles of intracellularly located TRPV1 channel, *J. Cell. Physiol* 232 (8) (2017) 1957–1965. [PubMed: 27891582]
- [140]. Mezey E, Toth ZE, Cortright DN, Arzubi MK, Krause JE, Elde R, et al. Distribution of mRNA for vanilloid receptor subtype 1 (VR1), and VR1-like immunoreactivity, in the central nervous system of the rat and human, *Proc. Natl. Acad. Sci. U. S. A* 97 (7) (2000) 3655–3660. [PubMed: 10725386]
- [141]. Szabo T, Biro T, Gonzalez AF, Palkovits M, Blumberg PM, Pharmacological characterization of vanilloid receptor located in the brain, *Brain Res. Mol. Brain Res* 98 (1–2) (2002) 51–57. [PubMed: 11834295]
- [142]. Szallasi A, Blumberg PM, Vanilloid (Capsaicin) receptors and mechanisms, *Pharmacol. Rev* 51 (2) (1999) 159–212. [PubMed: 10353985]
- [143]. Darmani NA, Chebolu S, Zhong W, Trinh C, McClanahan B, Brar RS, Additive antiemetic efficacy of low-doses of the cannabinoid CB(1/2) receptor agonist Delta (9)-THC with ultralow-doses of the vanilloid TRPV1 receptor agonist resiniferatoxin in the least shrew (*Cryptotis parva*), *Eur. J. Pharmacol* 722 (2014) 147–155. [PubMed: 24157976]
- [144]. Darmani NA, Henry DA, Zhong W, Chebolu S, Ultra-low doses of the transient receptor potential vanilloid 1 agonist, resiniferatoxin, prevents vomiting evoked by diverse emetogens in the least shrew (*Cryptotis parva*), *Behav. Pharmacol* (2019).
- [145]. Bevan S, Hothi S, Hughes G, James IF, Rang HP, Shah K, et al. Capsazepine: a competitive antagonist of the sensory neurone excitant capsaicin, *Br. J. Pharmacol* 107 (2) (1992) 544–552. [PubMed: 1422598]
- [146]. Chakraborty S, Rebecchi M, Kaczocha M, Puopolo M, Dopamine modulation of transient receptor potential vanilloid type 1 (TRPV1) receptor in dorsal root ganglia neurons, *J. Physiol* 594 (6) (2016) 1627–1642. [PubMed: 26563747]
- [147]. Naitou K, Nakamori H, Horii K, Kato K, Horii Y, Shimaoka H, et al. Descending monoaminergic pathways projecting to the spinal defecation center enhance colorectal motility in rats, *Am. J. Physiol. Gastrointest. Liver Physiol* 315 (4) (2018) G631–G637. [PubMed: 30070581]
- [148]. Vellani V, Mapplebeck S, Moriondo A, Davis JB, McNaughton PA, Protein kinase C activation potentiates gating of the vanilloid receptor VR1 by capsaicin, protons, heat and anandamide, *J. Physiol* 534 (Pt 3) (2001) 813–825. [PubMed: 11483711]
- [149]. Bhawe G, Zhu W, Wang H, Brasier DJ, Oxford GS, Gereau RWT, cAMP-dependent protein kinase regulates desensitization of the capsaicin receptor (VR1) by direct phosphorylation, *Neuron* 35 (4) (2002) 721–731. [PubMed: 12194871]
- [150]. Nam JH, Park ES, Won SY, Lee YA, Kim KI, Jeong JY, et al. TRPV1 on astrocytes rescues nigral dopamine neurons in Parkinson's disease via CNTF, *Brain* 138 (Pt 12) (2015) 3610–3622. [PubMed: 26490328]
- [151]. Patel JC, Witkovsky P, Avshalumov MV, Rice ME, Mobilization of calcium from intracellular stores facilitates somatodendritic dopamine release, *J. Neurosci* 29 (20) (2009) 6568–6579. [PubMed: 19458227]
- [152]. Pozzan T, Rizzuto R, Volpe P, Meldolesi J, Molecular and cellular physiology of intracellular calcium stores, *Physiol. Rev* 74 (3) (1994) 595–636. [PubMed: 8036248]
- [153]. Foskett JK, White C, Cheung KH, Mak DO, Inositol trisphosphate receptor Ca²⁺ release channels, *Physiol. Rev* 87 (2) (2007) 593–658. [PubMed: 17429043]
- [154]. Verkhratsky A, Shmigol A, Calcium-induced calcium release in neurones, *Cell Calcium* 19 (1) (1996) 1–14. [PubMed: 8653752]
- [155]. Fill M, Copello JA, Ryanodine receptor calcium release channels, *Physiol. Rev* 82 (4) (2002) 893–922. [PubMed: 12270947]

- [156]. Darmani NA, Wang Y, Abad J, Ray AP, Thrush GR, Ramirez J, Utilization of the least shrew as a rapid and selective screening model for the antiemetic potential and brain penetration of substance P and NK1 receptor antagonists, *Brain Res* 1214 (2008) 58–72. [PubMed: 18471804]
- [157]. Parker LA, Rock EM, Limebeer CL, Regulation of nausea and vomiting by cannabinoids, *Br. J. Pharmacol* 163 (7) (2011) 1411–1422. [PubMed: 21175589]
- [158]. Travagli RA, Hermann GE, Browning KN, Rogers RC, Musings on the wanderer: what's new in our understanding of vago-vagal reflexes? III. Activity-dependent plasticity in vago-vagal reflexes controlling the stomach, *Am. J. Physiol. Gastrointest. Liver Physiol* 284 (2) (2003) G180–7. [PubMed: 12529266]
- [159]. Travagli RA, Hermann GE, Browning KN, Rogers RC, Brainstem circuits regulating gastric function, *Annu. Rev. Physiol* 68 (2006) 279–305. [PubMed: 16460274]
- [160]. Hayakawa T, Takanaga A, Tanaka K, Maeda S, Seki M, Distribution and ultrastructure of dopaminergic neurons in the dorsal motor nucleus of the vagus projecting to the stomach of the rat, *Brain Res* 1006 (1) (2004) 66–73. [PubMed: 15047025]
- [161]. Manier M, Feuerstein C, Passagia JG, Mouchet P, Mons N, Geffard M, et al. Evidence for the existence of L-dopa- and dopamine-immunoreactive nerve cell bodies in the caudal part of the dorsal motor nucleus of the vagus nerve, *J. Chem. Neuroanat* 3 (3) (1990) 193–205. [PubMed: 1973044]
- [162]. Granata AR, Woodruff GN, Dopaminergic mechanisms in the nucleus tractus solitarius and effects on blood pressure, *Brain Res. Bull* 8 (5) (1982) 483–488. [PubMed: 7116196]
- [163]. Hyde TM, Knable MB, Murray AM, Distribution of dopamine D1-D4 receptor subtypes in human dorsal vagal complex, *Synapse* 24 (3) (1996) 224–232. [PubMed: 8923662]
- [164]. Bertrand PP, Bertrand RL, Serotonin release and uptake in the gastrointestinal tract, *Auton. Neurosci* 153 (1–2) (2010) 47–57. [PubMed: 19729349]
- [165]. Hakanson R, Owman C, Sjöberg NO, Spörng B, Amine mechanisms in enterochromaffin and enterochromaffin-like cells of gastric mucosa in various mammals, *Histochemie* 21 (3) (1970) 189–220. [PubMed: 4984998]
- [166]. Eisenhofer G, Aneman A, Friberg P, Hooper D, Fandriks L, Lonroth H, Hunyady B, Mezey E, Substantial production of dopamine in the human gastrointestinal tract, *J. Clin. Endocrinol. Metab* 82 (11) (1997) 3864–3871. [PubMed: 9360553]
- [167]. Donowitz M, Cusolito S, Battisti L, Fogel R, Sharp GW, Dopamine stimulation of active Na and Cl absorption in rabbit ileum: interaction with alpha 2-adren-ergic and specific dopamine receptors, *J. Clin. Invest* 69 (4) (1982) 1008–1016. [PubMed: 7076842]
- [168]. Marzio L, Neri M, Pieramico O, Delle Donne M, Peeters TL, Cuccurullo F, Dopamine interrupts gastrointestinal fed motility pattern in humans. Effect on motilin and somatostatin blood levels, *Dig. Dis. Sci* 35 (3) (1990) 327–332. [PubMed: 1968372]
- [169]. Kullmann R, Breull WR, Reinsberg J, Wassermann K, Konopatzki A, Dopamine produces vasodilation in specific regions and layers of the rabbit gastrointestinal tract, *Life Sci* 32 (18) (1983) 2115–2122. [PubMed: 6843285]
- [170]. Glavin GB, Szabo S, Dopamine in gastrointestinal disease, *Dig. Dis. Sci* 35 (9) (1990) 1153–1161. [PubMed: 2202571]
- [171]. Dawirs RR, Teuchert-Noodt G, Demonstration of dopamine-immunoreactive cells in the proximal convoluted tubule of gerbil (*Meriones unguiculatus*) kidney, *J. Histochem. Cytochem* 40 (11) (1992) 1685–1691. [PubMed: 1431057]
- [172]. Dawirs RR, Teuchert-Noodt G, Kampen WU, Demonstration of dopamine-immunoreactive cells in the gastrointestinal tract of gerbils (*Meriones unguiculatus*), *J. Histochem. Cytochem* 40 (8) (1992) 1197–1201. [PubMed: 1619282]
- [173]. Mezey E, Eisenhofer G, Hansson S, Harta G, Hoffman BJ, Gallatz K, Palkovits M, Hunyady B, Non-neuronal dopamine in the gastrointestinal system, *Clin. Exp. Pharmacol. Physiol. Suppl* 26 (1999) S14–22. [PubMed: 10386249]
- [174]. Vaughan CJ, Aherne AM, Lane E, Power O, Carey RM, O'Connell DP, Identification and regional distribution of the dopamine D(1A) receptor in the gastrointestinal tract, *Am. J. Physiol. Regul. Integr. Comp. Physiol* 279 (2) (2000) R599–609. [PubMed: 10938251]

- [175]. Anuras S, Effect of dopamine on opossum duodenal smooth muscle, *Gastroenterology* 80 (1) (1981) 51–54. [PubMed: 7450411]
- [176]. Valenzuela JE, Defilippi C, Diaz G, Navia E, Merino Y, Effect of dopamine on human gastric and pancreatic secretion, *Gastroenterology* 76 (2) (1979) 323–326. [PubMed: 759261]
- [177]. Mezey E, Eisenhofer G, Hansson S, Hunyady B, Hoffman BJ, Dopamine produced by the stomach may act as a paracrine/autocrine hormone in the rat, *Neuroendocrinology* 67 (5) (1998) 336–348. [PubMed: 9641616]
- [178]. Li ZS, Schmauss C, Cuenca A, Ratcliffe E, Gershon MD, Physiological modulation of intestinal motility by enteric dopaminergic neurons and the D2 receptor: analysis of dopamine receptor expression, location, development, and function in wild-type and knock-out mice, *J. Neurosci* 26 (10) (2006) 2798–2807. [PubMed: 16525059]
- [179]. Cai QQ, Zheng LF, Fan RF, Lian H, Zhou L, Song HY, et al. Distribution of dopamine receptors D1- and D2 -immunoreactive neurons in the dorsal motor nucleus of vagus in rats, *Auton. Neurosci* 176 (1–2) (2013) 48–53. [PubMed: 23403122]
- [180]. van der Graaf Y, Zielhuis GA, Vooijs GP, Cervical cancer mortality in the Netherlands, *Int. J. Epidemiol* 17 (2) (1988) 270–276. [PubMed: 3403122]
- [181]. Sigala S, Missale G, Missale C, Villanacci V, Cestari R, Grigolato PG, et al. Different neurotransmitter systems are involved in the development of esophageal achalasia, *Life Sci* 56 (16) (1995) 1311–1320. [PubMed: 8614252]
- [182]. Tonini M, Cipollina L, Poluzzi E, Crema F, Corazza GR, De Ponti F, Review article: clinical implications of enteric and central D2 receptor blockade by antidopaminergic gastrointestinal prokinetics, *Aliment. Pharmacol. Ther* 19 (4) (2004) 379–390. [PubMed: 14871277]
- [183]. Lindsley CW, Hopkins CR, Return of D4 dopamine receptor antagonists in drug discovery, *J. Med. Chem* 60 (17) (2017) 7233–7243. [PubMed: 28489950]
- [184]. Erspamer V, Asero B, Identification of enteramine, the specific hormone of the enterochromaffin cell system, as 5- hydroxytryptamine, *Nature* 169 (4306) (1952) 800–801.
- [185]. Cetin Y, Kuhn M, Kulaksiz H, Adermann K, Bargsten G, Grube D, et al. Enterochromaffin cells of the digestive system: cellular source of guanylin, a guanylate cyclase-activating peptide, *Proc. Natl. Acad. Sci. U. S. A* 91 (8) (1994) 2935–2939. [PubMed: 8159683]
- [186]. Manocha M, Khan WI, Serotonin and GI disorders: an update on clinical and experimental studies, *Clin. Transl. Gastroenterol* 3 (2012) e13. [PubMed: 23238212]
- [187]. Furness JB, Costa M, Distribution of intrinsic nerve cell bodies and axons which take up aromatic amines and their precursors in the small intestine of the guinea-pig, *Cell Tissue Res* 188 (3) (1978) 527–543. [PubMed: 25716]
- [188]. Li ZS, Pham TD, Tamir H, Chen JJ, Gershon MD, Enteric dopaminergic neurons: definition, developmental lineage, and effects of extrinsic denervation, *J. Neurosci* 24 (6) (2004) 1330–1339. [PubMed: 14960604]
- [189]. Rao M, Gershon MD, The bowel and beyond: the enteric nervous system in neurological disorders, *Nat. Rev. Gastroenterol. Hepatol* 13 (9) (2016) 517–528. [PubMed: 27435372]
- [190]. Nezami BG, Srinivasan S, Enteric nervous system in the small intestine: pathophysiology and clinical implications, *Curr. Gastroenterol. Rep* 12 (5) (2010) 358–365. [PubMed: 20725870]
- [191]. Gershon MD, 5-HT (serotonin) physiology and related drugs, *Curr. Opin. Gastroenterol* 16 (2) (2000) 113–120. [PubMed: 17024028]
- [192]. Holzer P, Holzer-Petsche U, Tachykinins in the gut. Part I. Expression, release and motor function, *Pharmacol. Ther* 73 (3) (1997) 173–217. [PubMed: 9175155]
- [193]. Eaker EY, Bixler GB, Dunn AJ, Moreshead WV, Mathias JR, Dopamine and norepinephrine in the gastrointestinal tract of mice and the effects of neurotoxins, *J. Pharmacol. Exp. Ther* 244 (2) (1988) 438–442. [PubMed: 3126292]
- [194]. Shichijo K, Sakurai-Yamashita Y, Sekine I, Taniyama K, Neuronal release of endogenous dopamine from corpus of guinea pig stomach, *Am. J. Physiol* 273 (5) (1997) G1044–50. [PubMed: 9374701]
- [195]. Mitsuma T, Rhue H, Hirooka Y, Kayama M, Wago T, Takagi J, et al. Distribution of dopamine transporter in the rat: an immunohistochemical study, *Endocr. Regul* 32 (2) (1998) 71–75. [PubMed: 10330520]

- [196]. Walker JK, Gainetdinov RR, Mangel AW, Caron MG, Shetzline MA, Mice lacking the dopamine transporter display altered regulation of distal colonic motility, *Am. J. Physiol. Gastrointest. Liver Physiol* 279 (2) (2000) G311–8. [PubMed: 10915639]
- [197]. Singaram C, Ashraf W, Gaumnitz EA, Torbey C, Sengupta A, Pfeiffer R, et al. Dopaminergic defect of enteric nervous system in Parkinson's disease patients with chronic constipation, *Lancet* 346 (8979) (1995) 861–864. [PubMed: 7564669]
- [198]. Ray AP, Chebolu S, Darmani NA, Receptor-selective agonists induce emesis and Fos expression in the brain and enteric nervous system of the least shrew (*Cryptotis parva*), *Pharmacol. Biochem. Behav* 94 (1) (2009) 211–218. [PubMed: 19699757]
- [199]. Breit S, Kupferberg A, Rogler G, Hasler G, Vagus nerve as modulator of the brain-gut axis in psychiatric and inflammatory disorders, *Front. Psychiatry* 9 (2018) 44. [PubMed: 29593576]
- [200]. Miller AD, Respiratory muscle control during vomiting, *Can. J. Physiol. Pharmacol* 68 (2) (1990) 237–241. [PubMed: 2178748]
- [201]. Lawrence AJ, Krstew E, Jarrott B, Functional dopamine D2 receptors on rat vagal afferent neurones, *Br. J. Pharmacol* 114 (7) (1995) 1329–1334. [PubMed: 7606337]
- [202]. Ziomber A, Thor P, Krygowska-Wajs A, Zalecki T, Moskala M, Romanska I, et al. Chronic impairment of the vagus nerve function leads to inhibition of dopamine but not serotonin neurons in rat brain structures, *Pharmacol. Rep* 64 (6) (2012) 1359–1367. [PubMed: 23406746]
- [203]. Elwood C, Devauchelle P, Elliott J, Freiche V, German AJ, Gualtieri M, et al. Emesis in dogs: a review, *J. Small Anim. Pract* 51 (1) (2010) 4–22.
- [204]. Fukuda H, Koga T, The Botzinger complex as the pattern generator for retching and vomiting in the dog, *Neurosci. Res* 12 (4) (1991) 471–485. [PubMed: 1665553]
- [205]. Fukuda H, Koga T, Non-respiratory neurons in the Botzinger complex exhibiting appropriate firing patterns to generate the emetic act in dogs, *Neurosci. Res* 14 (3) (1992) 180–194. [PubMed: 1331922]
- [206]. Koga T, Fukuda H, Descending pathway from the central pattern generator of vomiting, *Neuroreport* 8 (11) (1997) 2587–2590. [PubMed: 9261832]
- [207]. Horn CC, Why is the neurobiology of nausea and vomiting so important? *Appetite* 50 (2–3) (2008) 430–434. [PubMed: 17996982]
- [208]. Koga T, Qu R, Fukuda H, The central pattern generator for vomiting may exist in the reticular area dorsomedial to the retrofacial nucleus in dogs, *Exp. Brain Res* 118 (2) (1998) 139–147. [PubMed: 9547082]
- [209]. Onishi T, Mori T, Yanagihara M, Furukawa N, Fukuda H, Similarities of the neuronal circuit for the induction of fictive vomiting between ferrets and dogs, *Auton. Neurosci* 136 (1–2) (2007) 20–30. [PubMed: 17478125]
- [210]. Harris-Warrick RM, Neuromodulation and flexibility in central pattern generator networks, *Curr. Opin. Neurobiol* 21 (5) (2011) 685–692. [PubMed: 21646013]
- [211]. Chu CC, Hsing CH, Shieh JP, Chien CC, Ho CM, Wang JJ, The cellular mechanisms of the antiemetic action of dexamethasone and related glucocorticoids against vomiting, *Eur. J. Pharmacol* 722 (2014) 48–54. [PubMed: 24184695]
- [212]. Brooks DJ, Dopamine agonists: their role in the treatment of Parkinson's disease, *J. Neurol Neurosurg. Psychiatry* 68 (6) (2000) 685–689. [PubMed: 10811688]
- [213]. Wang SC, Borison HL, A new concept of organization of the central emetic mechanism: recent studies on the sites of action of apomorphine, copper sulfate and cardiac glycosides, *Gastroenterology* 22 (1) (1952) 1–12. [PubMed: 12980223]
- [214]. Harding RK, Hugenholtz H, Kucharczyk J, Lemoine J, Central mechanisms for apomorphine-induced emesis in the dog, *Eur. J. Pharmacol* 144 (1) (1987) 61–65. [PubMed: 3436361]
- [215]. Lotti VJ, Clark C, Carbidopa attenuation of L-DOPA emesis in dogs: evidence for a cerebral site of action outside the blood-brain barrier, *Eur. J. Pharmacol* 25 (3) (1974) 322–325. [PubMed: 4827858]
- [216]. Depoortere R, Barret-Grevoz C, Bardin L, Newman-Tancredi A, Apomorphine-induced emesis in dogs: differential sensitivity to established and novel dopamine D2/5- HT(1A) antipsychotic compounds, *Eur. J. Pharmacol* 597 (1–3) (2008) 34–38. [PubMed: 18773888]

- [217]. Bhandari P, Bingham S, Andrews PL, The neuropharmacology of loperamide-induced emesis in the ferret: the role of the area postrema, vagus, opiate and 5-HT₃ receptors, *Neuropharmacology* 31 (8) (1992) 735–742. [PubMed: 1326727]
- [218]. Morest DK, A study of the structure of the area postrema with Golgi methods, *Am. J. Anat* 107 (1960) 291–303. [PubMed: 13772533]
- [219]. Reynolds DJM, Andrews PLR, Davis CJ, Oxford Clinical Communications., Serotonin and the Scientific Basis of Anti-emetic Therapy, Oxford Clinical Communications, Oxford; Philadelphia, 1995.
- [220]. Darmani NA, Zhao W, Ahmad B, The role of D₂ and D₃ dopamine receptors in the mediation of emesis in *Cryptotis parva* (the least shrew), *J. Neural Transm. Vienna* 106 (11–12) (1999) 1045–1061. [PubMed: 10651102]
- [221]. Darmani NA, Ahmad B, Long-term sequential determination of behavioral ontogeny of 5-HT_{1A} and 5-HT₂ receptor functions in the rat, *J. Pharmacol. Exp. Ther* 288 (1) (1999) 247–253. [PubMed: 9862777]
- [222]. Gerlach M, Double K, Arzberger T, Leblhuber F, Tatschner T, Riederer P, Dopamine receptor agonists in current clinical use: comparative dopamine receptor binding profiles defined in the human striatum, *J. Neural Transm. Vienna* 110 (10) (2003) 1119–1127. [PubMed: 14523624]
- [223]. Sokoloff P, Diaz J, Le Foll B, Guillin O, Leriche L, Bezard E, et al. The dopamine D₃ receptor: a therapeutic target for the treatment of neuropsychiatric disorders, *CNS Neurol. Disord. Drug Targets* 5 (1) (2006) 25–43. [PubMed: 16613552]
- [224]. Rondou P, Haegeman G, Van Craenenbroeck K, The dopamine D₄ receptor: biochemical and signalling properties, *Cell. Mol. Life Sci* 67 (12) (2010) 1971–1986. [PubMed: 20165900]
- [225]. Mierau J, Schneider FJ, Ensinger HA, Chio CL, Lajiness ME, Huff RM, Pramipexole binding and activation of cloned and expressed dopamine D₂, D₃ and D₄ receptors, *Eur. J. Pharmacol* 290 (1) (1995) 29–36. [PubMed: 7664822]
- [226]. Piercey MF, Hoffmann WE, Smith MW, Hyslop DK, Inhibition of dopamine neuron firing by pramipexole, a dopamine D₃ receptor-preferring agonist: comparison to other dopamine receptor agonists, *Eur. J. Pharmacol* 312 (1) (1996) 35–44. [PubMed: 8891576]
- [227]. Millan MJ, Maïofiss L, Cussac D, Audinot V, Boutin JA, Newman-Tancredi A, Differential actions of antiparkinson agents at multiple classes of monoaminergic receptor. I. A multivariate analysis of the binding profiles of 14 drugs at 21 native and cloned human receptor subtypes, *J. Pharmacol. Exp. Ther* 303 (2) (2002) 791–804. [PubMed: 12388666]
- [228]. Eden RJ, Costall B, Domeney AM, Gerrard PA, Harvey CA, Kelly ME, et al. Preclinical pharmacology of ropinirole (SK&F 101468-A) a novel dopamine D₂ agonist, *Pharmacol. Biochem. Behav* 38 (1) (1991) 147–154. [PubMed: 1673248]
- [229]. Perachon S, Schwartz JC, Sokoloff P, Functional potencies of new antiparkinsonian drugs at recombinant human dopamine D₁, D₂ and D₃ receptors, *Eur. J. Pharmacol* 366 (2–3) (1999) 293–300. [PubMed: 10082211]
- [230]. Lam YW, Clinical pharmacology of dopamine agonists, *Pharmacotherapy* 20 (1 Pt 2) (2000) 17S–25S. [PubMed: 10641988]
- [231]. Yoshida N, Yoshikawa T, Hosoki K, A dopamine D₃ receptor agonist, 7-OH-DPAT, causes vomiting in the dog, *Life Sci* 57 (21) (1995) L347–50.
- [232]. Earley CJ, Connor J, Garcia-Borreguero D, Jenner P, Winkelman J, Zee PC, et al. Altered brain iron homeostasis and dopaminergic function in Restless Legs Syndrome (Willis-Ekbom Disease), *Sleep Med* 15 (11) (2014) 1288–1301. [PubMed: 25201131]
- [233]. Kesby JP, Eyles DW, McGrath JJ, Scott JG, Dopamine, psychosis and schizophrenia: the widening gap between basic and clinical neuroscience, *Transl. Psychiatry* 8 (1) (2018) 30. [PubMed: 29382821]
- [234]. Ehringer H, Hornykiewicz O, [Distribution of noradrenaline and dopamine (3-hydroxytyramine) in the human brain and their behavior in diseases of the extrapyramidal system], *Klin. Wochenschr* 38 (1960) 1236–1239. [PubMed: 13726012]
- [235]. Jankovic J, Aguilar LG, Current approaches to the treatment of Parkinson's disease, *Neuropsychiatr. Dis. Treat* 4 (4) (2008) 743–757. [PubMed: 19043519]

- [236]. Uitti RJ, Ahlskog JE, Comparative review of dopamine receptor agonists in Parkinson's disease, *CNS Drugs* 5 (5) (1996) 369–388. [PubMed: 26071049]
- [237]. Oertel WH, Quinn NP, Parkinson's disease: drug therapy, *Baillieres Clin. Neurol* 6 (1) (1997) 89–108. [PubMed: 9426870]
- [238]. Montastruc JL, Rascol O, Senard JM, Rascol A, A randomised controlled study comparing bromocriptine to which levodopa was later added, with levodopa alone in previously untreated patients with Parkinson's disease: a five year follow up, *J. Neurol Neurosurg. Psychiatry* 57 (9) (1994) 1034–1038. [PubMed: 8089666]
- [239]. Yarnall AJ, Lashley T, Ling H, Lees AJ, Coleman SY, O'Sullivan SS, et al. Apomorphine: a potential modifier of amyloid deposition in Parkinson's disease? *Mov. Disord* 31 (5) (2016) 668–675. [PubMed: 27156393]
- [240]. Ribaric S, The pharmacological properties and therapeutic use of apomorphine, *Molecules* 17 (5) (2012) 5289–5309. [PubMed: 22565480]
- [241]. Jarema M, The risk of neuroleptic discontinuation in schizophrenia, *Psychiatr. Pol* 33 (1) (1999) 69–81. [PubMed: 10786216]
- [242]. Zhou CQ, Zhang JW, Wang M, Peng GG, Meta-analysis of the efficacy and safety of long-acting non-ergot dopamine agonists in Parkinson's disease, *J. Clin. Neurosci* 21 (7) (2014) 1094–1101. [PubMed: 24786715]
- [243]. Kurin M, Bielefeldt K, Levinthal DJ, Prevalence of nausea and vomiting in adults using ropinirole: a systematic review and meta-analysis, *Dig. Dis. Sci* 63 (3) (2018) 687–693. [PubMed: 29383607]
- [244]. Ondo WG, Hunter C, Ferrara JM, Mostile G, Apomorphine injections: predictors of initial common adverse events and long term tolerability, *Parkinsonism Relat. Disord* 18 (5) (2012) 619–622. [PubMed: 22284728]
- [245]. Dewey RB Jr, Hutton JT, LeWitt PA, Factor SA, A randomized, double-blind, placebo-controlled trial of subcutaneously injected apomorphine for parkinsonian off-state events, *Arch. Neurol* 58 (9) (2001) 1385–1392. [PubMed: 11559309]
- [246]. Pahwa R, Koller WC, Trosch RM, Sherry JH, Investigators APOS, Subcutaneous apomorphine in patients with advanced Parkinson's disease: a dose-escalation study with randomized, double-blind, placebo-controlled crossover evaluation of a single dose, *J. Neurol. Sci* 258 (1–2) (2007) 137–143. [PubMed: 17466338]
- [247]. Pfeiffer RF, Gutmann L, Hull KL Jr, Bottini PB, Sherry JH, A.P.O. S. Investigators, Continued efficacy and safety of subcutaneous apomorphine in patients with advanced Parkinson's disease, *Parkinsonism Relat. Disord* 13 (2) (2007) 93–100. [PubMed: 17055329]
- [248]. Pietz K, Hagell P, Odin P, Subcutaneous apomorphine in late stage Parkinson's disease: a long term follow up, *J. Neurol. Neurosurg. Psychiatry* 65 (5) (1998) 709–716. [PubMed: 9810943]
- [249]. Michel MC, Charlton SJ, Biased agonism in drug discovery-is it too soon to choose a path? *Mol. Pharmacol* 93 (4) (2018) 259–265. [PubMed: 29326242]
- [250]. Tan L, Yan W, McCorvy JD, Cheng J, Biased ligands of g protein-coupled receptors (GPCRs): structure-functional selectivity relationships (SFSRs) and therapeutic potential, *J. Med. Chem* 61 (22) (2018) 9841–9878. [PubMed: 29939744]
- [251]. Allen JA, Yost JM, Setola V, Chen X, Sassano MF, Chen M, et al. Discovery of beta-arrestin-biased dopamine D2 ligands for probing signal transduction pathways essential for antipsychotic efficacy, *Proc. Natl. Acad. Sci. U. S. A* 108 (45) (2011) 18488–18493. [PubMed: 22025698]
- [252]. Urban JD, Clarke WP, von Zastrow M, Nichols DE, Kobilka B, Weinstein H, et al. Functional selectivity and classical concepts of quantitative pharmacology, *J. Pharmacol. Exp. Ther* 320 (1) (2007) 1–13. [PubMed: 16803859]
- [253]. Urs NM, Gee SM, Pack TF, McCorvy JD, Evron T, Snyder JC, et al. Distinct cortical and striatal actions of a beta-arrestin-biased dopamine D2 receptor ligand reveal unique antipsychotic-like properties, *Proc. Natl. Acad. Sci. U. S. A* 113 (50) (2016) E8178–E8186. [PubMed: 27911814]
- [254]. Mitchelson F, Pharmacological agents affecting emesis. A review (Part I), *Drugs* 43 (3) (1992) 295–315. [PubMed: 1374316]

- [255]. Seigel LJ, Longo DL, The control of chemotherapy-induced emesis, *Ann. Intern. Med* 95 (3) (1981) 352–359. [PubMed: 7023313]
- [256]. Schultz W, Multiple dopamine functions at different time courses, *Annu. Rev. Neurosci* 30 (2007) 259–288. [PubMed: 17600522]
- [257]. Schenker E, Herbst H, Phenothiazines and Azaphenothiazines as drugs, *Fortschr. Arzneimittelforsch* 5 (1963) 269–627. [PubMed: 14287130]
- [258]. Girault JA, Greengard P, The neurobiology of dopamine signaling, *Arch. Neurol* 61 (5) (2004) 641–644. [PubMed: 15148138]
- [259]. Loeser EA, Bennett G, Stanley TH, Machin R, Comparison of droperidol, haloperidol and prochlorperazine as postoperative anti-emetics, *Can. Anaesth. Soc. J* 26 (2) (1979) 125–127. [PubMed: 466547]
- [260]. Madej TH, Simpson KH, Comparison of the use of domperidone, droperidol and metoclopramide in the prevention of nausea and vomiting following gynaecological surgery in day cases, *Br. J. Anaesth* 58 (8) (1986) 879–883. [PubMed: 3524643]
- [261]. Xiao M, Qiu X, Yue D, Cai Y, Mo Q, Influence of hippocampal rhamnoides on two appetite factors, gastric emptying and metabolic parameters, in children with functional dyspepsia, *Hell. J. Nucl. Med* 16 (1) (2013) 38–43.
- [262]. Huang X, Lv B, Zhang S, Fan YH, Meng LN, Itopride therapy for functional dyspepsia: a meta-analysis, *World J. Gastroenterol* 18 (48) (2012) 7371–7377. [PubMed: 23326147]
- [263]. Reddymasu SC, Soykan I, McCallum RW, Domperidone: review of pharmacology and clinical applications in gastroenterology, *Am. J. Gastroenterol* 102 (9) (2007) 2036–2045. [PubMed: 17488253]
- [264]. Harrington RA, Hamilton CW, Brogden RN, Linkewich JA, Romankiewicz JA, Heel RC, Metoclopramide. An updated review of its pharmacological properties and clinical use, *Drugs* 25 (5) (1983) 451–494. [PubMed: 6345129]
- [265]. Pinnock RD, Woodruff GN, Turnbull MJ, Sulpiride blocks the action of dopamine in the rat substantia nigra, *Eur. J. Pharmacol* 56 (4) (1979) 413–414. [PubMed: 477736]
- [266]. Alander T, Anden NE, Grabowska-Anden M, Metoclopramide and sulpiride as selective blocking agents of pre- and postsynaptic dopamine receptors, *Naunyn Schmiedeberg's Arch. Pharmacol* 312 (2) (1980) 145–150. [PubMed: 7402361]
- [267]. Hadley MS, King FD, McRitchie B, Turner DH, Watts EA, Substituted benzamides with conformationally restricted side chains. 1. Quinolizidine derivatives as selective gastric prokinetic agents, *J. Med. Chem* 28 (12) (1985) 1843–1847. [PubMed: 4068007]
- [268]. Rowbotham DJ, Current management of postoperative nausea and vomiting, *Br. J. Anaesth* 69 (7 Suppl 1) (1992) 46S–59S. [PubMed: 1486014]
- [269]. Taubel J, Ferber G, Fox G, Fernandes S, Lorch U, Camm AJ, Thorough QT study of the effect of intravenous amisulpride on QTc interval in Caucasian and Japanese healthy subjects, *Br. J. Clin. Pharmacol* 83 (2) (2017) 339–348. [PubMed: 27618796]
- [270]. Abbas AI, Hedlund PB, Huang XP, Tran TB, Meltzer HY, Roth BL, Amisulpride is a potent 5-HT7 antagonist: relevance for antidepressant actions in vivo, *Psychopharmacology (Berl)* 205 (1) (2009) 119–128. [PubMed: 19337725]
- [271]. Kranke P, Eberhart L, Motsch J, Chassard D, Wallenborn J, Diemunsch P, et al. I.V. APD421 (amisulpride) prevents postoperative nausea and vomiting: a randomized, double-blind, placebo-controlled, multicentre trial, *Br. J. Anaesth* 111 (6) (2013) 938–945. [PubMed: 23872464]
- [272]. Zhong W, Darmani NA, The pivotal role of glycogen synthase kinase 3 (GSK-3) in vomiting evoked by specific emetogens in the least shrew (*Cryptotis parva*), *Neurochem. Int* 132 (2020), 104603. [PubMed: 31738972]
- [273]. Boyle A, Ondo W, Role of apomorphine in the treatment of Parkinson's disease, *CNS Drugs* 29 (2) (2015) 83–89. [PubMed: 25676564]
- [274]. Bodde HE, Van Laar T, Van der Geest R, Danhof M, An integrated pharmacokinetic-pharmacodynamic approach to optimization of R-apomorphine delivery in Parkinson's disease, *Adv. Drug Deliv. Rev* 33 (3) (1998) 253–263. [PubMed: 10837665]
- [275]. Mottola DM, Kilts JD, Lewis MM, Connery HS, Walker QD, Jones SR, et al. Functional selectivity of dopamine receptor agonists. I. Selective activation of postsynaptic dopamine D2

receptors linked to adenylate cyclase, *J. Pharmacol. Exp. Ther* 301 (3) (2002) 1166–1178. [PubMed: 12023552]

- [276]. Navarro JF, Maldonado E, Behavioral profile of quinpirole in agonistic encounters between male mice, *Methods Find. Exp. Clin. Pharmacol* 21 (7) (1999) 477–480. [PubMed: 10544391]
- [277]. Culm KE, Lugo-Escobar N, Hope BT, Hammer RP Jr., Repeated quinpirole treatment increases cAMP-dependent protein kinase activity and CREB phosphorylation in nucleus accumbens and reverses quinpirole-induced sensorimotor gating deficits in rats, *Neuropsychopharmacology* 29 (10) (2004) 1823–1830. [PubMed: 15138441]
- [278]. Kvernmo T, Hartter S, Burger E, A review of the receptor-binding and pharmacokinetic properties of dopamine agonists, *Clin. Ther* 28 (8) (2006) 1065–1078. [PubMed: 16982285]
- [279]. Piercey MF, Pharmacology of pramipexole, a dopamine D3- preferring agonist useful in treating Parkinson's disease, *Clin. Neuropharmacol* 21 (3) (1998) 141–151. [PubMed: 9617505]
- [280]. Winlow W, Pramipexole in restless legs syndrome: an evidence-based review of its effectiveness on clinical outcomes, *Core Evid* 1 (1) (2005) 35–42. [PubMed: 22496675]
- [281]. Quilici S, Abrams KR, Nicolas A, Martin M, Petit C, Lléu PL, et al. Meta-analysis of the efficacy and tolerability of pramipexole versus ropinirole in the treatment of restless legs syndrome, *Sleep Med* 9 (7) (2008) 715–726. [PubMed: 18226947]
- [282]. Wood M, Dubois V, Scheller D, Gillard M, Rotigotine is a potent agonist at dopamine D1 receptors as well as at dopamine D2 and D3 receptors, *Br. J. Pharmacol* 172 (4) (2015) 1124–1135. [PubMed: 25339241]
- [283]. Scheller D, Ullmer C, Berkels R, Gwarek M, Lubbert H, The in vitro receptor profile of rotigotine: a new agent for the treatment of Parkinson's disease, *Naunyn Schmiedebergs Arch. Pharmacol* 379 (1) (2009) 73–86. [PubMed: 18704368]
- [284]. Davies S, Rotigotine for restless legs syndrome, *Drugs Today (Barc)* 45 (9) (2009) 663–668. [PubMed: 19956807]
- [285]. Chen JJ, Swope DM, Dashtipour K, Lyons KE, Transdermal rotigotine: a clinically innovative dopamine-receptor agonist for the management of Parkinson's disease, *Pharmacotherapy* 29 (12) (2009) 1452–1467. [PubMed: 19947805]
- [286]. Reynolds NA, Wellington K, Easthope SE, Rotigotine: in Parkinson's disease, *CNS Drugs* 19 (11) (2005) 973–981. [PubMed: 16268667]
- [287]. Moinuddin M, Rockett JF, Splenic cysts demonstrated on radionuclide angiogram, *Clin. Nucl. Med* 3 (11) (1978) 449. [PubMed: 729332]
- [288]. Jouhari S, Mohammadzadeh A, Soltanghorae H, Mohammadi Z, Khazali S, Mirzadegan E, Lakpour N, et al. Effects of silymarin, cabergoline and letrozole on rat model of endometriosis, Taiwan. *J. Obstet. Gynecol* 57 (6) (2018) 830–835. [PubMed: 30545536]
- [289]. Rains CP, Bryson HM, Fitton A, Cabergoline. A review of its pharmacological properties and therapeutic potential in the treatment of hyperprolactinaemia and inhibition of lactation, *Drugs* 49 (2) (1995) 255–279. [PubMed: 7729332]
- [290]. Fuller RW, Clemens JA, Pergolide: a dopamine agonist at both D1 and D2 receptors, *Life Sci* 49 (13) (1991) 925–930. [PubMed: 1832202]
- [291]. Lang AE, Quinn N, Brincat S, Marsden CD, Parkes JD, Pergolide in late-stage Parkinson disease, *Ann. Neurol* 12 (3) (1982) 243–247. [PubMed: 6753730]
- [292]. Brown R, Taylor MJ, Geddes J, Aripiprazole alone or in combination for acute mania, *Cochrane Database Syst. Rev* (12) (2013), CD005000. [PubMed: 24346956]
- [293]. Beaulieu JM, Gainetdinov RR, The physiology, signaling, and pharmacology of dopamine receptors, *Pharmacol. Rev* 63 (1) (2011) 182–217. [PubMed: 21303898]
- [294]. Yang CS, Huang H, Zhang LL, Zhu CR, Guo Q, Aripiprazole for the treatment of tic disorders in children: a systematic review and meta-analysis, *BMC Psychiatry* 15 (2015) 179. [PubMed: 26220447]
- [295]. Wood M, Reavill C, Aripiprazole acts as a selective dopamine D2 receptor partial agonist, *Expert Opin. Investig. Drugs* 16 (6) (2007) 771–775.
- [296]. Cox JH, Seri S, Cavanna AE, Safety and efficacy of aripiprazole for the treatment of pediatric Tourette syndrome and other chronic tic disorders, *Pediatric Health Med. Ther* 7 (2016) 57–64. [PubMed: 29388585]

- [297]. Koch HJ, Severe quetiapine withdrawal syndrome with nausea and vomiting in a 65-year-old patient with psychotic depression, *Therapie* 70 (6) (2015) 537–538. [PubMed: 26242495]
- [298]. Lahti AC, Weiler MA, Corey PK, Lahti RA, Carlsson A, Tamminga CA, Antipsychotic properties of the partial dopamine agonist (-)-3-(3-hydroxyphenyl)-N-n-propylpiperidine (preclamol) in schizophrenia, *Biol. Psychiatry* 43 (1) (1998) 2–11. [PubMed: 9442338]
- [299]. Tadori Y, Miwa T, Tottori K, Burris KD, Stark A, Mori T, et al. Aripiprazole's low intrinsic activities at human dopamine D2L and D2S receptors render it a unique antipsychotic, *Eur. J. Pharmacol* 515 (1–3) (2005) 10–19. [PubMed: 15894311]
- [300]. Hashimoto K, Sugawara N, Ishioka M, Nakamura K, Yasui-Furukori N, The effects of additional treatment with terguride, a partial dopamine agonist, on hyperprolactinemia induced by antipsychotics in schizophrenia patients: a preliminary study, *Neuropsychiatr. Dis. Treat* 10 (2014) 1571–1576. [PubMed: 25187719]
- [301]. Kalda A, Herm L, Rinken A, Zharkovsky A, Chen JF, Co-administration of the partial dopamine D2 agonist terguride with L-dopa attenuates L-dopa-induced locomotor sensitization in hemiparkinsonian mice, *Behav. Brain Res* 202 (2) (2009) 232–237. [PubMed: 19463706]
- [302]. Distler O, Eich W, Dokoupilova E, Dvorak Z, Fleck M, Gaubitz M, et al. Evaluation of the efficacy and safety of terguride in patients with fibromyalgia syndrome: results of a twelve-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study, *Arthritis Rheum* 62 (1) (2010) 291–300. [PubMed: 20039417]
- [303]. Filipova M, Filip V, Macek Z, Mullerova S, Markova J, Kas S, et al. Terguride in parkinsonism. A multicenter trial, *Eur. Arch. Psychiatry Neurol. Sci* 237 (5) (1988) 298–303. [PubMed: 3049101]
- [304]. Lin CH, Haadsma-Svensson SR, Phillips G, Lahti RA, McCall RB, Piercey MF, et al. Centrally acting serotonergic and dopaminergic agents. 2. Synthesis and structure-activity relationships of 2,3,3a,4,9,9a-hexahydro-1H-benz [f]indole derivatives, *J. Med. Chem* 36 (8) (1993) 1069–1083. [PubMed: 8097538]
- [305]. Adams CE, Awad GA, Rathbone J, Thornley B, Soares-Weiser K, Chlorpromazine versus placebo for schizophrenia, *Cochrane Database Syst. Rev* (1) (2014), CD000284. [PubMed: 24395698]
- [306]. Dudley K, Liu X, De Haan S, Chlorpromazine dose for people with schizophrenia, *Cochrane Database Syst. Rev* 4 (2017), CD007778. [PubMed: 28407198]
- [307]. Stephen CR, Dent S, Bourgeois-Gavardin M, Control of nausea and vomiting with chlorpromazine; incidence of side-effects, *AMA Arch. Intern. Med* 96 (6) (1955) 794–798. [PubMed: 13268104]
- [308]. Estrada E, Clinical uses of chlorpromazine in veterinary medicine, *J. Am. Vet. Med. Assoc* 128 (6) (1956) 292–294. [PubMed: 13295139]
- [309]. Tardy M, Huhn M, Engel RR, Leucht S, Fluphenazine versus low-potency first-generation antipsychotic drugs for schizophrenia, *Cochrane Database Syst. Rev* (8) (2014), CD009230.
- [310]. Laffan RJ, Papandrianos DP, Burke JC, Cr Aver BN, Antiemetic action of fluphenazine (Prolixin): a comparison with other phenothiazines, *J. Pharmacol. Exp. Ther* 131 (1961) 130–134. [PubMed: 13758172]
- [311]. Mallet E, Bounoure F, Skiba M, Saussereau E, Goulle JP, Castanet M, Pharmacokinetic study of metopimazine by oral route in children, *Pharmacol. Res. Perspect* 3 (3) (2015), e00130. [PubMed: 26171218]
- [312]. Schnabel A, Eberhart LH, Muellenbach R, Morin AM, Roewer N, Kranke P, Efficacy of perphenazine to prevent postoperative nausea and vomiting: a quantitative systematic review, *Eur. J. Anaesthesiol* 27 (12) (2010) 1044–1051. [PubMed: 20739894]
- [313]. Din L, Preuss CV, Prochlorperazine, StatPearls, Treasure Island (FL), 2020.
- [314]. Chokhawala K, Stevens L, Antipsychotic Medications, StatPearls, Treasure Island (FL), 2020.
- [315]. Smith HS, Cox LR, Smith BR, Dopamine receptor antagonists, *Ann. Palliat. Med* 1 (2) (2012) 137–142. [PubMed: 25841474]
- [316]. Deitrick CL, Mick DJ, Lauffer V, Prostka E, Nowak D, Ingersoll G, A comparison of two differing doses of promethazine for the treatment of postoperative nausea and vomiting, *J. Perianesth. Nurs* 30 (1) (2015) 5–13. [PubMed: 25616881]

- [317]. Talebpour M, Ghiasnejad Omrani N, Imani F, Shariat Moharari R, Pourfakhr P, et al. Comparison effect of promethazine/dexamethasone and metoclopramide/dexamethasone on postoperative nausea and vomiting after laparoscopic gastric placcation: a randomized clinical trial, *Anesth. Pain Med* 7 (4) (2017), e57810. [PubMed: 29226110]
- [318]. Scorza Barcellona P, Campana A, Caranti S, D'Onofrio E, Silvestrini B, Pretreatment with bendazac attenuates retinal damage induced by intense light in rats, *Pharmacol. Res* 24 (1) (1991) 105–112. [PubMed: 1946139]
- [319]. Einarson A, Boskovic R, Use and safety of antipsychotic drugs during pregnancy, *J. Psychiatry Pract* 15 (3) (2009) 183–192.
- [320]. Ritchie HE, Huss IB, Webster WS, The effect of anti-emetic drugs on rat embryonic heart activity, *Reprod. Toxicol* 87 (2019) 140–145. [PubMed: 31199962]
- [321]. Purkis IE, Ishii M, The effectiveness of anti-emetic agents: a comparison of the anti-emetic activity of trifluopromazine (vesprin), perphenazine (trilafon), and trifluoperazine (stelazine) with that of dimenhydrinate (gravol) in postanesthetic vomiting, *Can. Anaesth. Soc. J* 10 (1963) 539–549. [PubMed: 14076153]
- [322]. Li P, Snyder GL, Vanover KE, Dopamine targeting drugs for the treatment of schizophrenia: past, present and future, *Curr. Top. Med. Chem* 16 (29) (2016) 3385–3403. [PubMed: 27291902]
- [323]. Leucht S, Hartung B, Benperidol for schizophrenia, *Cochrane Database Syst. Rev* (2) (2005), CD003083. [PubMed: 15846648]
- [324]. Kumar S, Chowdhury S, Kumar S, In silico repurposing of antipsychotic drugs for Alzheimer's disease, *BMC Neurosci* 18 (1) (2017) 76. [PubMed: 29078760]
- [325]. Peroutka SJ, Synder SH, Relationship of neuroleptic drug effects at brain dopamine, serotonin, alpha-adrenergic, and histamine receptors to clinical potency, *Am. J. Psychiatry* 137 (12) (1980) 1518–1522. [PubMed: 6108081]
- [326]. Lai PC, Huang YT, Evidence-based review and appraisal of the use of droperidol in the emergency department, *Ci Ji Yi Xue Za Zhi* 30 (1) (2018) 1–4. [PubMed: 29643708]
- [327]. Ahmad-Sabry MH, Shareghi G, Long-term use of intrathecal droperidol as an excellent antiemetic in nonmalignant pain—a retrospective study, *Middle East J. Anaesthesiol* 21 (6) (2012) 857–862. [PubMed: 23634568]
- [328]. Antipsychotic Agents, LiverTox: Clinical and Research Information on Drug-Induced Liver Injury, Bethesda (MD), 2012.
- [329]. Buttner M, Walder B, von Elm E, Tramer MR, Is low-dose haloperidol a useful antiemetic?: A meta-analysis of published and unpublished randomized trials, *Anesthesiology* 101 (6) (2004) 1454–1463. [PubMed: 15564955]
- [330]. Brand ED, Harris TD, Borison HL, Goodman LS, The anti-emetic activity of 10-(gamma-dimethylaminopropyl)-2-chlorophenothiazine (chlorpromazine) in dog and cat, *J. Pharmacol. Exp. Ther* 110 (1) (1954) 86–92. [PubMed: 13118482]
- [331]. Whiskey E, Vavrova M, Gaughran F, Taylor D, Melperone in treatment-refractory schizophrenia: a case series, *Ther. Adv. Psychopharmacol* 1 (1) (2011) 19–23. [PubMed: 23983923]
- [332]. Rohricht F, Gadhia S, Alam R, Willis M, Auditing clinical outcomes after introducing off-licence prescribing of atypical antipsychotic melperone for patients with treatment refractory schizophrenia, *ScientificWorldJournal* 2012 (2012), 512047. [PubMed: 22566771]
- [333]. Meltzer HY, Sumiyoshi T, Jayathilake K, Melperone in the treatment of neuroleptic-resistant schizophrenia, *Psychiatry Res* 105 (3) (2001) 201–209. [PubMed: 11814539]
- [334]. Poldinger WJ, Melperone in low doses in anxious neurotic patients. A double-blind placebo-controlled clinical study, *Neuropsychobiology* 11 (3) (1984) 181–186. [PubMed: 6147789]
- [335]. Perrault G, Depoortere R, Morel E, Sanger DJ, Scatton B, Psychopharmacological profile of amisulpride: an antipsychotic drug with presynaptic D2/D3 dopamine receptor antagonist activity and limbic selectivity, *J. Pharmacol. Exp. Ther* 280 (1) (1997) 73–82. [PubMed: 8996184]
- [336]. Kranke P, Bergese SD, Minkowitz HS, Melson TI, Leiman DG, Candiotti KA, et al. Amisulpride prevents postoperative nausea and vomiting in patients at high risk: a randomized, double-blind, placebo-controlled trial, *Anesthesiology* 128 (6) (2018) 1099–1106. [PubMed: 29543631]

- [337]. Silva SM, Carneiro FP, Oliveira PG, Morais PH, Silva NG, Sousa JB, Effects of bromopride on the healing of left colonic anastomoses in rats with induced abdominal sepsis, *Acta Cir. Bras* 27 (6) (2012) 370–375. [PubMed: 22666753]
- [338]. French-Mullen JM, Murphy TH, Coyle JT, Fisher RS, Dicarboxylic amino acids block epileptiform activity in hippocampal slice, *Epilepsia* 27 (6) (1986) 678–684. [PubMed: 2877868]
- [339]. Lenz HJ, Schuler U, Hicking W, Ehninger G, Phase I-trial of clebopride, a new antiemetic, in chemotherapy-induced nausea and vomiting, *Eur. J. Clin. Pharmacol* 38 (5) (1990) 525.
- [340]. Matsunaga Y, Tanaka T, Yoshinaga K, Ueki S, Hori Y, Eta R, et al. Acotiamide hydrochloride (Z-338), a new selective acetylcholinesterase inhibitor, enhances gastric motility without prolonging QT interval in dogs: comparison with cisapride, itopride, and mosapride, *J. Pharmacol. Exp. Ther* 336 (3) (2011) 791–800. [PubMed: 21123674]
- [341]. Scarpellini E, Vos R, Blondeau K, Boecxstaens V, Farre R, Gasbarrini A, et al. The effects of itopride on oesophageal motility and lower oesophageal sphincter function in man, *Aliment. Pharmacol. Ther* 33 (1) (2011) 99–105. [PubMed: 21083582]
- [342]. DeVane CL, Wolin RE, Jusko WJ, Pharmacokinetic basis for predicting steady-state serum drug concentrations of imipramine from single dose data, *Commun. Psychopharmacol* 3 (5) (1979) 353–357. [PubMed: 548214]
- [343]. Li J, Yao QY, Xue JS, Wang LJ, Yuan Y, Tian XY, et al. Dopamine D2 receptor antagonist sulpiride enhances dexamethasone responses in the treatment of drug-resistant and metastatic breast cancer, *Acta Pharmacol. Sin* 38 (9) (2017) 1282–1296. [PubMed: 28649130]
- [344]. Kumakura K, Frattola L, Spano PF, Trabucchi M, The system of cyclic nucleotides in the growth regulation of cerebral tumors in the young, *Mod. Probl. Paediatr* 18 (1976) 30–34. [PubMed: 22808]
- [345]. Guslandi M, Antiemetic properties of levo-sulpiride, *Minerva Med* 81 (12) (1990) 855–860. [PubMed: 2280876]
- [346]. Sedvall G, Nyback H, Farde L, Persson A, Neurotransmitter receptor imaging in Alzheimer's disease, *J. Neural Transm. Suppl* 24 (1987) 43–48. [PubMed: 2824693]
- [347]. Nadal R, Pharmacology of the atypical antipsychotic remoxipride, a dopamine D2 receptor antagonist, *CNS Drug Rev* 7 (3) (2001) 265–282. [PubMed: 11607043]
- [348]. Joshi R, Sivaganesanathan A, Tiapride versus metoclopramide: comparison after minor gynaecological surgery, *Eur. J. Anaesthesiol* 10 (2) (1993) 109–112. [PubMed: 8462535]
- [349]. Scatton B, Cohen C, Perrault G, Oblin A, Claustre Y, Schoemaker H, et al. The preclinical pharmacologic profile of tiapride, *Eur. Psychiatry* 16 (Suppl. 1) (2001) 29s–34s. [PubMed: 11520476]

Fig. 1. Schematic representation of the main emesis - mediating components of the brain-gut axis involved in the vomiting reflex.

The dorsal vagal complex nuclei include the area postrema, nucleus of the solitary tract, and the dorsal motor nucleus of the vagus in the brainstem. The area postrema zone has both fenestrated capillaries and active transport systems, allowing blood-borne chemicals or those secreted from the intestinal mucosa to bypass the brain-blood barrier and directly stimulate the dorsal vagal complex to induce vomiting. The intestinal enterochromaffin cells reside alongside the epithelium lining the lumen of the digestive tract and act as custodian cells in the intestinal mucosa. The afferent and efferent nerves connect the gastrointestinal tract to the CNS dorsal vagal complex vomiting nuclei. Vagal afferent nerves = blue arrows; Vagal efferent nerves = red arrows.

Fig. 2. Structurally based summary of primary pathways of biosynthesis and metabolism of dopamine.

Dopamine biosynthesis: L-tyrosine is converted to L-DOPA in the presence of the TH. In a second reaction, the enzyme AADC converts L-DOPA into dopamine. Dopamine is converted into norepinephrine by the enzyme DBH, with O_2 and L-ascorbic acid as cofactors. Norepinephrine is converted into epinephrine by the enzyme PMNT with S-adenosyl-L-methionine as the cofactor. **Dopamine metabolism:** Dopamine is broken down into inactive metabolites by a set of enzymes including MAO and COMT. Several breakdown pathways exist but the major end-product is the HVA, which has unknown biological activity.

Abbreviations: AADC: aromatic L-amino acid decarboxylase; COMT: Catechol-O-methyltransferase; DOPAC: 3,4-Dihydroxyphenylacetic acid; L-DOPA: levodopa or L-3,4-dihydroxyphenylalanine; HVA: homovanillic acid; MAO: monoamine oxidase; PMNT: phenylethanolamine N-methyltransferase, TH: tyrosine hydroxylase.

Fig. 3. Proposed dopamine receptor signaling pathways, some of which may be involved in emesis.

(A) Dopamine D₁- and D₂-receptors mediated cAMP/PKA signaling cascades.

Dopamine D₁-like receptors are coupled with Gα/o proteins. Adenylyl cyclase stimulation by GPCRs causes cAMP production, which in turn activates PKA. PKA phosphorylates DARPP-32. DARPP-32 phosphorylated on Thr³⁴ is a potent inhibitor of PP₁, which results in PP₁ targets being phosphorylated. Dopamine D₂-like receptors coupled with G_o proteins block AC and lower the intracellular concentration of cAMP causing PKA inhibition. Additionally, dopamine D₂-like receptors activate the protein phosphatase calcineurin, which dephosphorylates DARPP-32 at Thr³⁴. Like the dopamine D₁ receptors, these depicted dopamine D₂ receptor signaling pathways are not involved in vomiting. **Abbreviations:** cAMP: cyclic adenosine monophosphate or cyclic AMP; P: phosphorylation of protein; PKA: protein kinase A; GPCRs: G protein-coupled receptors; DARPP-32: dopamine and cyclic AMP-regulated phosphoprotein relative molecular mass 32,000; PP₁: protein

phosphatase 1. Black solid arrows = emesis; Red arrows = increase or decrease of cAMP; Dashed solid arrows = no emesis.

(B) Dopamine D₂ receptor - mediated ERK activation signaling pathway. ERK protein is an integral part of the Ras-MEK-ERK signaling cascade. Dopamine D₂ receptors can activate ERK by two signaling cascades via: i) the Ras/Raf/MEK1/ERK pathway where dopamine through tyrosine kinase receptors activates Ras, which binds and phosphorylate Raf. The Raf kinase phosphorylates and activates MEK, which in turn activates ERK protein; and ii) Dopamine D₂ receptor can recruit Arrestins (Arr-2 and -3) proteins, which terminate G protein signaling, facilitates receptor internalization, and engages non-canonical G protein-independent signaling pathways. Dopamine D₂ receptor - mediated ERK activation may potentially cause emesis. D₁-like receptors regulate a protein complex composed of β -Arr₂/ERK and MEK and induce ERK activation. However, dopamine D₁-like receptors are devoid of emetic activity. **Abbreviations:** Arr: Arrestin; ERK_{1/2}: extracellular signal-regulated kinase 1 and 2; Raf: rapidly accelerated fibrosarcoma; Ras: rapidly accelerated sarcoma. Black solid arrows = emesis; Dashed solid arrows = no emesis.

(C) Dopamine D₂-receptors mediated activation of GSK-3/Akt pathway. From current findings one could envisage that direct phosphorylation of Akt following dopamine D₂ receptor stimulation may promote emesis. Dopamine can exert part of its actions by modulating the activity of Akt/GSK-3 proteins acting through various mechanisms. Two mechanisms have an opposite effect on the activity of these two kinases. On one hand, dopamine D₂ receptor activation leading to phosphorylation of GSK-3 causes its deactivation and reduction of emesis. On the other hand, the opposite may take place where activation of dopamine D₂ receptors deactivate Akt by the PP_{2A}. The inactivation of Akt and formation of an Akt, β -Arr₂, and PP_{2A} signaling complex facilitate both the inactivation of Akt by the phosphatase and the increase in GSK-3 activity, which may promote emesis. **Abbreviations:** GSK-3: glycogen synthase kinase-3; Akt/PKB: thymoma viral proto-oncogene; P: phosphorylation of protein; PP_{2A}: protein phosphatase 2A. Black solid arrows = emesis; Dashed solid arrows = no emesis; Red T lines = inhibition.

(D) PLC signaling pathways. Dopamine receptors can couple to G α_q to activate PLC causing the hydrolysis of PIP₂ into two-second messengers; DAG and IP₃. DAG activates PKC. IP₃ stimulates IP₃ receptor with subsequent release of Ca²⁺ into the cytosol. The released Ca²⁺ regulates CaMKII and protein phosphatase 2B (calcineurin) both of which may contribute to emesis. LTCCs activated by dopamine D₂ receptor agonists such as quinpirole can cause the influx of extracellular Ca²⁺ into the cell. The influx of extracellular Ca²⁺ can also be partly due to evoked intracellular Ca²⁺ release from SER stores via G α_q -mediated PLC pathway. Overall, the increase cytosolic Ca²⁺ may potentially support the incidence of emesis. **Abbreviations:** PLC: phospholipase C; DAG: 1,2-diacylglycerol; IP₃: inositol-1,4,5-trisphosphate; PKC: protein kinase C; IP₃R: IP₃ receptors; CaMKII: Ca²⁺/calmodulin-dependent kinase II; LTCC: L-type Ca²⁺ channels; SER: sarcoplasmic and endoplasmic reticulum. Ca²⁺-induced Ca²⁺ release (CICR) is a biological process whereby Ca²⁺ can activate Ca²⁺ release from intracellular Ca²⁺ stores (e.g., endoplasmic reticulum or sarcoplasmic reticulum). Black solid arrows = emesis; Dashed solid arrows = no emesis; Blue arrows = influx of Ca²⁺.

Table 1

Dopamine receptor agonists.

Chemical names, formula, and structure	Affinity	Pre- and clinical utilization	Nausea and vomiting
Non-ergot agonists			
<p>Apomorphine (PubChem CID: 6005) Trade name: Apokyn <u>Chemical formula and structure:</u> $C_{17}H_{17}NO_2$</p>	<p>- $K_i = 52$ and 26 nM for dopamine D_2 and D_3 receptors, respectively. - $K_i = 484$ nM for dopamine D_1-like receptors [227].</p>	<p>- Used for the treatment of Parkinson's disease [273] [274], and restless leg syndrome. Additional uses are detailed in the text.</p>	<p>- Induces nausea and vomiting.</p>
<p>Quinpirole (PubChem CID: 54562) <u>Trade name:</u> Unavailable <u>Chemical formula and structure:</u> $C_{13}H_{21}N_3$</p>	<p>- $K_i = 4.8$, ~ 24, ~ 30 and 1900 nM at dopamine D_2, D_3, D_4, and D_1 receptors, respectively [275].</p>	<p>- Low doses (e.g. 0.2 mg/kg) cause a decrease in offensive behavior without impacting motility or exploratory behaviors. - Higher doses (e.g. 0.8 mg/kg) produce a significant elevation in defense/submission, avoidance/fleeing, and social investigation behaviors [276]. - Repeated treatment re-verses quinpirole-induced sensorimotor gating deficits in rats [277].</p>	<p>- Induces nausea and vomiting.</p>
Non-ergot agonists			
<p>Pramipexole (PubChem CID: 119570) Trade name: Mirapex <u>Chemical formula and structure:</u> $C_{10}H_{17}N_3S$</p>	<p>- $K_i = 79.5$ μM for dopamine D_2 receptors [222]. - It has a high selectivity for dopamine D_2-like receptors with preferential affinity for dopamine D_3 receptor subtype [227]. - $K_i = 0.5$ nM for dopamine D_3 receptors [278].</p>	<p>- Used for the treatment of Parkinson's disease where new patients are started with pramipexole therapy and L-DOPA is added only as necessary [279]. - Pramipexole decreases leg movements in restless leg syndrome [280].</p>	<p>- Significant incidence of nausea with pramipexole [281].</p>

Chemical names, formula, and structure	Affinity	Pre- and clinical utilization	Nausea and vomiting
Rotigotine (PubChem CID: 59227) Trade name: Neupro <u>Chemical formula and structure:</u> $C_{19}H_{25}NOS$	- $K_i = 0.71$ nM For dopamine D_3 receptor [282]. - Affinities to other dopamine receptors being (K_i in nM): D_2 (13.5), $D_{4,2}$ (3.9), $D_{4,4}$ (15), $D_{4,7}$ (5.9), D_5 (5.4), and D_1 (83) [283].	- Used in the treatment of Parkinson's disease and restless leg syndrome [284, 285].	- Most frequent (>20%) adverse effects include nausea, and somnolence [286].
Ergot agonists			
Bromocriptine (PubChem CID: 31101) Trade name: Parlodel <u>Chemical formula and structure:</u> $C_{32}H_{40}BrN_5O_5$	- $K_i = 2.96$ nM for dopamine D_2 - $K_i = 5.42$ nM for dopamine D_3 receptors.	- Used to treat Parkinson's disease, hyperprolactinaemia, and neuroleptic malignant syndrome.	- Nausea, vomiting, headache, and dizziness [287].
Cabergoline (PubChem CID: 54746) Trade name: Dostinex <u>Chemical formula and structure:</u> $C_{26}H_{37}N_5O_2$	- $K_i = 0.95$ nM for dopamine D_2 receptors. - $K_i = 0.79$ nM for dopamine D_3 receptors. - $K_i = 56.2$ nM for dopamine D_4 receptors. - $K_i = 214$ nM for dopamine D_1 receptors.	- Prescribed for treatment of hyperprolactinemic disorders due to either idiopathic or pituitary adenomas. - Decreases the size and histopathologic grade in endometrial lesions in rats [288]. - Used for motor fluctuations associated with Parkinson's disease.	- Nausea and vomiting [289].
Pergolide (PubChem CID: 47811) Trade name: Permax <u>Chemical formula and structure:</u> $C_{19}H_{26}N_2S$	- $K_i = 447$ nM for dopamine D_1/D_2 receptors. - $K_i = 0.86$ nM for dopamine D_3 receptor.	- Used for treatment of Parkinson's disease [290]. FDA withdrew pergolide from the human market due to cardiac complications. - In veterinary, pergolide is the agent of choice for the treatment of common endocrine diseases in older horses and ponies.	- Nausea and vomiting [291].

Chemical names, formula, and structure	Affinity	Pre- and clinical utilization	Nausea and vomiting
Partial agonists			
<p>Alizapride (PubChem CID: 135413504) Trade name: Litican Chemical formula and structure: $C_{16}H_{21}N_5O_2$</p>		<p>- Used for treatment of schizophrenia, bipolar disorder (mania) [292], depression [293], and tic disorders [294].</p>	<p>- Used in the treatment of nausea and vomiting, including postoperative nausea and vomiting.</p>
<p>Atipiprazole: (PubChem CID: 60795) Trade names: Abilify Chemical formula and structure: $C_{23}H_{27}Cl_2N_3O_4$</p>	<p>- $K_i = 0.34$ nM for dopamine D_2 (partial agonist) [295]) - K_i 1.7–5.6 nM for 5-HT$_{1A}$ (partial agonists) - $K_i = 0.11$–0.36 nM for 5-HT$_2B$ (inverse agonist) - $K_i = 3.4$–35 nM 5-HT$_{2A}$ (antagonist).</p>	<p>- Used for bipolar disorder, irritability linked with autism spectrum disorder, schizophrenia, Tourette's disorder, and as an adjunctive treatment of major depressive disorder.</p>	<p>- The most frequently cited adverse effects of atipiprazole included nausea and vomiting [296].</p>
<p>Quetiapine (PubChem CID: 5002) Trade name: Seroquel Chemical formula and structure: $C_{21}H_{25}N_3O_2S$</p>	<p>- $K_i = 428$ nM for dopamine D_1. - $K_i = 626$ nM for dopamine D_2. - $K_i = 38$ nM for 5-HT$_{2A}$.</p>	<p>Used to treat schizophrenia or bipolar disorder</p>	<p>- Severe withdrawal syndrome with nausea and vomiting have been reported with quetiapine treatment [297].</p>
<p>Preclamol 3-PPP (N-n-propyl-3-(3-hydroxyphenyl) piperidine) (PubChem CID: 5311189) Trade name: Preclamol (INN) Chemical formula and structure: $C_{14}H_{21}NO$</p>	<p>- It has substantial affinities for non-dopamine D_2 receptors (for example, σ-, α_{2B}- or α_{2C}- adrenoceptors</p>	<p>- It was suggested as a potential clinical utility in the treatment of psychotic disorders, whilst lacking the seriously debilitating motor dysfunctions caused by current neuroleptic therapy. - It was also being investigated for the schizophrenia [298].</p>	<p>- May block vomiting in animal models.</p>

Chemical names, formula, and structure	Affinity	Pre- and clinical utilization	Nausea and vomiting
Terguride (PubChem CID: 443951) Trade names: Dronyl Chemical formula and structure: $C_{20}H_{28}N_4O$	Ki = 0.8 nM for dopamine D ₂ L receptors [299].	<ul style="list-style-type: none"> - Its use in schizophrenia patients is lowered due to its low tolerability [300]. - Co-administration of terguride with L- DOPA may prophylactically decrease L-DOPA-induced abnormal behavioral responses such as dyskinesia [301]. 	<ul style="list-style-type: none"> - It may induce nausea and vomiting [302,303].

Table 2

Major phenothiazine used as antiemetics.

Chemical names, formula, and structure	Affinity	Pre- and clinical utilization	Anti-nausea and vomiting
Chlorpromazine (PubChem CID: 2726) Trade name: Thorazine <u>Chemical formula and structure:</u> $C_{17}H_{19}ClN_2S$	- $K_i = 0.003 \mu M$ for dopamine D_2 [304]. - Contrary to most drugs of this class, it has a high affinity for dopamine D_1 receptors as well.	- Treatment of schizophrenia [305,306].	- Used against nausea and vomiting [307]. - In veterinary medicine, chlorpromazine is utilized as antiemetic agent and boosting effect of the activity of other drugs including anesthetics and sedatives [308].
Fluphenazine (PubChem CID: 3372) Trade name: Prolixin <u>Chemical formula and structure:</u> $C_{22}H_{26}F_3N_3OS$	- $K_i = 0.2$ and 0.11 nM for dopamine D_2 and D_3 receptors, respectively.	- Effective treatment for symptoms of schizophrenia [309].	- Fluphenazine has a greater antiemetic potency <i>versus</i> trifluoperazine [310].
Metopimazine (PubChem CID: 26388) Trade name: Vogalène <u>Chemical formula and structure:</u> $C_{22}H_{27}N_3O_3S_2$	- $K_i = 0.07 \text{ nM}$ for dopamine D_2 receptors.	- It can potentially be used as an alternative to metoclopramide and domperidone for the treatment of gastroparesis.	- Often used to treat nausea and vomiting [311].
Perphenazine (PubChem CID: 4748) Trade name: Trilafon <u>Chemical formula and structure:</u> $C_{21}H_{26}ClN_3OS$	- $K_i = 3.4 \text{ nM}$ for dopamine D_2 . - $K_i = 0.13 \text{ nM}$ for dopamine D_3 .	- Alleviates psychotic symptoms, such as hallucinations and delusions.	- Also used as an antiemetic, which is effective in the prevention of postoperative nausea and vomiting in children and adults without serious adverse effects compared with placebo [312].

Chemical names, formula, and structure	Affinity	Pre- and clinical utilization	Anti-nausea and vomiting
<p>Prochlorperazine (PubChem CID: 4917) Trade name: Compazine <u>Chemical formula and structure:</u> $C_{20}H_{24}ClN_3S$</p>	<p>- $K_i = 3.4$ nM for dopamine D_2-L.</p>	<p>- Is a potent typical anti- psychotic used to treat acute and chronic mental illnesses [313]. - Specifically used to treat delusions, hallucinations, agitation, disorganized speech, and behavior [314].</p>	<p>- Utilized in antiemetic treatments.</p>
<p>Promethazine (PubChem CID: 4927) Trade names: Phenergan <u>Chemical formula and structure:</u> $C_{17}H_{20}N_2S$</p>	<p>- $K_i = 250$ nM for dopamine D_2 receptors.</p>	<p>- Is a potent synthetic antihistamine, antipsychotic [315,316].</p>	<p>- Is used alone against nausea and vomiting or with dexamethasone, more effective than metoclopramide/dexamethasone in preventing and reducing nausea, epigastric fullness, and reflux in morbidly obese patients undergoing laparoscopic gastric plication [317].</p>
<p>Thiopropazate (PubChem CID: 6762) Trade name: Artalan <u>Chemical formula and structure:</u> $C_{23}H_{28}ClN_3O_2S$</p>	<p>- A potent neuroleptic with antipsychotic properties - Has no anti serotonin and hypotensive action and no antihistaminic properties.</p>	<p>- Has a marked general antiemetic effect.</p>	<p>- Used as an anti- psychotic [318, 319].</p>
<p>Trifluoperazine (PubChem CID: 5566)</p>	<p>- Used as an anti- psychotic [318, 319].</p>	<p>- Used as an antiemetic [320].</p>	

Chemical names, formula, and structure	Affinity	Pre- and clinical utilization	Anti-nausea and vomiting
<p>Trade name: The brand name Stelazine has been discontinued. This medication is obtainable in generic form only.</p> <p>Chemical formula and structure: $C_{21}H_{24}F_3N_3S$</p>
<p>Triflupromazine (PubChem CID: 5568)</p> <p>Trade name: Vesprin</p> <p>Chemical formula and structure: $C_{18}H_{19}F_3N_2S$</p>		<p>- Used to treat psychotic disorders [31,4].</p>	<p>- Used as an antiemetic [32,1].</p>

Table 3

Major butyrophenones used as antiemetics.

Chemical names, formula, and structure	Affinity	Pre- and clinical utilization	Anti-nausea and vomiting
Benperidol (PubChem CID: 16363) Trade name: Anquil Chemical formula and structure: $C_{22}H_{24}FN_3O_2$	- $K_i = 0.027$ nM for dopamine D_2 receptors [322].	- Has highest neuroleptic potency in terms of dopamine D_2 receptor blockade [323]. - Best candidate drug interacting with various target proteins participating in Alzheimer's disease [324].	- Used for the treatment of nausea and vomiting.
Domperidone (PubChem CID: 3151) Trade name: Motilium Chemical formula and structure: $C_{22}H_{24}ClN_5O_2$	$K_i = 0.3$ – 3.4 nM for dopamine D_2 -like receptors [182].	- Utilized in functional dyspepsia in adults and children [261].	- Used to treat nausea and vomiting [263].
Droperidol (PubChem CID: 3168) Trade name: Inapsin Chemical formula and structure: $C_{22}H_{22}FN_3O_2$	- $K_i = 0.25$ nM for dopamine D_2 receptors [322] with some histamine and serotonin antagonism [325].	- Used in patients with acute psychotic episodes, especially those with agitation or violent behavior [326].	- Is a short-acting neuroleptic drug with enhanced antiemetic effects [293,327].
Haloperidol (PubChem CID: 11495267) Trade name: Haldol Chemical formula and structure: $C_{21}H_{23}ClFN_3O_2$	- $K_i = 2$ nM for dopamine D_2 receptors. - $K_i = 4$ nM for dopamine D_3 receptors [322].	- Used mainly in the treatment of psychotic conditions [328].	- Used postoperatively and in as antiemetic, with minimal toxicity [329,330].
Melperone (PubChem CID: 15387) Trade name: Flubuprone Chemical formula and structure: $C_{16}H_{22}FNO$	- $K_i = 180$ nM for dopamine D_2 receptors. - It also has antagonistic activity at $5HT_{2A}$ receptors [331].	- It has been tried in treatment-resistant cases of schizophrenia with some limited success [332,333]. - It also possesses anxiolytic properties [334].	- Its reactions include nausea and vomiting.

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Chemical names, formula, and structure	Affinity	Pre- and clinical utilization	Anti-nausea and vomiting

Table 4

Major benzamides used as antiemetics.

Chemical names	Affinity	Pre- and clinical utilization	Anti-nausea and vomiting
Anisulpride (PubChem CID: 2159) Trade name: Solian <u>Chemical formula and structure:</u> $C_{17}H_{27}N_3O_4S$	- $K_i = 2.8$ and 3.2 nM for dopamine D_2 and D_3 receptors, respectively [335].	- Used as an antipsychotic, antidepressant and to treat bipolar disorder [293].	- Effective treatment for preventing postoperative nausea and vomiting as well as chemotherapy-induced emesis [336].
Bromopride (PubChem CID: 2446) Trade name: Bromoprída <u>Chemical formula and structure:</u> $C_{14}H_{22}BrN_3O_2$	- $K_i \sim 14$ nM for dopamine D_2 receptors [182].	- Was associated with decreased tensile strength and hydroxyproline concentration in colonic anastomoses in rats three days after surgery [337].	- Used as an antiemetic [338].
Clebopride (PubChem CID: 2780) Trade name: Clebopride Malate <u>Chemical formula and structure:</u> $C_{20}H_{24}ClN_3O_2$	- $K_i \sim 2$ nM for dopamine D_2 receptors [182].	- Has prokinetic properties and is used for functional gastro intestinal disorders [339].	- Has antiemetic properties [339].
Itopride (PubChem CID: 3792) Trade name: Ganaton <u>Chemical formula and structure:</u> $C_{20}H_{26}N_3O_4$	$K_i = 3.7 \pm 0.8$ μ M for dopamine D_{2S} receptor [340].	- Used for treatment of dyspepsia, and gastroparesis [341].	- Used for the treatment of nausea and vomiting [341].
(-) Sulpride (PubChem CID: 5355) Trade name: Abilit <u>Chemical formula and structure:</u> $C_{15}H_{23}N_3O_4S$	- $K_i = 38$ nM for dopamine D_2 receptors [342]. - Levosulpride has a $K_i = 27-134$ nM for dopamine D_2 receptors [182].	- Increases dexamethasone responses during the treatment of drug-resistant and metastatic breast cancer [343]. - Used as anti-depressant [293].	- It prevents chemotherapy-induced and post-operative vomiting. - Also used in the treatment of nausea and vomiting during hepatic, biliary and gastroduodenal disorders, functional dyspepsia, motion sickness, and vertigo [344]. - Levo-sulpride is a substituted benzamide with antiemetic activity [345].

Chemical names	Affinity	Pre- and clinical utilization	Anti-nausea and vomiting
Raclopride (PubChem CID: 3033769) Trade names: Not available <u>Chemical formula and structure:</u> $C_{15}H_{20}Cl_2N_2O_3$	Ki = 1.1–13 nM for dopamine D ₂ receptor antagonists in monkeys [342]. - Ki = 2.3–2.5 for dopamine D ₂ receptor antagonists in rats [342].	- Used in schizophrenia, [346] senile dementia, or transient psychosis after surgery.	- Used against nausea and vomiting.
Remoxipride (PubChem CID: 54477) Trade name: Remoxiprida <u>Chemical formula and structure:</u> $C_{16}H_{23}BrN_2O_3$	- Ki = 113 nM for dopamine D ₂ receptors [342,347].	- Use was restricted in 1993 due to aplastic anemia in some patients. But it is still an appealing tool for neurochemical and behavioral studies [347].	- Used to relieve severe nausea and vomiting.
Tiapride (PubChem CID: 5467) Trade name: Delpal <u>Chemical formula and structure:</u> $C_{15}H_{24}N_2O_4S$	- Ki = 114 nM for dopamine D ₂ receptors [348]. - Lacks affinity for dopamine D ₁ and D ₄ receptors, and histamine H ₁ , adrenergic α_1 , α_2 and serotonergic receptor [349].	- Is an atypical neuroleptic and sedative agent [347]. - Used for the treatment of agitation and aggressiveness in elderly patients [349].	- Has sedative as well as antiemetic properties [348].
Trimethobenzamide (PubChem CID: 5577) Trade name: Tigan <u>Chemical formula and structure:</u> $C_{21}H_{28}N_2O_5$	Ki = 640 nM for dopamine D ₂ in neural membranes.		- Was approved for use in the United States in 1974 and is widely used in therapy of nausea, vomiting caused by gastroenteritis, medications, and other illnesses. - It acts centrally to block dopamine D ₂ receptors, thereby inhibiting the medullary chemoreceptor trigger zone blocking emetic impulses to the vomiting center [315].