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Regulation of striatal dopamine release by presynaptic auto- and heteroreceptors

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Summary

Striatal dopamine neurotransmission is critical for normal voluntary movement, affect and cognition. Dysfunctions of its regulation are implicated in a broad range of behaviors and disorders including Parkinson's disease, schizophrenia and drug abuse. Extracellular dopamine levels result from a dynamic equilibrium between release and reuptake by dopaminergic terminals. Both processes are regulated by multiple mechanisms. Here we review data characterizing how dopamine levels are regulated by presynaptic autoreceptors and heteroreceptors, an area intensively investigated due to advances in real time electrochemical detection of extracellular dopamine, i.e., fast-scan cyclic voltammetry and amperometry, and the development of mutant mouse lines with deletions for specific receptors.

Keywords

dopamine; release; autoreceptor; heteroreceptor; cyclic voltammetry; striatum

1. Introduction

The neurotransmitter dopamine is important for movement, motivation, and cognition. Acting as a neuromodulator of ionotropic synapses, dopamine sets a threshold for striatal activity that underlies motor learning, motivation, and decision making [1-3]. As might be presumed from these complex and important functions, there are multiple presynaptic mechanisms that regulate dopamine release, particularly due to receptor-mediated mechanisms driven by additional neural pathways present in these brain regions.

Dopaminergic neurotransmission is generally initiated by synaptic vesicle fusion, which can be modulated at different levels including dopamine synthesis, uptake and vesicular transport as well as Ca²⁺-homeostasis and exocytotic proteins [4]. In addition, dopamine autoreceptors and heteroreceptors expressed on dopamine somatodendritic regions [5-9] and presynaptic axon terminals provide feedback and regulate dopamine release.

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Advances in electrochemical detection of extracellular dopamine using carbon fiber electrodes in acute brain striatal brain slices [10, 11], along with an explosion of receptor deficient mutant (“knockout”) mouse lines [12, 13], has vastly contributed to the characterization of autoreceptor and heteroreceptor regulation of this system. While newer approaches, including the use of optical methods such as channelrhodopsins and fluorescent false neurotransmitters may lead to further insights in the future, we review advances from the past decade at the terminal level in the striatum since it is the major point of entry into the basal ganglia for information emanating from the cortex, and plays important roles in motor control, cognition, learning and addiction. In addition, the regulation of dopamine release in this region is best understood since it has the richest dopamine innervation in the central nervous system (CNS).

2. Regulation of release by autoreceptors

It has long been known that dopamine autoreceptors expressed on dopamine presynaptic axon terminals provide feedback and regulate dopamine release. There are multiple pathways or mechanisms at different time scales to achieve this. Activation of dopamine autoreceptors can decrease release by inhibiting dopamine synthesis and enhancing dopamine reuptake by the dopamine transporter as well as regulating vesicular monoamine transporter (VMAT2) expression [4, 14, 15]. These are slow processes that may last for minutes to hours. Here we specifically review newer data on quick effects on evoked dopamine release by modulating ion channel conductance.

2.1. Dopamine autoreceptors

Dopamine autoreceptors belong to the D2-family (D2, D3, D4) of dopamine receptors that are coupled to inhibitory G proteins and modulate ion channel activity and/or inhibit adenylyl cyclase. D2 receptors are expressed along the somatodendritic extent of midbrain dopamine neurons, as well as at their axon terminals in the dorsal striatum and nucleus accumbens (also called the ventral striatum) [16]. Of two isoforms of the D2 receptors generated by alternative splicing, the shorter version (D2-S) may be the dominant presynaptic autoreceptor [17-19].

D2 receptor knockout mice exhibited no detectable autoreceptor response to D2-class receptor agonists in firing rate, dopamine release or dopamine synthesis. Recently, fast-scan cyclic voltammetry (FCV) recordings in a mouse line that is deficient for D2 receptors selectively in dopamine neurons confirmed that it is the autoreceptor regulating dopamine neuron firing and release [20]. Thus, results implicated the D2 receptor as the only functional autoreceptor in the D2-family [20-24].

In contrast, a role for axonal D3 autoreceptors remains unproven. D3 immunoreactivity has been found in almost all midbrain dopamine neurons, but is undetectable in the terminal regions [25]. While it has been suggested that D2 and D3 receptors may both function as autoreceptors [26-29], no clear deficits have been identified in D3 receptor knockout mice, although extracellular dopamine was elevated in the ventral striatum [30] and one study of D3 KO mice using FCV in striatal slices has demonstrated a small D3 role for regulation of secretion but not synthesis in the striatum [31].

Studies on transfected cells demonstrated that D3 receptors can modulate the same G protein-activated inwardly rectifying potassium channels (GIRKs) as D2 receptors [32-34], and have the potential to affect dopamine release [35]. However, a study from D2 receptor knockout mice did not find evidence for D3 receptor activation of GIRK currents on genuine ventral midbrain dopamine neurons [36].

There is little evidence supporting a role of D4 receptors as autoreceptors beyond an immunohistochemistry study that demonstrated presynaptic D4 receptor localization in a subset of mesoaccumbal terminals in the nucleus accumbens shell [37]. In summary, dopamine autoreceptor function is predominantly carried out by D2 receptors.

2.2. In vitro studies

The regulation of dopamine release by dopaminergic autoreceptors was initially studied *in vitro* with neurochemical approaches [38]. D2 autoreceptor activation inhibits axon terminal [39-45, 46] and somatodendritic dopamine release [41].

The molecular mechanism underlying the inhibition of dopamine release through terminal D2 autoreceptor is not fully understood. One possibility is that D2 autoreceptors inhibit voltage-gated Ca^{2+} channels in axon terminals, thus directly inhibiting Ca^{2+} -dependent exocytosis. Patch clamp studies on dopamine midbrain neurons *in vitro* have revealed a D2 receptor regulation of voltage-gated calcium currents [47] and axon terminal dopamine release is dependent on N and P/Q type calcium channels [11, 48]. A presynaptic effect of D2 on these channels has not been proven directly, however, and a study on autapses (i.e., synapses that a neuron makes on itself) of midbrain neurons in culture found no evidence for a D2 autoreceptor regulation of calcium influx [49] but that 4-aminopyridine-sensitive K^{+} channels acting downstream from calcium influx are involved. Autapses of cultured dopamine neurons are glutamatergic [50], however, and it is not known whether this finding can be extrapolated to dopamine release. Nevertheless, the broad-spectrum K^{+} channel blockers 4-aminopyridine and tetraethylammonium reduce the ability of a D2 agonist, quinpirole, to inhibit evoked dopamine release in slices [51], supporting a role for presynaptic K^{+} channels. Using Kv subtype-selective blockers, it was recently shown that Kv1.2, Kv1.3 and Kv1.6 are located in dopamine axonal processes in the dorsal striatum. These channels are likely to be key players in regulating axonal dopamine release and may act as mediators or regulators of presynaptic D2 receptor function [52, 53]. Nevertheless, given that the non-linear nature of the threshold for action potential initiation and consequent dopamine release, blocking any class of K^{+} channels could alter the efficacy of D2 agonists to inhibit release. Thus, such data are not necessarily mechanistically informative. Further studies are required to evaluate whether the D2 receptor can directly regulate the function of Kv1 channel subtypes in DA neurons. Furthermore, as Kv1 potassium channel blockers can only partially block the inhibition effect of quinpirole, it is possible that other classes of potassium channels are also involved. GIRK2 potassium channels are expressed in dopamine neurons [36, 54] and K_{ATP} potassium channels are expressed in dopamine terminals [55], however, they appear to only play minor roles in regulating presynaptic dopamine release [53]. Therefore, other additional mechanisms need to be explored.

2.3. In vivo studies

Consistent with the *in vitro* studies, the regulation of dopamine release by dopamine autoreceptors was subsequently shown *in vivo* using microdialysis. Indeed, systemic administration of D2 antagonists enhances the extracellular dopamine level in the dorsal striatum [56]. Moreover, intrastriatal infusion of D2 agonists or antagonists decreases or enhances extracellular dopamine, respectively [57]. This autoregulation acts on the impulse flow-dependent dopamine release [56] and is not mediated by an indirect action on striatal neurons [58]. However, the extracellular dopamine level results from a dynamic equilibrium between dopamine release and dopamine reuptake and microdialysis does not clearly distinguish between changes in release and reuptake.

In contrast, in vivo electrochemical studies have shed light on the D2 autoregulation of dopamine release and of dopamine reuptake. These studies confirmed that the tonic level of extracellular dopamine concentration is sufficient to exert a tonic stimulation of D2 autoreceptors, which inhibits the impulse flow-dependent dopamine release [59, 60]. However, the electrochemical techniques used in these initial studies were too slow to describe the kinetics of the D2 autoregulation. The use of a faster technique (i.e., amperometry) and of control experiments with mice lacking D2 receptors made it possible to describe the dynamic characteristics of D2 autoregulation [21]. The onset of the D2 inhibition is between 50 ms and 100 ms, reaching a maximum between 150 and 300 ms after the end of the conditioning stimulation and disappearing by 800 ms [21]. Similar kinetics was described with in vitro experiments [24, 46] with a maximum effect around 500 ms and duration of less than 5 sec. The slightly longer time course determined in the in vitro studies is likely due to the larger amount of dopamine released per stimulation in slice preparations.

3. Regulation of dopamine release by heteroreceptors

In addition to D2 autoreceptors, there are additional neurotransmitter receptors on dopamine cell bodies and terminals, but their modulatory roles in dopamine release are less well characterized. Many addictive drugs, including nicotine, ethanol, opioids, morphine, and cannabinoids appear to enhance dopamine neuronal activity by acting directly on dopamine neurons or indirectly on GABA interneurons through the mechanism of disinhibition [9, 61, 62].

Electron microscopic demonstration of heteroreceptor immunolabel in dopamine terminals is invaluable for establishing their presence, but there are relatively few studies in this area due to technical challenges. To date, only the GDNF receptor [63], nicotinic receptors (nAChRs) [64], delta and kappa opioid receptors [65, 66], the metabotropic receptor mGluR1 [67], and possibly the GABA_B receptor [68] have been observed by ultrastructural immunolabel in dopamine terminals.

Although the presence of other presynaptic receptors in dopamine terminals remains to be fully elucidated, studies using synaptosomes preparations, microdialysis, and CV recordings in vivo and in vitro suggest important roles for heteroreceptor modulation on dopamine release, albeit with conflicting results.

3.1. Glutamate receptors

The effects of ionotropic glutamate-receptors (iGluRs) on dopamine release are most likely indirect given that mature dopamine terminals appear to lack these receptors [69, 70], although axonal growth cones possess NMDA receptors [71]. While microdialysis studies indicated a stimulatory effect for iGluRs on dopamine release, FCV recordings demonstrated an inhibitory role on evoked dopamine release in the terminal region [72-74]. Direct perfusion of the acute striatal slices with iGluR agonists (NMAD, AMPA, and KA) causes a profound inhibition in evoked dopamine release in the first 4 minutes, but then a huge release of dopamine, similar to massive release that occurs with 70mM KCl [75, Zhang and Sulzer, unpublished results]. This is consistent with the suggestion that iGluR agonists may induce wide-spread depolarization and then spreading depression [76, 77].

Presynaptic regulation of dopamine release by iGluRs has been more clearly resolved in striatal slices using train stimulation using FCV [72, 78] since the effect of concurrently released glutamate during train stimulation on dopamine release could be revealed by corresponding antagonists. Recent studies by Margaret Rice's group suggest that glutamatergic regulation of dopamine release is indeed inhibitory. The effect is indirect and mediated by AMPA receptors on striatal cells, which is in turn mediated through retrograde

signaling by diffusible H_2O_2 generated in striatal cells, rather than in dopamine axons [78]. Activity-dependent H_2O_2 generated in striatal cells inhibits dopamine release via ATP-sensitive K^+ channels located on dopamine terminals [55].

In contrast to iGluRs, the metabotropic receptor mGluR1 has been detected by ultrastructural immunolabel on striatal dopamine terminals [79], and evoked dopamine release can be inhibited via group I metabotropic glutamate receptors on dopamine terminals [80]. By monitoring evoked dopamine release directly using FCV, we found a reciprocal modulation by glutamate spillover on evoked striatal DA release, induced by either glutamate uptake blockade or high-frequency stimulation of corticostriatal tracts. Therefore, glutamate released from the cortical terminals during short bursts of cortical activity may escape the confines of its synapse in the striatum and depress dopaminergic transmission by activating presynaptic group I mGluRs. This inhibition is mediated by the mobilization of internal Ca^{2+} stores which in turn activates apamin-sensitive Ca^{2+} -dependent potassium currents.

3.2. GABA receptors

By local infusion of GABA_A and GABA_B receptor agonists and antagonists in the striatum of intact and kainic acid lesioned rats, microdialysis data support a direct influence of GABA on the dopaminergic terminals via presynaptic GABA_B receptors, while the effects via the GABA_A receptors seem to be postsynaptic and mediated by striatal interneurons [81]. A direct effect of GABA_B receptors on dopamine release is further supported by a study using FCV recordings, which shows that GABA_B receptor agonists inhibit single-pulse-evoked dopamine release in the striatal slice with kinetic parameters similar to those of the D2 autoreceptor [24]. There is ultrastructural evidence consistent with expression of GABA_B receptors on dopamine terminals [68].

Functional studies suggest that GABA_A receptors might be colocalized on the dopamine terminals. Muscimol, a GABA_A receptor agonist, inhibits the evoked dopamine release in striatal synaptosomes [82] and also inhibits evoked dopamine release by single pulse stimulation measured by FCV in striatal slices (Zhang and Sulzer, unpublished results). However, the results could be complicated by possible actions on cholinergic interneurons. Further experiments with depletion of ACh tone are needed to determine whether the regulation is direct or not (please also refer to the conclusion section).

3.3. Acetylcholine receptors

Classical pharmacological studies of the effects of muscarinic acetylcholine receptors (mAChRs) on dopamine release in the striatum have led to contradictory results [83-89], due in part to the diversity of the mAChR subtypes and the limited receptor subtype selectivity of the muscarinic agonists and antagonists [90]. Activation of mAChRs was shown to inhibit dopamine release in dorsal striatal slices examined by FCV [91]. A human-brain imaging study indicated a tonic muscarinic inhibition of dopamine release in striatum [92]. A study using genetically altered mice that lacked functional M1-M5 mAChRs provides evidence of the different physiological roles of individual mAChRs in a direct manner [13]. The results show that M3 receptors inhibit potassium-stimulated [^3H] dopamine release, whereas M4 and M5 receptors facilitate release, and M1 and M2 receptors have no effect. It seems that the modulating effects of M3 and M4 receptors are mediated via striatal GABA release. This view however has been recently challenged by studies by Cragg's group suggesting that modulating effects of mAChRs are mediated by effects on cholinergic interneurons [93, 94]. Application of a mixture of antagonists for GABA and glutamate receptors does not alter the inhibitory effect of oxotremorine-M (Oxo-M), a broad mAChR agonist on dopamine release, ruling out the involvement of GABA or glutamate as the intermediary. In contrast, blockade

of $\beta 2$ -nAChRs completely precludes the effect of Oxo-M, suggesting mAChRs govern dopamine release via manipulating ACh tone at $\beta 2$ -nAChRs on DA terminals [93].

M5 receptor mRNA is the only mAChR subtype mRNA detectable in the dopamine-containing cells of the substantia nigra pars compacta [95, 96], strongly suggesting that the dopamine release-facilitating M5 receptors are located on dopaminergic nerve terminals [97, 98]. Recently FCV studies in striatal slices show that evoked dopamine release in M5 mAChR KO mice is reduced, whereas inhibition of evoked dopamine release by oxotremorine-M (Oxo-M), a broader mAChR agonist is enhanced, consistent with a release-potentiating function of dopaminergic terminal M5 receptors [98]. Oxo-M can inhibit dopamine release indirectly by acting on M2, M4 receptors on cholinergic interneurons, whereas enhance dopamine release directly by acting on M5 receptor on dopamine axons [93]. The overall effect of Oxo-M on dopamine release is inhibitory as shown by experiments [13, 93, 98] probably due to the greater affinity of ACh for nAChRs than mAChRs. In the M5 mAChR KO mice, the inhibition effect of Oxo-M is enhanced because of the loss of the excitatory component. Although this explanation seems reasonable, to some extent, it conflicts with the fact that blockade of $\beta 2$ -nAChRs completely precludes the effect of Oxo-M [93]. Other possibilities such as down-regulation of $\beta 2$ -nAChRs in the M5 KO mice should be explored in the future.

Nicotinic acetylcholine receptors possessing $\beta 2$ -subunits are expressed on dopamine terminals in the striatum all [64, 99, 100]. Nicotine enhanced the extracellular dopamine level by microdialysis [101] and results *in vivo* indicate that nicotine, like cocaine and alcohol, increase the frequency of non-evoked dopamine transients in the nucleus accumbens [102]. FCV studies demonstrated an inhibition of evoked dopamine release in slices by nicotinic agonists [91, 103]. Because nAChR antagonists also inhibit dopamine release, it appears that activation of nAChRs by endogenous ACh is excitatory for dopamine release, but the receptor is rapidly desensitized by nicotine application, and so nicotine inhibits evoked dopamine release by single pulse stimulation [103-105]. In summary, activation of nAChRs normally keeps dopamine release probability high, but curbs subsequent release during pulse trains due to synaptic depression; nAChR blockade or desensitization decreases dopamine release probability, but facilitates subsequent release during high frequencies (please refer to section 4 for further discussion).

3.4. Opioid receptors

Kappa-opioid receptors are located on dopamine axon terminals [65] while mu-opioid receptors are not expressed on striatal dopamine axon terminals [106]. Using FCV, Schlosser et al. [107] first demonstrated that mu, delta, and kappa opioid receptors inhibit striatal dopamine release. It seems that the effect of kappa opioid receptors on dopamine overflow is likely to be direct, while the influence of mu opioid receptors is indirect and mediated by an inhibition of cholinergic interneuron activity, since nicotine produced negligible effects on dopamine release when applied subsequent to a saturating dose of endomorphin-1, a mu receptor agonist [65, 108]. The similarities between the effects on evoked dopamine overflow elicited by mu-opioid agonists and nicotine suggested a common mechanism of action. Although kappa-agonists profoundly inhibit single-pulse-evoked dopamine overflow throughout the striatum, this inhibition is unusual in that it cannot be overcome by high-frequency stimuli. This is confirmed by the observation that kappa-opioid receptor activation did not alter the paired-pulse ratio of dopamine release, suggesting that the effects are not mediated by changes in either calcium influx or axon terminal membrane potential [108]. Whether the effect of delta opioid receptors on dopamine release is direct remains unclear, but ultrastructural studies show that delta opioid receptors are present on dopamine terminals [66].

3.5. Adenosine receptors

Adenosine, an important neuromodulator in the brain, is a metabolite generated by dephosphorylation of ATP as a function of neuronal activity. There are four adenosine receptors, A1, A2a, A2b and A3. The A2 subtypes are Gs /Golf /Gq coupled, stimulating adenylyl cyclase, whilst A1 and A3 couple to Gi /Go and inhibit adenylyl cyclase. In the basal ganglia, the receptors of interest are A1 and A2a [109].

It remains unclear whether there is a direct heteroreceptor modulation by adenosine on dopamine release. In the striatum, activation of A1 receptors inhibits [110-112], whereas activation of A2a receptors enhances dopamine release [113]. FCV studies also demonstrate that A1 receptor agonist decrease single-pulse-evoked dopamine release in vitro, but the inhibition is dependent at least in part on the simultaneous activation of D1 dopamine receptors. While the mechanism underlying this interaction remains to be determined, it does not appear to involve an intramembrane interaction between A1 and D1 receptors [112, 114].

To date, the morphological evidence of presynaptic localization of A1 receptors on dopamine terminals is indirect [115-117]. Furthermore, the lesion of glutamatergic, but not dopaminergic, striatal afferents significantly decreases striatal A1 receptor function and agonist binding [118]. In addition, there are no A2a receptors on dopamine terminals [119, 120]. Therefore, the main mechanism underlying adenosine-mediated modulation of striatal dopamine release may be indirect.

3.6. Cannabinoid receptors

These receptors consist of two GPCRs, CB1 and CB2, with the CB1 highly expressed in CNS [121-123]. Marijuana and its main psychoactive component, delta9-tetrahydrocannabinol (THC) act on CB1 receptors in the CNS. CB1 receptor is coupled through G_o or Gi to inhibit adenylyl cyclase, and activation of presynaptic CB1 receptors is well known to inhibit glutamate and GABA release [124]. FCV studies have not identified a direct presynaptic modulation of dopamine release by CB1 receptors in either dorsal striatum or ventral striatum [80, 125, 126], in agreement with the lack of anatomical evidence of CB1 receptors on dopamine terminals [127-131]. Nevertheless, there are indirect effects by cannabinoids on dopamine release. Ventral tegmental area (VTA) dopamine neurons are thought to produce the cannabinoids [132-134], which would be expected to activate local receptors. CB1 agonists inhibit evoked dopamine release while increasing the frequency of non-evoked dopamine concentration transients in rat striatum in vivo, responses that may be related to effects on dopamine neuronal firing via a reduction of afferent GABAergic transmission [61]. This indirect influence on dopamine cell activity and then release may underlie the psychoactive actions of cannabis.

CB1 agonists alter motor function in a complex way and the suppression of movement might be due to inhibition of dopamine release in the dorsal striatum [135]. Although a CB1 agonist had no effect on single-pulse-evoked-dopamine in striatal slices, it decreased dopamine release over trains of stimuli, suggesting cannabinoids exert indirect changes via a local striatal circuit. Rice and colleagues have suggested this could occur via a nonsynaptic mechanism involving inhibition of GABA release, generation of hydrogen peroxide, and activation of K_{ATP} channels to inhibit dopamine release [126].

Recently an intriguing study demonstrates that the inhibition of dopamine release by D2 autoreceptor is attenuated by activation of CB1 receptors [136]. Although the underlying mechanisms are not clear, the results provide a functional correlate to previous observations that CB1 receptors are antagonistic to D2 receptors in the region [137].

In addition, there are additional ionotropic and G-protein-linked receptor candidates that may act as heteroreceptors on dopamine terminals, and elucidation of their effects is fundamental for understanding their roles in modulating dopaminergic transmission.

4. Frequency dependent modulation of dopamine release

Dopaminergic neurons exhibit two patterns of discharge activity: a continuous mode with regularly spaced spikes at a frequency between 2 and 5 Hz, and a bursting activity characterized by brief bursts of 2 to 6 action potentials [138]. Single dopaminergic neurons switch between the patterns. In resting condition and during sleep most dopaminergic neurons discharge with the tonic mode, but rewarding or sensorial stimuli predicting a reward trigger in most dopaminergic neurons a single burst both in rats [139] and monkeys [140, 141]. In rats the intra-burst frequency is 15-30 Hz [138, 139]. Grace and Bunney hypothesized that the bursting mode would be more potent than the tonic pattern to induce dopamine release [138]. Accordingly, electrical stimulations mimicking the bursting mode were twice as potent as regularly spaced stimulation having the same whole duration and number of pulse to enhance the extracellular dopamine level in vivo [142].

As detailed above, numerous studies provide evidence for heteroreceptor regulation of dopamine release, although some results are controversial due in large part to different preparations, stimulation and recording paradigms. In vivo and in vitro data in slices with local stimulation cannot exclude circuit effects. There are striking differences between such results in the slice preparation where there is significant paired pulse depression, and in vivo, where there is typically no detectable depression. While the basis for such differences remains unclear an important factor is presumably due to the loss of most ongoing synaptic activity in the slice. Furthermore, most previous voltammetry studies in striatal slices only examine the effects evoked by single pulse stimuli mimicking the tonic firing mode, while recent studies have demonstrated the frequency dependent modulation of dopamine release by nAChRs [104, 105, 143].

Nicotine shifts VTA neurons from tonic to burst firing modes [5, 144] and enhances extracellular dopamine as measured by microdialysis [101]. On the other hand, nicotine at levels thought to be experienced by smokers (~250-300 nM) desensitizes nAChRs so rapidly that tonic ACh activation is blocked and evoked dopamine release is potently inhibited [91, 103].

In order to resolve the question of how nicotine both elevates extracellular dopamine and depresses evoked dopamine release, the effects of nicotine on the modulation of evoked dopamine release were compared under different firing patterns and found to be dependent on the firing pattern of dopamine neurons. While desensitization of nAChRs indeed curbs dopamine released by stimuli emulating tonic firing, it allows a rapid rise in dopamine from stimuli emulating the phasic firing patterns associated with incentive/salience paradigms. Nicotine may thus enhance the contrast of dopamine signals associated with behavioral cues [104, 105] (Fig. 1). Interestingly, mu opioid agonists inhibit dopamine overflow elicited with single-pulse stimuli while leaving that produced by burst stimuli unaffected, but these differential effects are mediated by nAChRs and caused by inhibition of cholinergic interneurons [108].

Activation of mAChRs also inhibits single-pulse-evoked dopamine release while the depression is alleviated at high frequency stimuli. This frequency dependent modulation is again mediated by nAChRs and cholinergic interneurons: activation of mAChRs on cholinergic interneurons inhibits their firing [145] and thus release, which decreases the activation of nAChRs on dopamine terminals [93, 94].

This frequency dependent modulation may apply to other heteroreceptors, in addition to nAChRs, mAChRs and opioids mu receptors. In order to have much more dopamine to be released during phasic firing compared to tonic firing, the release probability must be low. A broad range of studies by multiple groups using the acute striatal slice find no detectable tonic activation of iGluRs, mGluRs, GABA_A receptors (GABA_AR), GABA_B receptors (GABA_BR), mAChRs, adenosine subtype receptor A2aR and A1R, opioid receptors, and D2 autoreceptor (D2R), and tonic activation appears to be limited to nAChRs (Table 1). This is however directly only applicable to the slice, in which with the exception of cholinergic interneurons, there are very few active neurons. This clearly strongly contrasts with the living organism, in which there are certainly highly variable and complex inputs from multiple pathways, and where antagonists might be expected to thus show very complex effects.

Remarkably, with the exception of ACh receptors, the effects of receptor agonists indicate that most heteroreceptors studied to date have been found to depress dopamine release (Table 1). Therefore, in addition to D2Rs, most heteroreceptors in vivo may maintain the dopamine release probability at a low level, which may then provide a marked and rapid increase in dopamine concentration during phasic firing. We speculate the outcome of change of dopamine release by the various heteroreceptors will depend critically on the accompanying changes in the cholinergic interneurons. While dopamine neurons signal salient contextual stimuli by brief burst firing, simultaneously striatal cholinergic interneurons typically pause, which will lead to decreased ACh tone and less activation of nAChRs on dopamine terminals. Thus, the pauses in cholinergic neurons enhance the sensitivity of dopamine synapse to temporally correlated changes in dopamine neurons activity. A range of drugs that affect the dopamine system may exert their actions via altering the signal/noise ratio of dopamine by affecting heteroreceptors on dopamine terminals as well as on cell bodies [146].

5. Conclusions

The striatum is a highly heterogeneous structure organized into different but overlapping territories [147]. Modulation of dopamine release by heteroreceptors moreover appears to be region specific and dependent. For example, although a similar frequency dependent modulation by nicotine is found in the dorsal striatum as in the shell, the increased ratio of phasic burst relative to tonic firing caused by nicotine is smaller compared to that in the shell [143]. In the dorsal striatum, a region associated with sensorimotor function, both M2 and M4 mAChRs are necessary for mAChR regulation of dopamine release, whereas in the ventral striatum, a region associated with limbic function, only the M4 mAChR is necessary for mAChRs regulation of dopamine release [93]. The modulation of dopamine release by mu opioid receptors only exists in specific subregions of the nucleus accumbens [108].

We have reviewed here most of the data using FCV in striatal slices. Whereas the effect on dopamine release by single pulse stimulation usually suggests a direct action, however, the indirect circuitry effect cannot be completely excluded given the tonic cholinergic tone in the striatum. It is challenging to distinguish a direct effect on the heteroreceptors expressed on dopamine terminals from an indirect effect through the control of ACh release by influencing heteroreceptors expressed on the cholinergic interneurons, unless completely depleting the cholinergic tone first.

Optical techniques appear poised to further define effects of presynaptic receptors on release probability [148-150]. Using a fluorescent false neurotransmitter to directly visualize dopamine release from individual terminals, we have found a frequency-dependent heterogeneity of presynaptic terminals, which is dependent in part on D2 receptors,

indicating a mechanism for frequency-dependent coding of presynaptic selection [151]. These data suggest that modulation of dopamine release is not fixed; it could be frequency dependent, region specific, sub-territory specific, even individual terminal specific. We should therefore consider all of these when considering potential therapeutic targets for treating dopamine related disorders.

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Figure 1. Modulation of evoked dopamine (DA) release by nAChRs depends on firing pattern (a,b) Voltammetric responses before and after 10-min bath application of nicotine (Nic, 300 nM) or mecamylamine (Meca, 2 μ M) at different stimuli. The inhibition of evoked release was not blocked by D2 dopamine, GABA_A, GABA_B or ionotropic glutamate receptor antagonists. (c,d) Frequency modulation of nicotine and mecamylamine effects on dopamine release (mean $\pm$ s.e.m., $n = 8$ for control; $n = 5$ for nicotine, $n = 4$ for mecamylamine; * $P < 0.05$ compared with respective control values by Student's t -test). Top panels: evoked dopamine release normalized to that elicited by 1p stimulation under control condition. Bottom panels: relative evoked dopamine release after nicotine and mecamylamine at different stimulation frequencies. (e-h) Effects of number of pulses, nicotine and mecamylamine on dopamine release at 20 Hz (e,f) and 100 Hz (g,h) (mean $\pm$ s.e.m., $n = 4-8$, * $P < 0.05$ compared with respective control values by Student's t -test). Data from Zhang and Sulzer (2004), copyright by Nature Publishing Group.

Table 1

Heteroreceptor Regulation of Evoked Dopamine Release by 1 pulse stimulation

Receptors	Tonic Tone (revealed by antagonists)	Agonist/Effect	Notes	Subregion
iGluRs --NMDA --AMPA --KA	No	NMDA AMPA KA	Inhibition within 4 min but mass release due to spreading depression	Dorsal striatum
mGluRs	No	Inhibition (DHPG)	through mGluR1	Dorsal striatum
GABA _A R	No	Inhibition		Dorsal and ventral striatum
GABA _B R	No	Inhibition		Dorsal and ventral striatum
Adenosine (A1R, A2aR)	No	A1: Inhibition		Dorsal striatum
Opioid receptors (mu, delta, kappa)	No	Inhibition		ventral striatum
Cannabinoid CB1	No	NO		Dorsal and ventral striatum
mAChRs	No	Inhibition		Dorsal and ventral striatum
nAChRs	Yes (excitatory)			Dorsal and ventral striatum

There is no detectable tonic activation of iGluRs, mGluRs, GABA_AR, GABA_BR, mAChRs, adenosine subtype receptor A2aR and A1R, opioid receptors, and D2 autoreceptors in the striatal slice, except nAChRs. Activation of these receptors inhibits evoked dopamine release elicited by single pulse at various levels of the controls (ref [75, 80, 91, 93, 103, 104, 105, 108, 112, 126, 136, 146]).