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Pharmacologic mechanisms of serotonergic regulation of dopamine neurotransmission

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Abstract

The neurotransmitter dopamine (DA) has a long association with normal functions such as motor control, cognition, and reward, as well as a number of syndromes including drug abuse, schizophrenia, and Parkinson's disease. Studies show that serotonin (5-HT) acts through several 5-HT receptors in the brain to modulate DA neurons in all three major dopaminergic pathways. There are at least 14 5-HT receptor subtypes, many of which have been shown to play some role in mediating 5-HT/DA interactions. Several subtypes, including the 5-HT1A, 5-HT1B, 5-HT2A, 5-HT3 and 5-HT4 receptors, act to facilitate DA release, while the 5-HT2C receptor mediates an inhibitory effect of 5-HT on DA release. Most 5-HT receptor subtypes only modulate DA release when 5-HT and/or DA neurons are stimulated, but the 5-HT2C receptor, characterized by high levels of constitutive activity, inhibits tonic as well as evoked DA release. This review summarizes the anatomical evidence for the presence of each 5-HT receptor subtype in dopaminergic regions of the brain and the neuropharmacological evidence demonstrating regulation of each DA pathway. The relevance of 5-HT receptor modulation of DA systems to the development of therapeutics used to treat schizophrenia, depression, and drug abuse is discussed. Lastly, areas are highlighted in which future research would be maximally beneficial to the treatment of these disorders.

Introduction

Alterations in the brain monoamines dopamine (DA) and serotonin (5-HT) have been implicated in the etiology and/or pharmacotherapy of multiple mental disorders including schizophrenia and depression. Basic science research has shown that 5-HT receptors modulate dopaminergic function. Thus, the clinical efficacy of psychotherapeutic drugs that act on 5-HT systems may be due in part to their effects on DA systems. However, while multiple preclinical studies have shown that 5-HT regulates DA cellular activity and release, there were initially many conflicting reports regarding the nature and direction of this interaction. Work was hampered by the multiplicity of 5-HT receptor subtypes and the lack of selective ligands that distinguished between these subtypes. The recent development of more selective drugs has enabled the delineation of the specific roles of some 5-HT receptor subtypes. Investigators

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have recently determined that, in some cases, the nature of these interactions depends upon the baseline activity of DA and/or 5-HT systems, i.e. whether they are activated or not. In addition, most of the effects of 5-HT on DA neurons may be indirect, mediated via actions on complex neuronal circuitry, rather than direct effects on DA terminals. It is important to understand this circuitry since the different 5-HT receptor subtypes are differently distributed in dopaminergic brain regions. It thus may be possible to specifically “target” individual brain regions with serotonergic ligands and thereby affect dopaminergic function selectively in these areas. This is important therapeutically since individual patients have a range of symptoms that may reflect dopaminergic dysfunction in some brain areas but not others. In addition, undesirable medication side effects may be eliminated through the targeting of selective brain regions. This review will begin with an introduction of the most pertinent background information and then discuss the neuroanatomical basis for 5-HT receptor/DA interactions. Subsequently, the neuropharmacological evidence supporting a role for each 5-HT receptor subtype in the modulation of the three major DA pathways will be summarized. *In vivo* work will be emphasized. Directions for future research and the significance of the findings for our understanding of brain function in mental illness and drug abuse will be discussed.

DA Systems

There are three major DA systems in the brain (Wolf et al., 1987). The cell bodies of the nigrostriatal pathway reside in the substantia nigra pars compacta (SNpc) and project to the dorsal striatum (caudate-putamen). Degeneration of these neurons results in the subsequent motor deficits of Parkinson’s disease. The mesolimbic pathway originates in the ventral tegmental area (VTA) and terminates in the nucleus accumbens (NA); one function of this system is the mediation of natural and drug-induced reward (see Wise et al., 1989 for review). The mesocortical DA pathway, which also originates in the VTA but terminates in the prefrontal cortex (PFC), regulates complex cognitive processes such as selective attention and working memory (the ability to hold information in mind in order to guide future action).

The cell bodies and terminal regions of all three DA pathways are innervated by 5-HT neurons originating in the medial and dorsal raphe nuclei (Geyer et al., 1976; Parent et al., 1981; Beart and McDonald, 1982; Nedergaard et al., 1988). Studies show that there are direct synaptic contacts between 5-HT terminals and DA cells in the midbrain (Herve et al., 1987; Nedergaard et al., 1988). Thus, 5-HT could potentially regulate the function of DA neurons via actions on midbrain DA cell bodies and/or DA terminals.

5-HT Receptors

There are seven main types of 5-HT receptors (1–7) with subtypes of most of these for a total of at least 14 different receptors (Roth, 1994; Barnes and Sharp, 1999; Hoyer et al., 2002). In addition, there are a number of isoforms as a result of pre-mRNA editing of most of these receptors. With the exception of the ionotropic 5-HT₃ receptor, all other 5-HT receptors are G-protein coupled receptors (metabotropic) and act through intracellular signaling pathways to hyperpolarize (in the case of 5-HT₁ receptors) or depolarize (5-HT_{2/4/5/6/7}) their host cells (see Barnes and Sharp, 1999 for review). In contrast, the 5-HT₃ receptor is an ion channel (Yakel and Jackson, 1988; Derkach et al., 1989) and agonist binding at these receptors results in an inward flux of cations and thus an excitation of the host cell (Yakel and Jackson, 1988). Table I lists 5-HT ligands that have been utilized to investigate 5-HT receptor subtype regulation of DA neurons.

While all 5-HT receptor subtypes are localized postsynaptically on 5-HT target cells, the 5-HT_{1A} and 5-HT_{1B/D} subtypes are also located presynaptically on 5-HT neurons. In the raphe nuclei, 5-HT_{1A} autoreceptors are localized on 5-HT cell bodies and dendrites where they function as autoreceptors. 5-HT is released somatodendritically and decreases 5-HT cell firing

by activating these receptors. At low doses, experimentally employed 5-HT_{1A} agonists such as 8-OHDPAT preferentially stimulate these autoreceptors and thus decrease serotonergic function (Carey et al., 2004). At higher doses, postsynaptic 5-HT_{1A} receptors are also stimulated with a net increase in 5-HT_{1A}-mediated functions. In addition to their localization on non-5-HT neurons, 5-HT_{1B/1D} receptors also serve as autoreceptors. However, these receptors are localized presynaptically on 5-HT nerve terminals where they serve to regulate 5-HT release.

5-HT/DA Interactions and Mental Disorders/States

Schizophrenia

The hallmark of schizophrenia is a profound disturbance of thought processes. This is manifested by cognitive impairments such as deficits in working memory. In addition, so-called positive symptoms such as hallucinations and delusions, and negative symptoms such as anhedonia may be present. Antipsychotic drugs bind to a multiplicity of receptor subtypes including the DA D₂ receptor. Typical antipsychotic drugs like haloperidol are strong D₂ antagonists, blocking dopaminergic action in the striatum, and thereby inducing extrapyramidal motor side effects. In contrast, many newer atypical antipsychotic drugs that by definition do not induce extrapyramidal motor symptoms (e.g. clozapine, ziprasidone) display relatively higher affinities for several 5-HT receptor subtypes, including the 5-HT_{1A}, 5-HT_{2A}, and 5-HT_{2C} receptors.

The ability of antipsychotic drugs to alleviate positive symptoms is highly correlated with their ability to bind to D₂ receptors. This finding led to the proposition that schizophrenia reflects excessive dopaminergic activity. Current evidence suggests that this proposition is valid for mesostriatal DA neurons. Recent imaging studies of the dorsal striatum suggest enhanced DA release following amphetamine administration in schizophrenics relative to controls (Laurelle et al., 1999). However, many clinically efficacious atypical antipsychotic drugs are relatively poor DA receptor blockers. Despite this fact, preclinical *in vivo* studies demonstrate that these drugs profoundly affect the physiology of DA neurons. Administration of most of these atypical agents selectively increases mesocortical DA activity. Since diminished activity of the PFC has been associated with the negative symptoms and cognitive deficits of schizophrenia, a hypofunction of the mesocortical DA pathway has been postulated (Weinberger, 1987). Thus, the efficacy of atypical drugs may be related to their ability to elevate baseline DA tone in the PFC. There is increasing evidence that this stimulatory effect is indirect and mediated by actions on 5-HT receptors that regulate DA cell function, perhaps in concert with other properties such as affinity for DA D₁, D₂, and/or other receptors. In this regard, most research has focused on the 5-HT_{2A}, 5-HT_{2C}, and 5-HT_{1A} receptors. Hallucinogens such as LSD are agonists at the 5-HT_{2A} receptor and their behavioral effects resemble the positive symptoms of schizophrenia (Vollenweider et al., 1998). As a class, atypical antipsychotic drugs have high affinities for this site. Initially thought to be pure antagonists, it is now known that many of these drugs (e.g. clozapine) are 5-HT_{2A} inverse agonists (Weiner et al., 2001). Additionally, many atypicals are also 5-HT_{2C} inverse agonists and/or 5-HT_{1A} agonists. Their ability to alter dopaminergic function and treat schizophrenic symptoms may be due in part to actions on one or more of these 5-HT receptor subtypes.

Depression/Anxiety

Antidepressant drugs are used to treat both depression and anxiety and thus these disorders may share some common neurobiological mechanisms. Most drugs block the reuptake sites (transporters) that remove 5-HT and/or norepinephrine (NE) from the synapse. Selective-serotonin-reuptake inhibitors (SSRIs) selectively block the 5-HT transporter (SERT), elevating synaptic 5-HT by blocking 5-HT clearance and non-specifically activating all 5-HT receptors.

Although neurobiological theories of depression have focused on 5-HT and/or NE systems per se, recent evidence suggests a contributing role for DA in symptoms and/or efficacy of therapeutics (Zangen et al., 2001). Several antidepressant drugs (e.g. mianserin, nefazadone) bind with high affinity to 5-HT₂ receptors, receptors that have been implicated in the regulation of DA systems (Millan, 2005). In fact, the prototypical SSRI fluoxetine is a 5-HT_{2C} antagonist (Ni and Miledi, 1997). Alterations in 5-HT_{2C} receptors have also been observed in suicide victims (Niswender et al., 2001). Deficits in dopaminergic signaling in the mesolimbic pathway have been implicated in the anhedonia associated with depression and psychostimulant drug withdrawal (Nestler and Carlezon, 2006). Many of the symptoms of depression resemble the negative symptoms of schizophrenia (e.g. apathy, psychomotor retardation) and thus may be related to dopaminergic dysfunction of the PFC. Increasingly, atypical antipsychotic drugs are used to treat depression (Brugue and Vieta, 2006). In addition, stress has been implicated in the etiology of depression and anxiety and has profound effects on the PFC, including the relatively selective activation of the mesocortical DA pathway (e.g. Abercrombie et al., 1989; Thierry et al., 1976). 5-HT_{2C} receptors have also been implicated in anxiety (Kennett et al., 1996, 1997). Thus, it is increasingly important to understand the role of 5-HT/DA interactions in depression, anxiety, and their treatments.

Drug Abuse/Addiction

A common action of acutely administered addictive drugs is an increase in mesolimbic DA activity. For some classes of drugs this is a direct effect. For example, psychostimulants such as cocaine block the DA transporter (DAT) and thereby increase synaptic levels of DA by reducing DA clearance. Amphetamines have the additional property of directly inducing DA release through this transporter site. However, many other abused drugs indirectly enhance mesolimbic function by acting on non-dopaminergic receptors that modify activity in a neuronal circuit. For example, opiates inhibit the activity of γ -aminobutyric acid (GABA) interneurons that normally inhibit mesolimbic DA neurons, resulting in a disinhibition of dopaminergic activity. Since studies also implicate DA in natural reward, much research has focused on the dopaminergic substrates of addiction. However, multiple previous studies have also demonstrated interactions with serotonergic systems. As described in later sections, blocking or stimulating several 5-HT receptor subtypes including the 5-HT_{1B}, 5-HT_{2A}, 5-HT_{2C}, and 5-HT₃ subtypes modulates both the neurochemical (increase of mesolimbic DA activity) and the behavioral effects of addictive drugs. These findings suggest that 5-HT receptors regulate mesolimbic DA activity in response to the acute administration of abused substances. Thus, elucidating how 5-HT modulates DA for each 5-HT receptor subtype and each drug of abuse is important for the understanding of drug abuse/addiction and the development of potential therapeutics.

5-HT_{1A}

Localization

The 5-HT_{1A} receptor is negatively coupled to adenylate cyclase through the G protein G_{i/o}. Receptor binding, *in situ* hybridization and protein immunohistochemistry have been utilized to examine the distribution and the cellular and subcellular localization of 5-HT_{1A} receptors in the brain. As previously mentioned, 5-HT_{1A} receptors are dense in the raphe nuclei where they serve as somatodendritic autoreceptors (Pazos and Palacios, 1985; Pompeiano et al., 1992). These receptors are also localized postsynaptically in corticolimbic DA terminal brain areas such as the PFC, amygdala, and hippocampus. Neither receptor binding nor mRNA has been detected in the striatum although low levels are found in other basal ganglia regions such as the claustrum (Pompeiano et al., 1992). There are few 5-HT_{1A} receptors in the NA (Pompeiano et al., 1992) but they appear to be functionally important as discussed below. While earlier studies did not observe mRNA or protein in the substantia nigra (SN) or VTA

(Pompeiano et al., 1992), a more recent electron microscopy study found colabeling of 5-HT_{1A} receptor protein with tyrosine hydroxylase (TH), the rate-limiting enzyme for the synthesis of DA (Doherty and Pickel, 2001). The receptor was primarily localized to the parabrachial subdivision of the VTA which projects preferentially to the PFC. In the hippocampus and cortex, 5-HT_{1A} receptors are found in pyramidal cells. In the PFC, they are co-localized with 5-HT_{2A} receptors (Santana et al., 2004). 5-HT_{1A} mRNA is also observed in cortical GABAergic cells (Santana et al., 2004). However, there is controversy regarding their subcellular localization. Riad et al. (2000) reported a primarily somatodendritic localization of 5-HT_{1A} receptor protein in rat brain, including cells in the raphe as well as pyramidal neurons in the cortex and hippocampus. However, using a different receptor antibody, Azmitia and colleagues (1996) localized protein in axons of pyramidal cells in the cortex and hippocampus in rat, monkey, and human (DeFelipe et al, 2001; Cruz et al., 2004). Thus, further work must be performed in order to resolve this issue.

Nigrostriatal Pathway

In vivo extracellular recordings of midbrain DA neurons have demonstrated a stimulatory effect of systemically administered 5-HT_{1A} receptor agonists. Intravenous administration of the agonist 8-OHDPAT increased the firing rate of a subpopulation of nigrostriatal neurons, those that were slowly firing (Kelland et al., 1990). However, evidence indicates that this effect is indirect and reflects a *decrease* in serotonergic function mediated by 5-HT_{1A} autoreceptor-induced decreases in 5-HT release. In support of this explanation, depletion of 5-HT by the neurotoxin 5,7-dihydroxytryptamine (5,7-DHT) blocked the augmentation of firing rate induced by 8-OHDPAT administration (Kelland et al., 1990). Thus, 5-HT may normally inhibit SN DA cell firing and removal of this inhibition (disinhibition) by activation of 5-HT_{1A} autoreceptors may increase DA cell firing rate. However, increasing endogenous 5-HT by the administration of fenfluramine or administration of a non-selective 5-HT receptor agonist increases somatodendritic (but not nerve terminal) DA release (Cobb and Abercrombie, 2003). This dendritic release is believed to be mediated by 5-HT-induced calcium spikes. It is possible that this released DA acts to stimulate presynaptic DA autoreceptors, thereby reducing SN cell firing.

In vivo studies are generally not supportive of a role for 5-HT_{1A} receptors in the regulation of DA release in the striatum. 8-OHDPAT administration was reported to preferentially increase cortical DA relative to the dorsal striatum and NA (Arborelius et al., 1993a). While administration of 8-OHDPAT reverses D2 antagonist-induced catalepsy (Wadenberg and Ahlenius, 1991), others have provided evidence that this effect is not mediated by alterations in DA neurotransmission (Neal-Beliveau et al., 1993; Lucas et al., 1997). These latter authors demonstrated that while 8-OHDPAT administration reversed haloperidol-induced catalepsy, it did not modify basal or haloperidol-stimulated DA outflow in the striatum. This lack of effect is parsimonious with the lack of anatomical data showing 5-HT_{1A} receptor localization in the SN or dorsal striatum. However, one report found that treatment with 8-OHDPAT inhibited basal and clozapine-stimulated DA release in the striatum and NA; these decreases were blocked by administration of the 5-HT_{1A} receptor antagonist WAY 100,635 (Ichikawa and Meltzer, 2000). Thus, more studies of the nigrostriatal system must be conducted.

Mesolimbic Pathway

In vivo electrophysiological studies demonstrate that systemic administration of the 5-HT_{1A} receptor agonist 8-OHDPAT increased the firing rate and burst firing of DA neurons in the VTA (Arborelius et al., 1993b). Stimulation of DA neurons was also observed with the agonists flesinoxan and S 15535 and these effects were blocked by the selective antagonist WAY 100,635 (Lejeune and Millan, 1998). The iontophoretic application of 8-OHDPAT into the

midbrain excited DA neurons in VTA and SNpc *in vivo* (Arborelius et al., 1993a), suggesting a midbrain site of action.

Corresponding to these findings, multiple studies have shown that 5-HT_{1A} receptor ligands modulate DA-mediated behavior and DA release in the NA. However, the direction of agonist effects may depend upon whether presynaptic 5-HT_{1A} autoreceptors in the raphe are preferentially stimulated or postsynaptic 5-HT_{1A} sites in other brain regions are also engaged. Systemic administration of low doses of 8-OHDPAT (0.05 mg/kg) have been reported to preferentially stimulate autoreceptors. Administration of these doses decreased locomotion; these effects were reversed by treatment with the antagonist WAY 100,635 (Carey et al., 2004). Systemic administration of the 5-HT_{1A} receptor *antagonist* p-MPPF augmented cocaine-induced, but not basal, DA release in the NA (Andrews et al., 2005). These authors provided further evidence that this effect was mediated by blockade of 5-HT autoreceptors in the raphe nucleus. In support of this interpretation, infusions of the agonist 8-OHDPAT directly into the dorsal raphe decreased basal 5-HT and DA release (Yoshimoto and McBride, 1992) and acute cocaine-stimulated 5-HT release (Szumlinski et al., 2004) in the NA. However, this latter study found that such infusions increased extracellular DA and glutamate in the NA and potentiated cocaine-induced motor activity. Recent evidence indicates the presence of 5-HT_{1A} receptors on distinct DA cell subpopulations in the VTA (Doherty and Pickel, 2001). Thus, conflicting studies may reflect actions on different subpopulations and require further clarification.

While few studies have been conducted, stimulation of postsynaptic 5-HT_{1A} receptors in the NA may enhance mesolimbic DA function. The effects of higher doses of systemically administered 8-OHDPAT may reflect actions on this receptor population. Systemic treatment with moderate doses of 8-OHDPAT increased cocaine-induced locomotion (De La Garza and Cunningham, 2000; Carey et al., 2004). Local infusions of 8-OHDPAT by reverse dialysis into the NA potentiated cocaine-stimulated locomotion but did not affect cocaine-mediated increases in NA 5-HT, arguing that the effects of 8-OHDPAT on postsynaptic receptors were not caused by changes in NA 5-HT release. These investigators did not measure DA so no conclusions can be reached regarding the potential mediation of 8-OHDPAT behavioral effects by alterations in mesolimbic DA. Thus, similar to the nigrostriatal system, much more work must be performed in order to determine if and how 5-HT_{1A} receptors regulate the mesolimbic DA system.

Mesocortical Pathway

Much more data is available for the mesocortical DA system. Multiple studies have shown that the systemic administration of 5-HT_{1A} receptor agonists increases DA release in the PFC and this is blocked by treatment with the 5-HT_{1A} antagonist WAY 100,635 (Rollema et al., 2000). For example, recent work demonstrates that the 5-HT_{1A} receptor agonist BAY x 3702, administered i.v., increased the firing rate and burst firing of VTA DA neurons (Díaz-Mataix et al., 2005). BAY x 3702 administration also increased DA release in the VTA and the PFC and these effects were blocked by treatment with WAY-100,635. The atypical antipsychotic drug clozapine is a weak partial agonist at the 5-HT_{1A} receptor (Assié et al., 2005). This has led to the suggestion that the therapeutic properties of atypical antipsychotic drugs may be related to 5-HT_{1A} receptor agonism alone or after combination with D₂ receptor antagonism (Millan, 2000; Meltzer et al., 2003). In support of this, 8-OHDPAT administration potentiated D₂ receptor antagonist (sulpiride)-induced DA efflux in the PFC and NA but not the striatum (Ichikawa and Meltzer, 1999). However, while clozapine-induced increases in cortical DA were partially antagonized by WAY 100,635 administration in one study (Rollema et al., 1997), this blockade was not observed by others (Millan et al., 1998b). Evidence has been provided that combined 5-HT_{2A} and D₂ receptor blockade increases cortical DA release

via 5-HT_{1A} receptor activation (Ichikawa et al., 2001). Thus, while it is clear that 5-HT_{1A} agonism increases mesocortical DA function, it is not clear whether the dopaminergic effects of clozapine are due to this property.

Recent work has addressed the localization of 5-HT_{1A} receptor effects in the mesocortical system (Díaz-Mataix et al., 2005). Reverse dialysis of the 5-HT_{1A} receptor agonist BAY x 3702 produced a biphasic effect on PFC DA in the mouse and the rat: a low concentration increased, while a higher concentration decreased, DA. Both effects appeared to be due to actions on 5-HT_{1A} receptors for they were not observed in the 5-HT_{1A} receptor knockout mouse (Díaz-Mataix et al., 2005). The observed increase in cortical DA after local administration was similar to that observed following the systemic (i.v.) administration of BAY x3702. This increase may be due to actions on pyramidal glutamatergic cells projecting to the VTA for frontocortical transection blocked the effects of i.v. BAY x3702. The decrease in DA following a higher concentration may have been mediated by actions on cells containing GABA) in the cortex for it was not observed when GABA-A receptors were blocked by perfusion with bicuculline. Thus, a complex circuitry may underlie the regulation of DA release by cortical 5-HT_{1A} receptors.

Summary

While 5-HT_{1A} receptors appear to regulate nigrostriatal DA cell activity, most data do not indicate an effect on DA release in this pathway. There is more evidence to support a role for a stimulatory effect of postsynaptic 5-HT_{1A} receptors on mesocorticolimbic DA cell activity, release, and behavior. This is particularly true for the mesocortical system, where data indicate that 5-HT_{1A} activation may modulate the activity of corticotegmental, presumably glutamatergic, projections regulating DA neurons.

5-HT_{1B}

Localization

Like the 5-HT_{1A} receptor, the 5-HT_{1B} receptor is negatively coupled to adenylate cyclase (Bouhelal et al., 1988; Hoyer and Schoeffter, 1988; Adham et al., 1991; Hamblin and Metcalf, 1991; Levy et al., 1992; Weinshank et al., 1992). *In situ* hybridization studies have revealed high levels of 5-HT_{1B} receptor mRNA in several brain areas including the NA, caudate putamen, dorsal raphe nucleus and some cortical areas (Boschert et al., 1994; Brunivels et al., 1994). High levels of 5-HT_{1B} binding are present in both the SN and the VTA but DA cells do not express 5-HT_{1B} mRNA (Brunivels et al., 1993; Sari et al., 1999). Rather, multiple studies demonstrate that 5-HT_{1B} receptors are located on axon terminals where they act as autoreceptors or presynaptic heteroreceptors (Boschert et al., 1994; Sari et al., 1999).

Nigrostriatal Pathway

In vivo work shows that striatal 5-HT_{1B} receptors facilitate nigrostriatal DA release (Benloucif and Galloway, 1991; Benloucif et al. 1993; Galloway et al 1993; Ng et al., 1999). Work in striatal synaptosomes, however, suggests an inhibitory role for these receptors (Sarhan et al. 1999, 2000). It is possible that an overall facilitation overshadows this inhibitory effect *in vivo* but requires feedback to the SN and is therefore not observed in synaptosomes. Additional studies are required to resolve these conflicting results.

Mesolimbic Pathway

The bulk of the research to date on 5-HT_{1B} receptor-mediated control of dopaminergic activity involves the mesolimbic pathway, where these receptors have been shown to facilitate DA release. Studies have shown that the administration of a 5-HT_{1B} agonist, such as CP 93129, into the terminal region of this pathway, the NA, results in a local increase in DA (Hallbus et

al., 1997; Yan and Yan, 2001a). It is doubtful that the relevant 5-HT_{1B} receptors reside on dopaminergic terminals in the NA, as 5-HT_{1B} receptor mRNA has not been detected in the cell body region for these projection neurons (Boschert et al., 1994; Bruinvels et al., 1994). While stimulation of NA 5-HT_{1B} receptors phasically increases DA release, administration of the 5-HT_{1B} antagonist GR127935 alone into the NA has no effect on basal NA DA levels (Hallbus et al. 1997). This result indicates that NA 5-HT_{1B} receptors do not tonically modulate mesolimbic DA release.

More is known about the regulation of this pathway by 5-HT_{1B} receptors located in the VTA. Administration of the 5-HT_{1B} receptor agonist CP 93129 into the VTA has been shown to increase DA levels in the NA (Yan and Yan, 2001a; O'Dell and Parsons, 2004; Yan et al., 2004) and concurrently decrease GABA in the VTA (O'Dell and Parsons, 2004; Yan et al., 2004). Systemic 5-HT_{1B} agonism also decreases VTA GABA (Parsons et al., 1999). These studies suggest that 5-HT_{1B} receptors within the VTA regulate mesolimbic DA activity by inhibiting GABA release. Supporting this circuitry, administration of the 5-HT_{1B} agonist CP 93129 inhibits high-potassium-induced [³H]GABA release from VTA slices (Yan and Yan, 2001b). Additionally, work in rat and guinea pig slices of the VTA has shown that the application of 5-HT or a 5-HT_{1B} agonist reduces the amplitude of GABA-B IPSPs in DA neurons (Johnson et al., 1992; Cameron and Williams, 1994, 1995). Coadministration of a 5-HT_{1B} antagonist blocked the inhibitory effect of 5-HT on the GABA-B IPSP (Johnson et al., 1992; Cameron and Williams, 1995), while spiperone, an antagonist for 5-HT_{1A/2} receptors, did not (Johnson et al., 1992). Some investigators propose that the relevant 5-HT_{1B} heteroreceptors are located on the axon terminals of GABAergic projection neurons from the NA (O'Dell and Parsons, 2004; Yan and Yan 2001a). This proposed circuitry would parallel that of the nigrostriatal system where anatomical studies have provided strong evidence that 5-HT_{1B} receptors are located on the terminals of striatonigral GABA neurons and modulate nigrostriatal DA release in a GABA-mediated manner (Bruinvels et al., 1994; Sari et al., 1999; Waeber and Palacios, 1989). However, it must be noted that the circuitry for the mesolimbic system has not yet been extensively studied. Because *in situ* hybridization studies show a lack of 5-HT_{1B} receptor mRNA in the VTA (Bruinvels et al., 1994), it is unlikely that 5-HT_{1B} receptors on GABAergic interneurons in this region are responsible for the GABA-mediated effects of 5-HT_{1B} agonists on mesolimbic DA activity. It is, however, possible that the relevant 5-HT_{1B} receptors are located on terminals of GABA afferents from regions other than the NA, such as the ventral pallidum (Yan and Yan, 2001b).

The ability of extracellular 5-HT to facilitate mesolimbic DA release through 5-HT_{1B} receptors has implications for psychostimulant abuse. It is known that 5-HT_{1B} receptor agonism partially substitutes for cocaine in drug discrimination studies (Callahan and Cunningham, 1995, 1997) and enhances cocaine-conditioned place preference (Cervo et al., 2002), cocaine discriminative-stimulus effects (Callahan and Cunningham, 1995, 1997), and cocaine self administration (Parsons et al., 1998). In addition, overexpression of 5-HT_{1B} receptors on terminals of NA projection neurons to the VTA resulted in enhanced cocaine-induced hyperlocomotion and a left-ward shift in the dose-response curve for cocaine-conditioned place preference indicating an enhancement of the rewarding effects of cocaine (Neumaier et al., 2002). Likewise, studies have shown that systemic or intra-VTA 5-HT_{1B} receptor agonism (CP 93129 and RU 24969 respectively) potentiates the cocaine-induced increase in DA in the NA and decrease in GABA in the VTA (Parsons et al., 1999; O'Dell and Parsons, 2004). Figure 1 illustrates the circuitry suggested by this body of data. Presumably, in addition to blockade of DAT, cocaine acts at the 5-HT transporter to increase extracellular levels of 5-HT and thus 5-HT_{1B} receptor stimulation. Dopaminergic activity from the mesolimbic pathway may then be disinhibited by the stimulation of 5-HT_{1B} receptors on GABAergic projection neurons from the NA to the VTA, resulting in a potentiated response to cocaine. Indeed, studies have shown that pretreatment with a 5-HT_{1B} receptor antagonist (GR 55562 or GR 127935), disrupts the

discriminative stimulus effects of cocaine (Filip et al., 2003) as well as cocaine self-administration (David et al., 2004). Taken together, these data suggest that 5-HT_{1B} receptors play a permissive role in the reinforcing properties of cocaine. It must be noted, however, that cocaine acts at the 5-HT and DA transporters to increase extracellular levels of both transmitters and subsequent binding to a variety of receptors, notably the D1 and D2 DA receptor subtypes. Among 5-HT receptors, subtypes other than the 5-HT_{1B} also modulate the behavioral and neurochemical effects of cocaine (discussed below). Thus, the 5-HT_{1B} receptor is one of many receptors implicated in drug abuse, reward and addiction. The 5-HT_{1B} receptor studies described here suggest that ligands with properties that include the ability to antagonize 5-HT_{1B} receptors may have potential for the treatment of drug abuse.

Mesocortical Pathway

Less is known about 5-HT_{1B} receptor regulation of the mesocortical pathway, but studies suggest a facilitative role. Local application of 5-HT or a 5-HT_{1B} receptor agonist (CP 93129 or CP 94253) in the PFC increases PFC DA and this effect is blocked by the 5-HT_{1B} receptor antagonist GR 127935 (Iyer and Bradberry 1996). In addition, local pretreatment with GR 127935 has been shown to attenuate the increase in PFC DA seen in response to intracortical administration of the SSRI fluoxetine. This result suggests that fluoxetine-induced increases in synaptic 5-HT levels activate 5-HT_{1B} receptors and thereby act to facilitate DA release in the PFC (Matsumoto et al., 1999).

Summary

Studies to date suggest that 5-HT_{1B} receptors facilitate DA release. However, there is some controversy over the facilitatory role for these receptors in the nigrostriatal pathway. While evidence suggests a permissive role for 5-HT_{1B} receptors in the mesocortical system, more studies are needed to corroborate these data. The mesolimbic system has been extensively studied and it is known from these data that 5-HT_{1B} receptors in the VTA have the ability to facilitate DA release by inhibiting the release of GABA in this region. Likewise, 5-HT_{1B} antagonists have both the ability to prevent the facilitation of DA release in stimulated conditions and to prevent the reinforcing effects of cocaine, rendering 5-HT_{1B} antagonism a desired property for putative treatments for drug abuse.

5-HT_{1D}

What was once called the 5-HT_{1D} receptor in guinea pig and human is now known to be a species homologue of the 5-HT_{1B} receptor and is now called the 5-HT_{1D β} receptor (see Adham et al., 1991 for review). The 5-HT_{1D α} receptor is, however, a distinct subtype. 5-HT_{1D α} receptors have been shown to have a similar distribution in the brain as 5-HT_{1B} receptors, albeit at much lower levels in all regions (Bruinvels et al., 1993, 1994). To date, 5-HT_{1D α} receptors have no known role in modulating DA release in the brain.

5-HT_{1E} and 5-HT_{1F}

mRNA for the 5-HT_{1E} receptor subtype is present in dopaminergic brain regions including the caudate, putamen and amygdala as well as cortical areas (Bruinvels et al., 1994). Likewise, mRNA for the 5-HT_{1F} receptor subtype has been detected in hippocampus as well as cortical areas (Bruinvels et al., 1994). No evidence has yet been presented suggesting a role for 5-HT_{1E} or 5-HT_{1F} receptors in the modulation of dopaminergic activity.

5-HT2A

Localization

5-HT2 receptors, including the 5-HT2A, are coupled to Gq. Receptor activation results in the stimulation of phospholipase C and the production of inositol phosphates. These receptors have considerable constitutive activity as many 5-HT2A “antagonists” are actually inverse agonists (Weiner et al., 2001). However, since the physiological significance of this is not known, and these ligands are widely referred to as antagonists, this term will be used here. Autoradiographic binding studies indicate that 5-HT2A/C receptors are located in 5-HT terminal regions, and are particularly dense in the deeper cortical layers, including the prefrontal and anterior cingulate cortices (Pazos et al., 1985; Fischette et al., 1987). More recently, immunohistochemical (Willins et al., 1997; Cornea-Hebert et al., 1999) and *in situ* hybridization studies (Pompeiano et al., 1994; Wright et al., 1995) have also demonstrated high levels of 5-HT2A receptors in the rat PFC. Multiple laboratories have shown that prefrontal 5-HT2A receptors are localized primarily to the apical dendrites of pyramidal neurons with a minor localization to parvalbumin-labeled GABA interneurons (Willins et al., 1997; Hamada et al., 1998; Jakab and Goldman-Rakic, 1998; Cornea-Hebert et al., 1999; Miner et al., 2003). These studies suggest that prefrontocortical 5-HT2A receptors are localized postsynaptically on excitatory amino acid efferents or GABAergic interneurons. Recent work indicates that 5-HT2A receptors may regulate the activity of corticotegmental projection neurons which, in turn, regulate the activity of DA neurons (Pehek et al., 2006; see below). There is also evidence that some 5-HT2A receptors are localized on axonal fibers of pyramidal cells in the monkey (Jakab and Goldman-Rakic, 1998) and that 5-HT stimulates glutamate release from these fibers in the rat (Aghajanian and Marek, 1997).

Earlier work indicated that 5-HT2A receptors are not on DA or 5-HT presynaptic terminals since neither 6-OHDA lesions of DA neurons or 5,7-DHT lesions of 5-HT neurons altered 5-HT2 receptor binding (Leysen et al., 1982; Leysen et al., 1983). However, a recent electron microscopy study found that 24% of PFC profiles labeled with a 5-HT2A receptor antibody were presynaptic axons and varicosities (Miner et al., 2003). Most of these had morphological features of monoamine axons. Thus, a role for presynaptic regulation of DA release cannot be discounted. We have previously shown that intracortical infusions of the 5-HT2A antagonist M100907 block local potassium (K^+)-stimulated DA release in the PFC (Pehek et al., 2001). Since high K^+ stimulates transmitter release by depolarizing nerve terminals, it is possible that M100907 may have acted to block DA efflux through actions on 5-HT2A receptors localized presynaptically on DA terminals. Further work must be performed to test this hypothesis.

Immunohistochemical studies with conventional microscopy have indicated there is a low density of 5-HT2A receptors in the VTA and SN (Cornea-Hebert et al., 1999). Employing immunohistochemistry with confocal microscopy, we have recently demonstrated that some of these receptors are colocalized with TH, indicating that they are on DA neurons in the VTA (Nocjar et al., 2002). This is in agreement with a previous electron microscopy study (Doherty and Pickel, 2000). Our work with confocal microscopy also indicated that 5-HT2A receptors were sparsely distributed on non-TH-positive cells in the VTA. While these cells are presumably GABAergic, this has not been tested.

While receptor binding studies demonstrate relatively high levels of 5-HT2A receptors in the striatum, mRNA levels are very low (Bubser et al., 2001). Corresponding to this, an immunohistochemical study employing retrograde labeling indicated that most 5-HT2A receptors are localized on striatal afferents with a low density on parvalbumin-containing interneurons (Bubser et al., 2001). These afferents arise mainly from the cortex and globus pallidus but not the SN.

Nigrostriatal Pathway

In vivo microdialysis studies have shown that systemic administration of the 5-HT_{2A} receptor antagonist SR46349B blocks haloperidol-induced DA release in the striatum (Lucas and Spampinato, 2000). M100907 also blocked 3,4-methylenedioxymethamphetamine (MDMA)-evoked DA efflux in the striatum (Schmidt et al., 1994). The mixed 5-HT_{2A/C} receptor agonist DOI potentiated amphetamine-stimulated DA outflow and attenuated apomorphine-induced decreases in DA (Ichikawa and Meltzer, 1995). Few studies have examined the localization of 5-HT_{2A} effects on nigrostriatal DA. One report provided evidence for a role for striatal and nigral 5-HT₂ receptors in MDMA-evoked DA release (Yamamoto et al., 1995). Infusions of the 5-HT_{2A/C} receptor antagonist ritanserin into either the striatum or the ipsilateral SN attenuated MDMA-induced DA release. MDMA treatment also increased GABA release in the SN and this was also blocked by local ritanserin infusions in either brain site. These data indicate a role for striatal and nigral 5-HT₂ receptors in MDMA-evoked nigrostriatal DA release and further suggest potential mediation by GABAergic input to the nigra. Recent electrophysiological work in the freely moving rat demonstrates that systemic administration of SR46349B, but not the 5-HT_{2C} receptor inverse agonist SB 206553, blocked MDMA-induced excitation of striatal neurons (Ball and Rebec, 2005). An imaging study in humans demonstrated that administration of psilocybin, a 5-HT_{2A} and 5-HT_{1A} receptor agonist, displaced binding of the D₂ receptor antagonist [¹¹C]raclopride in the striatum (Vollenweider et al., 1999). This result suggests that psilocybin, possibly by binding to 5-HT_{2A} receptors, increases striatal DA release in humans. Thus, studies to date indicate that 5-HT_{2A} agonism increases activity in the nigrostriatal DA pathway while antagonism decreases evoked release.

Mesolimbic Pathway

Work in the midbrain slice demonstrated that 5-HT acts on 5-HT_{2A} receptors to increase firing in a large population of cells in the VTA (Pessia et al., 1994; Prisco et al., 1994). The depolarization of DA cells was direct because it was not blocked by tetrodotoxin (TTX). However, it was blocked by ketanserin, which displays some selectivity for the 5-HT_{2A} (average K_i = 4.35 nM) versus the 5-HT_{2C} (average K_i = 92.43 nM) receptor (Psychoactive Drug Screening Program (PDSP): <http://pdsp.cwru.edu/pdsp.htm>). This work agrees with our findings that 5-HT_{2A} receptors are localized directly on DA cells in the VTA (Nocjar et al., 2002). Pessia and colleagues (1994) further determined that 5-HT either depolarized or hyperpolarized presumed GABAergic neurons in the VTA. However, the receptor(s) mediating these effects was not determined.

In vivo work in the NA demonstrated that 5-HT-induced increases in NA DA were blocked by local administration of a 5-HT_{2A} receptor antagonist (Parsons and Justice, 1993). Corresponding to this latter finding, McBride and colleagues found that reverse dialysis of the 5-HT₂ receptor agonist DOI increased DA release in the posterior, but not the anterior, NA (Bowers et al., 2000). These studies implicate receptors localized in the NA in the regulation of mesolimbic DA.

Mesocortical Pathway

Atypical, but not typical, antipsychotic drugs robustly increase DA release in the PFC. A common property of these drugs that distinguishes them from the typical agents is high affinity for the 5-HT_{2A} receptor. Thus, a plausible hypothesis was that 5-HT_{2A} receptor antagonism increases cortical DA efflux. Earlier studies demonstrated that administration of the non-selective 5-HT₂ receptor antagonist ritanserin increased nigrostriatal and mesocorticolimbic DA efflux (Devaud et al., 1992; Pehek, 1996; Pehek and Bi, 1997). However, subsequent work has shown that ritanserin may facilitate DA cell activity by antagonizing D₂ receptors (Shi et al., 1995). Multiple subsequent studies have since been performed with the selective 5-HT_{2A} receptor antagonist M100907 and demonstrate that systemic or intracortical administration

blocks DA release evoked by treatment with the 5-HT₂ receptor agonist DOI (Gobert and Millan, 1999; Pehek et al., 2001). More recently, others have demonstrated similar results in the PFC and NA with the systemic administration of 5-HT_{2A} ligands. The 5-HT_{2A} receptor antagonist SR46349B blocked DA release in the NA evoked by the stimulation of the raphe nucleus (De Deurwaerdere and Spampinato, 1999) or the administration of the non-competitive NMDA receptor antagonist MK-801 (Schmidt and Fadayel, 1996). Neither M100907 nor SR46349B affected basal DA release, indicating that 5-HT_{2A} receptors modulate phasic, but not tonic, DA efflux. In another study, injections of M100907 attenuated fluoxetine-induced increases in cortical DA (Zhang et al., 2000). Thus, selective antagonism of 5-HT_{2A} receptors attenuates mesocortical DA release.

In contrast to studies employing the administration of 5-HT_{2A} receptor antagonists alone, the *combined, systemic* administration of D₂ and 5-HT_{2A} receptor antagonists results in a potentiation of cortical DA release (Westerink et al., 2001; Liegeois et al., 2002). Evidence has been provided that this effect may be mediated by actions of released 5-HT interacting with 5-HT_{1A} receptors (Bonaccorso et al., 2002). In addition, this potentiation may result from actions of drugs on DA cells in the VTA. It is clear that, as a class, atypical antipsychotic drugs enhance DA release in the PFC. It is also clear that this effect is not mimicked by selective antagonism of 5-HT_{2A} receptors. Rather, it may result from a combination of receptor binding properties including blockade of 5-HT_{2C} receptors (see below).

Studies employing the local administration of 5-HT_{2A} ligands have examined the localization and neural circuitry underlying 5-HT_{2A} receptor modulation of mesocortical DA. We have demonstrated that intracortical infusions of the 5-HT_{2A} receptor antagonists M100907 or MDL 11,939 blocked the increases in cortical DA produced by the systemic administration of the 5-HT₂ receptor agonist DOI (Pehek et al., 2001; Pehek et al., 2006). Furthermore, infusions of M100907 blocked physiologically-induced DA release in the PFC, namely that produced by a mild stressor (gentle handling; Pehek et al., 2006). These results specifically implicate 5-HT_{2A} receptors localized in the cortex. As discussed above, regulation of mesocortical DA by cortical 5-HT_{2A} receptors may involve a polysynaptic neural circuit. One possibility is that the relevant 5-HT_{2A} receptors are localized on corticotegmental glutamatergic projections that synapse on mesocortical DA neurons (see Figure 2). It is known that a subset of cortical pyramidal neurons synapse on mesocortical DA cell bodies in the VTA (Sesack and Pickel, 1992). Electrophysiological studies indicate that stimulation of cortical 5-HT_{2A} receptors increases pyramidal cell activity (Marek and Aghajanian, 1996). Thus, 5-HT_{2A} receptor agonism may increase the activity of corticotegmental glutamatergic projection neurons. This suggestion is supported by our recent finding that systemic administration of the 5-HT₂ receptor agonist DOI increased glutamate efflux in the VTA (Pehek et al., 2006). Infusions of M100907, directly into the PFC, blocked this increase, implying that the relevant 5HT_{2A} receptors were localized in the PFC (Pehek et al., 2006). In the same animals, treatment with DOI increased PFC DA efflux and this was also blocked by intracortical administration of M100907 (Pehek et al., 2006). Thus, 5-HT_{2A} receptor-mediated stimulation of corticotegmental projections may result in enhanced glutamate efflux in the VTA, which subsequently stimulates glutamate receptors on VTA mesocortical neurons (Kalivas, 1993), increases DA neuronal activity (Seutin et al., 1990; Overton and Clark, 1992), and induces DA release in the PFC (Kalivas et al., 1989). In support of this, we have shown that combined blockade of NMDA and AMPA receptors in the VTA blocks 5-HT₂ receptor agonist (DOI)-induced DA efflux in the PFC (unpublished observations). Recent electrophysiological evidence by Artigas and co-workers also supports this interpretation (Bortolozzi et al., 2005). These investigators found that either the systemic or intracortical administration of DOI increased mesocortical DA neuronal activity which was blocked by the intracortical administration of 5-HT_{2A} receptor antagonists. This group has previously shown that cortical

5-HT_{2A} receptors regulate 5-HT release in the PFC through a similar long-loop pathway, in this case involving efferent projections to the dorsal raphe nucleus (Martin-Ruiz et al., 2001).

As previously mentioned, we have shown that 5-HT_{2A} receptors are localized on a subset of DA cells in the VTA (Nocjar et al., 2002). A physiological role for these receptors is largely unknown. One recent study provided evidence for a role for VTA 5-HT_{2A} receptors in the regulation of mesolimbic DA (Auclair et al., 2004). Injections of SR46349B into the VTA blocked both amphetamine-induced locomotion and DA release in the NA.

Recent behavioral studies demonstrate that selective 5-HT_{2A} receptor blockade attenuates DA-mediated behaviors. Administration of the 5-HT_{2A} antagonist SR 46349B (1.0 mg/kg or less) attenuates hyperactivity induced by either the acute or repeated administration of cocaine (Filip et al., 2004). Treatment with M100907 reversed behavioral deficits in locomotor activity and prepulse inhibition of acoustic startle in DAT knockout mice (Barr et al., 2004). In addition to behavioral abnormalities, these mice display elevated synaptic levels of DA (Gainetdinov et al., 1999). The authors suggest that 5-HT_{2A} antagonists may be useful in the treatment of conditions characterized by chronic, elevated dopaminergic tone.

Summary

Activation of 5-HT_{2A} receptors stimulates dopaminergic activity in all three pathways although most work has been performed in the mesocortical system. Investigations into the circuitry of this regulation indicate that 5-HT_{2A} receptors on corticotegmental projections regulate DA cellular activity. A functional role for 5-HT_{2A} receptors localized on VTA DA neurons remains to be determined.

5-HT_{2B}

Evidence suggests that 5-HT_{2B} receptors are located primarily in the stomach fundus (Duxon et al., 1997). The limited number of these receptors in the brain has been shown to be restricted to the cerebellum, lateral septum, dorsal hypothalamus, and medial amygdala (Duxon et al., 1997). There is a paucity of evidence favoring a role for 5-HT_{2B} receptors in modulating dopaminergic activity.

5-HT_{2C}

Localization

Like the 5-HT_{2A} receptor, 5-HT_{2C} (formerly 5-HT_{1C}) receptor stimulation results in phospholipase C-mediated phosphoinositide hydrolysis and a consequential rise in the intracellular calcium concentration of the host cell (Conn and Sanders-Bush, 1986; Julius et al., 1988; Sanders-Bush et al., 1988; Labrecque et al., 1995). The 5-HT_{2C} receptor has also been shown to exhibit substantial spontaneous accumulation of inositol phosphates, indicating that 5-HT_{2C} receptors possess a high level of constitutive activity in the absence of agonist stimulation (see Berg et al., 2005 for review).

In-situ hybridization studies have demonstrated that 5-HT_{2C} receptor mRNA is expressed in the VTA (Hoffman and Mezey, 1989; Molineaux et al., 1989; Pompeiano et al., 1994; Wright et al., 1995; Eberle-Wang et al., 1997), both the pars compacta and pars reticulata subdivisions of the SN (Molineaux et al., 1989; Pompeiano et al., 1994; Wright et al., 1995; Eberle-Wang et al., 1997), and in the terminal regions of the nigrostriatal and mesolimbic dopaminergic pathways: the striatum and the NA (Hoffman and Mezey, 1989; Pompeiano et al., 1994; Wright et al., 1995; Eberle-Wang et al., 1997). There is comparatively less evidence for 5-HT_{2C} receptor mRNA in the PFC, however, several studies have shown the presence of 5-HT_{2C} receptor mRNA in the cingulate or anterior cingulate cortex (Hoffman and Mezey, 1989;

Pompeiano et al., 1994; Wright et al., 1995). Additionally, a study in human brain showed a similar distribution of 5-HT_{2C} receptor mRNA as has been found in rat brain, including expression in the anterior cingulate cortex (Pasqualetti et al., 1999). Fewer studies have examined the localization of 5-HT_{2C} receptor protein. Several immunocytochemistry studies indicate the presence of 5-HT_{2C} receptors in the striatum (Abramowski et al., 1995; Sharma et al., 1997; Clemett et al., 2000) with the most recent study also showing 5-HT_{2C} receptors in the NA and cingulate cortex as well as the SNpr and SNpc (Clemett et al., 2000).

Recent work demonstrates 5-HT_{2C} immunoreactivity in the VTA and suggests that it is at least partially localized to cell bodies (Bubar et al., 2005; Ji et al., 2006). As for the cellular localization of 5-HT_{2C} receptors in other regions, little is known. In the NA and striatum, the morphology of 5-HT_{2C} mRNA containing cells indicates that they may be efferents, suggesting localization to GABAergic projection neurons (Eberle-Wang et al., 1997). This study also showed that 5-HT_{2C} mRNA present in the SN and VTA did not colocalize with TH mRNA, a marker for DA neurons. Rather, all cells in the SN that expressed 5-HT_{2C} receptor mRNA also expressed glutamic acid decarboxylase (GAD) mRNA, a marker for GABAergic cells (see Figure 2). Physiological data (discussed below) also provide evidence that 5-HT_{2C} receptors are localized on GABAergic neurons in the VTA and SN. However, recent work provides anatomical and behavioral support for a localization of 5-HT_{2C} receptors on DA neurons in the VTA (Ji et al., 2006). Because 5-HT_{2C} mRNA and immunoreactivity are, for the most part, expressed in the same brain regions, the receptors are likely to be predominately postsynaptic, rather than autoreceptors on presynaptic terminals (Clemett et al., 2000). However, the possibility that 5-HT_{2C} receptors act as presynaptic heteroreceptors in some regions can not be excluded.

The localization of 5-HT_{2C} receptors in the brain suggests that they are well-positioned to modulate dopaminergic activity in the cell body and/or terminal regions of all three major pathways. In agreement, a large body of evidence illustrates that 5-HT_{2C} receptors inhibit DA release in the striatum, NA and PFC and suggests subtle variations between the roles for these receptors in regulating each pathway.

Nigrostriatal Pathway

It is well established that systemic administration of the 5-HT_{2C} receptor inverse agonist SB 206553 increases the firing rate of DA neurons in the SNpc (DiGiovanni et al., 1999). Although systemic administration of 5-HT_{2C} receptor agonists, including the selective agonist Ro 60-0175, does not significantly decrease basal firing of these neurons (Di Matteo et al., 1999; Di Giovanni et al., 2000), such treatment decreases DA efflux in the striatum (Gobert et al., 2000; De Deurwaerdere et al., 2004; Alex et al., 2005). Likewise, systemic administration of antagonists (SB 242084) (De Deurwaerdere et al., 2004) and inverse agonists (SB 206553) at 5-HT_{2C} receptors increases DA efflux in this region (De Deurwaerdere and Spampinato, 1999; Di Giovanni et al., 1999; Porras et al., 2002b; De Deurwaerdere et al., 2004). These data suggest that 5-HT_{2C} receptors mediate the tonic inhibition of the nigrostriatal pathway either by endogenous 5-HT binding, constitutive activity or a combination of the two. One recent study showed that the 5-HT_{2C} receptor inverse agonist-induced increase in striatal DA was insensitive to the depletion of extracellular 5-HT, suggesting that constitutive activity does indeed play a role in the tonic inhibition (De Deurwaerdere et al., 2004).

There is also evidence that 5-HT_{2C} receptors can modulate the phasic activity of the nigrostriatal pathway. The 5-HT_{2C} inverse agonist SB 206553 has been shown to potentiate cocaine- and morphine-induced increases in striatal DA (Porras et al., 2002b; Navailles et al., 2004). Systemic administration of the 5-HT_{2C} agonist Ro 60-0175 attenuated haloperidol-induced increases in DA in the striatum (Navailles et al., 2004), as well as the nicotine-induced

increase in firing rate of SNpc DA neurons (Pierucci et al., 2004) and striatal DA (Di Matteo et al., 2004).

As most studies to date have employed systemic drug administration, less is known about the location of the relevant receptors. It has been shown that 5-HT_{2C} receptors in the SNpc or SNpr are at least in part responsible for the tonic inhibition of the nigrostriatal system and evidence points to a GABA-mediated effect. Systemic administration of the 5-HT_{2C} receptor agonist mCPP excited SNpr neurons that were presumably GABAergic neurons (DiGiovanni et al., 2001). This effect was blocked by pretreatment with the antagonist SB 242084 (DiGiovanni et al., 2001). Also, Rick et al. (1995) showed that a large percentage of (presumably GABAergic) SNpr cells are excited by a 5-HT_{2C} receptor agonist. Interestingly, these effects were TTX-resistant, and therefore the 5-HT_{2C} receptors responsible for these effects are located on the responsive SNpr neurons (Rick et al., 1995). In addition, we have shown recently that perfusion of the striatum with the 5-HT_{2C} receptor inverse agonist SB 206553 increased striatal DA in a concentration-dependent manner (Alex et al., 2005), supporting a role for striatal 5-HT_{2C} receptors in this regulation. Furthermore, systemic administration of the 5-HT_{2C} agonist mCPP decreased striatal DA and this was blocked by intrastriatal infusions of SB 206553. These results implicate 5-HT_{2C} receptors localized in the striatum in the regulation of nigrostriatal DA.

There is anatomical evidence suggesting that the tonic inhibition of nigrostriatal DA provided by 5-HT_{2C} receptors is indirect and mediated by the stimulation of GABAergic cells. Specifically, it can be proposed that the stimulation (or constitutive activity) of 5-HT_{2C} receptors on GABAergic neurons causes an elevation in GABA release in either the SNpr or the striatum that results in inhibition of dopaminergic activity in this pathway. While it is known that 5-HT_{2C} mRNA colocalizes with GAD mRNA in the SNpr and SNpc (Eberle-Wang et al., 1997), the localization of 5-HT_{2C} receptors or receptor mRNA in the striatum remains unknown. The relevant receptors could be located on the cell bodies of striatonigral GABA neurons that have been shown to synapse in the SN on the dopaminergic dendrites of the nigrostriatal neurons (Bolam and Smith, 1990). It is well known that modifications in striatonigral GABA release can produce downstream effects on nigrostriatal dopaminergic activity. Alternately, the relevant 5-HT_{2C} receptors could be located on GABAergic interneurons within the striatum. It has been shown that dopaminergic terminals in the striatum express GABA-B but not GABA-A receptors (Arias-Montano et al., 1991; Smolders et al., 1995). Additional anatomical studies are required to determine the cell types to which 5-HT_{2C} receptors are localized in each brain region and the circuitry involved in their regulation of nigrostriatal DA release.

Mesolimbic Pathway

5-HT_{2C} receptors also regulate the mesolimbic DA pathway. Here too, systemic administration of agonists (most commonly Ro 60-0175) at 5-HT_{2C} receptors decreases DA efflux in the NA (Di Matteo et al., 1999, 2000, 2004; Di Giovanni et al., 2000; Gobert et al., 2000; De Deurwaerdere et al., 2004) and decreases the firing rate of VTA DA neurons (Prisco et al., 1994; Prisco and Esposito, 1995; Di Matteo et al., 1999, 2000; Di Giovanni et al., 2000; Gobert et al., 2000). The inverse agonist SB 206553 (Di Giovanni et al., 1999; Gobert et al., 2000) and the antagonists mesulergine and SB 242084 (Prisco et al., 1994; Di Matteo et al., 1999 respectively) increase the firing rate of these neurons. Likewise, a corresponding increase in NA DA efflux is seen after systemic administration of inverse agonists (Di Matteo et al., 1998; De Deurwaerdere and Spampinato, 1999; Di Giovanni et al., 1999; Gobert et al., 2000; Porras et al., 2002b; De Deurwaerdere et al., 2004) and antagonists (Di Matteo et al., 1999; De Deurwaerdere et al., 2004). As has been shown for the nigrostriatal pathway, the 5-HT_{2C} receptor inverse agonist-induced increase in NA DA is insensitive to decreases in extracellular

5-HT, suggesting that constitutive activity at these receptors is responsible for the inhibition of DA efflux that is reversed by the drug (De Deurwaerdere et al., 2004).

There is evidence that 5-HT_{2C} receptors also play a role in modulating phasic mesolimbic activity, as concentrations of 5-HT_{2C} ligands that do not affect basal levels of DA in the NA can affect stimulated release. Systemic administration of a 5-HT_{2C} inverse agonist or antagonist potentiates the cocaine-induced increase in NA DA (Navailles et al., 2004). It is possible that the elevated levels of extracellular 5-HT seen after cocaine administration normally provide GABA-mediated negative feedback to the cocaine-stimulated mesolimbic system by acting at 5-HT_{2C} receptors. Thus, antagonism at these receptors would potentiate cocaine-induced increases in NA DA by blocking the 5-HT_{2C} receptor-mediated inhibitory tone (Navailles et al., 2004). In support of this mechanism of action, 5-HT_{2C} receptor knockout mice have been shown to exhibit enhanced cocaine-induced elevations of DA in the NA (Rocha et al., 2002). 5-HT_{2C} antagonists have also been shown to potentiate PCP-induced increases in NA DA, likely by a similar 5-HT-dependant mechanism (Hutson et al., 2000). In addition, the 5-HT_{2C} agonists Ro 60-0175 and MK-212 have been shown to attenuate haloperidol (Navailles et al., 2004) and morphine (Willins and Meltzer, 1998)-induced DA release in the NA respectively. Taken together, these findings suggest a role for 5-HT_{2C} agonists in attenuating the effects of psychostimulants and other drugs of abuse. Interestingly, one recent study suggests that overactivity of mesolimbic 5-HT_{2C} receptors leads to a reduced level of NA DA that may be involved in depression. The authors propose that effective putative antidepressants will antagonize 5-HT_{2C} receptors, which is known to cause these receptors to internalize over time, neutralizing the imbalance (Dremencov et al., 2005).

As previously mentioned, 5-HT_{2C} receptors have been detected on cell bodies in the VTA by immunohistochemistry (Bubar et al., 2005) and there is evidence that these receptors regulate mesolimbic DA release. As discussed for the nigrostriatal system, these effects may be mediated by actions on GABA cells in the VTA. Intra-VTA administration of the 5-HT_{2C} inverse agonist SB 206553 has been shown both to attenuate MDMA-induced increases in VTA GABA and potentiate the concurrent increase in NA DA (Bankson and Yamamoto, 2004). Likewise, systemic administration of a 5-HT_{2C} agonist has been shown to excite all non-DA, presumably GABAergic cells in the VTA, suggesting that 5-HT_{2C} receptors in this region are localized to GABAergic neurons (Di Giovanni et al., 2001). In addition, one study demonstrated that local administration of the 5-HT_{2C} receptor antagonist RS 102221 increased NA DA, suggesting that, like the nigrostriatal pathway, the mesolimbic pathway is tonically regulated by 5-HT_{2C} receptors in its terminal region (Dremencov et al., 2005). The cellular localization of these receptors in the NA is, however, unknown. While most work to date suggests that 5-HT_{2C} receptors tonically inhibit dopaminergic activity in a GABA-mediated manner, a recent study suggests an alternate mechanism. Ji et al. (2006) provide strong correlative evidence that 5-HT_{2C} receptors in the VTA are localized, at least in part, to DA neurons. Their data indicate that 5-HT_{2C} receptors on VTA DA neurons physically interact with the tumor suppressor PTEN (phosphatase and tensin homolog deleted on chromosome 10) and that like the systemic administration of a 5-HT_{2C} receptor agonist, disruption of this interaction results in inhibition of the mesolimbic DA pathway. Importantly, disrupting the interaction of PTEN with 5-HT_{2C} receptors mimics the action of 5-HT_{2C} receptor agonists in blocking both the increase in mesolimbic DA activity induced by Δ^9 -tetrahydrocannabinol (THC), the psychoactive component of marijuana, and conditioned place preference for both THC and nicotine (Ji et al., 2006). These findings provide further information on the role that 5-HT_{2C} receptors play in mediating the rewarding effects of drugs of abuse and suggest disruption of this protein-protein interaction as a potential treatment for drug addiction.

Mesocortical System

5-HT_{2C} receptors also appear to tonically inhibit release of DA from the mesocortical pathway. Systemic administration of 5-HT_{2C} receptor agonists decreases the firing rate of VTA DA neurons, while inverse agonists or antagonists increase the firing rate, as mentioned in the discussion of the mesolimbic pathway. Systemic administration of the 5-HT_{2C} receptor agonist Ro 60-0175 also causes a decrease in DA efflux in the PFC (Millan et al., 1998a; Gobert et al., 2000) while inverse agonists (Gobert et al., 2000) and antagonists (Millan et al., 1998a; Gobert et al., 2000; Pozzi et al., 2002) increase DA efflux in the PFC. As for the localization of the relevant receptors, studies suggest that 5-HT_{2C} receptors localized in the PFC do not modulate DA release in this region, either tonically (Pozzi et al., 2002; Alex et al., 2005) or phasically (Pozzi et al., 2002; Alex et al., 2005; Pehek et al., 2006). We have recently shown that infusions of SB 206553 directly into the PFC did not alter basal, K⁺-stimulated, or stress-induced cortical DA release (Alex et al., 2005; Pehek et al., 2006). Cortical 5-HT_{2C} receptors do modulate DA-mediated behaviors for intracortical infusions of a 5-HT_{2C} antagonist potentiated the hyperlocomotion induced by a systemic injection of cocaine (Filip and Cunningham, 2003). However, current evidence suggests that this effect is not mediated by alterations in extracellular DA in the PFC (Alex et al., 2005).

In contrast, it has been shown that administration of the 5-HT_{2C} agonist Ro 60-0175 in the cell body region, the VTA, completely antagonized stress-induced increases in PFC DA, indicating a role for VTA 5-HT_{2C} receptors in the modulation of PFC DA (Pozzi et al., 2002). Figure 2 depicts the hypothesized circuit underlying 5-HT_{2C} regulation of mesocortical DA. The lack of terminal-region 5-HT_{2C} receptor modulation of the mesocortical pathway represents a significant difference from the nigrostriatal and mesolimbic systems. Elucidating the complete neural circuitry of each pathway will be beneficial to the treatment of disorders that may differentially involve the major dopaminergic pathways.

Behavioral studies demonstrate that 5-HT_{2C} receptors may also play a role in the mechanism of action of psychostimulants. Recent studies have shown that systemic administration of the 5-HT_{2C} antagonists SB 242084 and SDZ SER-082 enhances cocaine-induced locomotor activity (Fletcher et al., 2002; Filip et al., 2004; Liu and Cunningham, 2006), the discriminative stimulus effects of cocaine (Filip et al., 2006) and cocaine self-administration (Fletcher et al., 2002). Likewise, systemic administration of 5-HT_{2C} agonists (MK-212, Ro 60-0175 or mCPP) attenuates cocaine-induced locomotor activity (Grottick et al., 2000; Liu and Cunningham, 2006), responding for both food and cocaine (Grottick et al., 2000), and the discriminative stimulus effects of cocaine (Callahan and Cunningham, 1995; Frankel and Cunningham, 2004). Further studies suggest that these effects are mediated, at least in part, by 5-HT_{2C} receptors in the VTA (Fletcher et al., 2004). Additionally, there is evidence that constitutive or agonist-induced activity at 5-HT_{2C} receptors in the PFC is capable of attenuating the hyperlocomotive and discriminative stimulus effects of cocaine (Filip and Cunningham, 2003). Taken together, these data suggest a role for the 5-HT_{2C} receptor in the treatment of psychostimulant drug abuse/addiction.

Summary

5-HT_{2C} receptors, perhaps because of their high level of constitutive activity, possess a unique ability to tonically regulate DA release from all three major pathways. This tonic inhibition of DA release has been shown to be regulated by 5-HT_{2C} receptors in the terminal regions of the nigrostriatal and mesolimbic pathways, whereas 5-HT_{2C} receptors in the PFC seem to be incapable of tonically or phasically inhibiting the mesocortical pathway. 5-HT_{2C} receptors in the cell body regions of all three pathways are, however, capable of modulating DA release in stimulated conditions. Thus, characterizing the role of the 5-HT_{2C} receptor in the regulation

of dopaminergic transmission may have implications for the treatment of schizophrenia, depression, Parkinson's disease, anxiety, and drug abuse.

5-HT₃

Localization

The 5-HT₃ receptor, unlike the other 5-HT receptor subtypes, is a cation channel (Yakel and Jackson, 1988; Derkach et al., 1989). Agonist binding at this receptor results in an inward flux of cations and thus an excitation of the host cell (Yakel and Jackson, 1988). 5-HT₃ receptors are thought to be most highly expressed in brainstem (Kilpatrick et al., 1989; Gehlert et al., 1991; Laporte et al., 1992; Parker et al., 1996) but have also been detected in dopaminergic brain regions such as the NA (Kilpatrick et al., 1987; Barnes et al., 1990; Gehlert et al., 1991; Parker et al., 1996; Morales et al., 1998), the PFC (Kilpatrick et al., 1987, 1989; Barnes et al., 1990; Gehlert et al., 1991; Tecott et al., 1993; Morales et al., 1998), the striatum (Kilpatrick et al., 1987, 1989; Laporte et al., 1992; Parker et al., 1996; Morales et al., 1998) and the SN (Laporte et al., 1992). It is worth noting that the expression of 5-HT₃ receptors in the striatum is low in comparison with the PFC and NA. It has been shown that 5-HT₃ receptors are present on striatal, potentially dopaminergic, nerve terminals (Nayak et al., 2000) and that striatal presynaptic 5-HT₃ receptors are highly permeable to calcium and may facilitate neurotransmitter release by increasing calcium concentrations within the terminal (Ronde and Nichols, 1998). In the PFC, one study has shown colocalization of 5-HT₃ receptors with GABAergic cells (Morales et al., 1996). For the most part, however, the specific localization of these receptors in each brain region has not been elucidated.

Nigrostriatal Pathway

While most studies agree that 5-HT₃ receptors facilitate release of DA from the nigrostriatal pathway, some controversy remains surrounding the mechanism of action by which they modulate dopaminergic activity in the striatum. 5-HT₃ agonism (using 2-Methyl-5-HT or 1-(*m*-chlorophenyl)biguanide (mCPBG)) has been shown to increase the release of endogenous DA from striatal slices (Blandina et al., 1988, 1989; King et al., 1995; Richter et al., 1995) and potentiate K⁺-evoked release (Blandina et al., 1989). From these studies it was suggested that 5-HT acts at 5-HT₃ receptors to facilitate DA release in the striatum. However, other studies have found that 5-HT₃ receptor agonism (using 5-HT, 2-Methyl-5-HT or phenylbiguanide) induces release of [³H]DA from rat striatal slices but that 5-HT₃ receptor antagonism does not block this effect. These studies thus provide evidence that this effect is not 5-HT₃ receptor-mediated. Instead, it can be blocked by a DA uptake inhibitor and thus appears to be carrier-mediated (Schmidt and Black, 1989; Benuck and Reith et al., 1992; Zazpe et al., 1994). An *in vivo* study also suggests that the 5-HT₃ agonist phenylbiguanide can act at DA transporters to induce DA release. Intrastriatal administration of this ligand increased striatal DA, an effect that was blocked by a DAT inhibitor but not affected by co-perfusion with the 5-HT₃ antagonist MDL 72222 (Santiago et al., 1995). One study in mice, however, indicated that a portion of the 5-HT₃-agonist stimulated DA release from striatal slices was not affected by the presence of a DAT inhibitor (Richter et al., 1995). Thus, conflicting data have been produced both *in vitro* and *in vivo*, and the question of 5-HT₃ receptor-mediated regulation of striatal DA must be further investigated with ligands selective for the 5-HT₃ receptor in the presence and absence of DAT inhibitors. Regardless of the controversy over the effects of 5-HT₃ receptor agonism on DA release, it is known that 5-HT₃ receptors do not regulate tonic levels of DA activity. Systemic treatment with a variety of 5-HT₃ antagonists (ondansetron, ICS 205930, metoclopramide, and DAU 6215) does not affect the 5-HT-stimulated release of [³H]DA from striatal slices (Jacocks and Cox, 1992) or the DA concentration in the striatum (Koulu et al., 1989; Invernizzi et al., 1995). Also, acute systemic administration of the 5-HT₃ antagonists DAU 6215 and zatosetron does not change the number of spontaneously active DA neurons

in the SNpc (Rasmussen et al., 1991; Prisco et al., 1992). The effects of chronic systemic 5-HT₃ antagonism, however, remain controversial. Some studies suggest that, like the acute treatment, chronic 5-HT₃ antagonism (using DAU 6215 or zatosetron) does not affect the number of spontaneously active DA neurons in the SNpc (Rasmussen et al., 1991; Prisco et al., 1992) or the concentration of DA in the striatum (Invernizzi et al., 1995). Other studies see a decrease in the number of spontaneously active DA neurons in the SNpc in response to chronic treatment with the 5-HT₃ antagonist MDL 73147EF (Sorenson et al., 1989; Palfreyman et al., 1993). It is possible that this discrepancy is caused by the different selectivities of the antagonists used. Again, further studies with selective ligands are required to resolve this question.

5-HT₃ receptors do appear to regulate *evoked* nigrostriatal DA release. Systemic administration of 5-HT₃ receptor antagonists (ICS 205-930, ondansetron, or MDL 72222) attenuates the increase in striatal DA release induced by morphine (Porrás et al., 2003) and ethanol (Wozniak et al., 1990), but not haloperidol, amphetamine or cocaine (Porrás et al., 2003). Also, pretreatment with the 5-HT₃ receptor antagonist ondansetron did not affect haloperidol-induced activation of DA turnover in the striatum (Koulu et al., 1989). Porrás et al. (2003) suggested that 5-HT₃ receptors only modulate nigrostriatal release when the stimulated DA release is depolarization-dependent *and* both DA and 5-HT tones are both elevated. When haloperidol was coadministered with a SSRI known to elevate 5-HT tone, the resulting increase in DA release was attenuated by 5-HT₃ receptor antagonism, supporting the authors' theory for selective modulation (Porrás et al., 2003).

Few have studied the localization of 5-HT₃ receptors capable of modulating DA release from the nigrostriatal pathway. It has been shown, however, that intrastriatal 5-HT₃ antagonism (ICS 205930, MDL 72222 or ondansetron) can attenuate induced increases in striatal DA, suggesting that at least a portion of the relevant receptors may be striatal (Benloucif et al., 1993; Porrás et al., 2003).

Mesolimbic Pathway

5-HT₃ receptor modulation of the mesolimbic system has been much better characterized. Systemic administration of the 5-HT₃ agonist 2-Methyl-5-HT is known to increase DA release in the NA and this effect is dependent on the impulse-flow of DA cells (Jiang et al., 1990). Likewise, 5-HT₃ receptor agonism with mCPBG facilitates K⁺-induced DA overflow from slices of rat NA (Matell and King, 1997) and 5-HT₃ antagonism (ondansetron or (S)-zacopride) attenuates dorsal raphe nucleus-stimulated-DA release in the NA (De Deurwaerdere et al., 1998). Also, mice overexpressing the 5-HT₃ receptor show an increase in DA release from slices (Allan et al., 2001). *In vivo* localization studies suggest that this modulation is mediated by NA 5-HT₃ receptors, as intra-NA 5-HT₃ agonism using 1-phenylbiguanide or mCPBG also increases DA in the NA (Chen et al., 1991; Campbell and McBride, 1995). Interestingly, this effect was also observed in 5-HT depleted rats, suggesting that the relevant 5-HT₃ receptors are located presynaptically on DA terminals in the NA (Chen et al., 1991). In addition, a role for VTA 5-HT₃ receptors in facilitating somatodendritic DA release in the VTA has been established (Campbell et al., 1996).

There is some controversy over a putative role for 5-HT₃ receptors in modulating release of DA from the mesolimbic pathway under basal conditions. One study found that acute administration of the 5-HT₃ antagonist zatosetron decreased the number of spontaneously active cells in the VTA (Rasmussen et al., 1991). However, research with another antagonist, DAU 6215, shows that acute administration can result in increased activation of VTA DA neurons (Prisco et al., 1992) while other studies show no effect of 5-HT₃ receptor antagonists (DAU 6215, ondansetron) on NA DA levels (Koulu et al., 1989; Invernizzi et al., 1995). Supporting this lack of effect, the 5-HT₃ antagonists ICS 205-930 and metoclopramide do not

affect the 5-HT-stimulated release of [³H]DA from NA slices (Jacocks and Cox, 1992). There is, however, consensus that chronic 5-HT₃ antagonism causes decreased DA in rat NA (Invernizzi et al., 1995) and decreases DA cell firing rate in the VTA (Sorenson et al., 1989; Rasmussen et al., 1991; Prisco et al., 1992; Palfreyman et al., 1993). Antipsychotic drugs also are known to decrease mesolimbic DA activity after chronic use. Because of their ability to mimic this action, 5-HT₃ antagonists were considered putative antipsychotic drugs until clinical trials were completed showing a lack of efficacy (Newcomer et al., 1992). Since then it has been shown that many antipsychotic drugs antagonize the 5-HT evoked current flow through 5-HT₃ receptors, suggesting that these drugs may derive some of their therapeutic action by blocking 5-HT₃ receptors (Rammes et al., 2004).

The majority of research on 5-HT₃ receptor control of mesolimbic function is focused on the modulation of drug-induced DA activity by this receptor subtype. While it is clear that 5-HT₃ receptors modulate phasic DA release in the NA, some conflicting results exist for acute treatments of particular drugs. For example, systemic administration of the 5-HT₃ antagonists MDL 72222, ondansetron and zacopride has been shown to attenuate the increases in NA DA induced by cocaine (McNeish et al., 1993; Kankaanpaa et al., 2002), and haloperidol (De Deurwaerdere et al., 2005). However, other studies have shown that systemic administration of the 5-HT₃ antagonists MDL 72222 and ondansetron had no effect on the increase in NA DA induced by cocaine (De Deurwaerdere et al., 2005), haloperidol (Koulu et al., 1989) or amphetamine (De Deurwaerdere et al., 2005). There is consensus that 5-HT₃ antagonism (MDL 72222, ondansetron and ICS 205-930) attenuates morphine-induced DA release in the NA (Imperato and Angeluci, 1989; Pei et al., 1993; De Deurwaerdere et al., 2005), and some studies have examined the localization of the receptors responsible. Intra-NA administration of the 5-HT₃ antagonist ondansetron reduced the DA effects elicited by morphine (De Deurwaerdere et al., 2005). Interestingly, intra-VTA 5-HT₃ antagonism with ICS 205-930 also attenuates the morphine-induced increases in NA DA (Imperato and Angelucci, 1989) and the morphine-induced increase in VTA DA (Campbell et al., 1996). Likewise, pretreatment with 5-HT₃ antagonists (MDL 72222, ondansetron or ICS 205-930) attenuated morphine-induced increases in behavioral activity (Pei et al., 1993) and morphine-place preference (Carboni et al., 1988; Higgins et al., 1992). These studies suggest that morphine induces DA release in the NA, as well as its rewarding effects, at least in part by activating mesolimbic DA neurons, and that 5-HT₃ receptors facilitate this activation. 5-HT₃ receptors may also play a role in the effects of continuous cocaine treatment. Perfusion of the 5-HT₃ agonist mCPBG in slices of rat NA facilitates K⁺-induced release of DA (Matell and King, 1997; King et al., 1999) and continuous cocaine treatment inhibits this effect of the agonist. Coadministration with the 5-HT₃ antagonist ondansetron during the period of continuous cocaine pretreatment reverses the inhibitory cocaine-effect (King et al., 1999) suggesting that 5-HT₃ receptors are downregulated in response to continuous cocaine and may play a role in tolerance (Matell and King, 1997; King et al., 1999). Lastly, a role for 5-HT₃ receptors in the rewarding effects of ethanol is suggested by the data. Coadministration of the 5-HT₃ agonist CPBG lowers the threshold dose for an ethanol-induced increase in NA DA (Campbell and McBride, 1995). Likewise, systemic pretreatment with the 5-HT₃ antagonist ICS 205-930 attenuated the ethanol-induced increase in DA in the NA (Wozniak et al., 1990). It is known that ethanol potentiates 5-HT₃ agonist-induced currents at 5-HT₃ receptors (Lovinger and White, 1991), and thus possible that the effects of ethanol on DA release are due to a direct action at 5-HT₃ receptors. Most importantly, coadministration of a 5-HT₃ antagonist (either zacopride or ICS 205-930) with ethanol completely prevented rats from self-infusing ethanol into the posterior VTA, suggesting that 5-HT₃ receptors play a permissive role in ethanol's rewarding effects (Rodd-Hendricks et al., 2003).

Mesocortical System

Aside from the facilitatory effect of 5-HT₃ receptors on VTA cell firing previously described, little is known about the role of these receptors in modulating the mesocortical system. Intracortical administration of the 5-HT₃ agonist 1-phenylbiguanide has been shown to increase PFC DA (Chen et al., 1992) suggesting a facilitative role for local receptors. Studies by Ashby et al. have shown that intra-PFC application of 5-HT₃ agonists (5-HT, 2-Methyl-5-HT or 1-phenylbiguanide) decreased the firing rate of PFC cells (Ashby et al., 1989; 1991; 1992). The cell type was not identified, however, and it is therefore unclear how this effect would influence DA release in the PFC. There is some evidence that intra-PFC administration of the 5-HT₃ receptor antagonist ICS 205-930 can block antidepressant-induced DA release in the PFC. This result indicates that 5-HT₃ receptors in the PFC may facilitate mesocortical DA activity when extracellular 5-HT levels are elevated (Tanda et al., 1995).

Summary

There is little evidence that 5-HT₃ receptors modulate basal DA release. However, studies suggest that 5-HT₃ receptors may modulate stimulated release from all three DA pathways. The most well-studied role of these receptors is their ability (when stimulated) to facilitate phasic DA release in the NA, particularly the potentiation of responses to reinforcing drugs such as cocaine, morphine, and ethanol. In addition, there is consensus that chronic treatment with 5-HT₃ antagonists causes a reduction of DA activity in the NA, a property shared by chronic treatment with atypical antipsychotic drugs and thus relevant to the development of new therapeutics. Only a handful of studies have examined the localization of the 5-HT₃ receptors responsible for the modulation of DA release. For all three pathways there is some evidence that 5-HT₃ receptors in terminal regions may be involved.

5-HT₄

Localization

5-HT₄ receptors couple positively to adenylate cyclase (Barnes and Sharp, 1999). At least 10 splice variants have been identified in 3 species: of these, the 5-HT₄(a), 5-HT₄(b), and 5-HT₄(e) have been described in the rat (Vilario et al., 2005). Quantitative autoradiographic studies have shown that 5-HT₄ receptors are dense in mesolimbic and nigrostriatal terminal regions as well as the SN (e.g. Patel et al., 1995). A recent paper combining this approach with *in situ* immunohistochemistry found high levels of 5-HT₄ binding sites and mRNA in the dorsal striatum and NA of the rat, guinea pig, and monkey (Vilario et al., 2005). This latter finding, coupled with autoradiographic results following selective lesions of either nigrostriatal DA neurons or cell bodies in the striatum, indicate that 5-HT₄ receptors are not localized on DA terminals (Patel et al., 1995; Compan et al., 1996). Rather, they appear to have a somatodendritic localization within the striatum (Vilario et al., 2005). 5-HT₄ binding but not mRNA was also localized to the SN suggesting an axonal localization of the receptor on striatonigral projections (Vilario et al., 2005). Very low densities were observed in neocortical regions including the frontal cortex.

Nigrostriatal Pathway

There is considerable evidence that stimulation of the 5-HT₄ receptor enhances striatal DA release *in vivo*. Work in anesthetized and freely moving rats demonstrated that local perfusion of 5-HT or 5-HT₄ agonists by reverse dialysis enhanced DA efflux that was attenuated by perfusion with 5-HT₄ antagonists, including the selective antagonists GR118303 or SB207710 (Benlucif et al., 1993; Bonhomme et al., 1995; Steward et al., 1996; Deurwaerdere et al., 1997). Administration of 5-HT₄ antagonists did not alter basal DA efflux indicating that 5-HT₄ receptors do not tonically modulate nigrostriatal DA release. Rather, these receptors

appear to modulate the nigrostriatal DA pathway only when DA and 5-HT systems are stimulated. Moreover, evidence indicates that 5-HT₄ receptors specifically regulate impulse-mediated rather than carrier-mediated DA release. Systemic administration of the 5-HT₄ antagonist GR 125487 reduced the increases in nigrostriatal cell firing, and the increases in striatal DA efflux, produced by the administration of haloperidol (Lucas et al., 2001) or morphine (Porrás et al., 2002a). Release induced by amphetamine or cocaine was not altered, indicating a specific effect on exocytotic DA release.

In agreement with anatomical studies, studies of DA release indicate that 5-HT₄ modulation of DA is mediated by alterations in neuronal circuits, rather than a direct effect on DA terminals (De Deurwaerdere et al., 1997). In striatal synaptosomes, the 5-HT₄ agonist (S)-zacopride did not alter [³H]DA outflow. Likewise, 5-HT₄ antagonists did not modify 5-HT-enhanced DA release in synaptosomes but did attenuate 5-HT-induced DA release *in vivo*. In the slice preparation, 5-HT₄ agonists stimulated and antagonists blocked DA release (Steward et al., 1996). In the slice or *in vivo*, 5-HT₄-mediated effects are blocked by perfusion with the sodium channel blocker TTX. These results suggest that 5-HT₄ receptors localized within the striatum that modulate DA release are postsynaptic and localized on neuronal circuits within the striatum.

There is also *in vivo* microdialysis evidence that 5-HT₄ receptors localized in the SN regulate DA release. Co-perfusion of the nigra with the 5-HT₄ antagonist RS 39604 blocked 5-HT-induced DA efflux in the SN (Thorre et al., 1998). Injection of GR118303 (10 µg/0.5 µl) into the SN blocked the increase in striatal DA observed after the systemic administration of morphine (Pozzi et al., 1995).

Mesocorticolimbic Pathway

Despite the high concentration of 5-HT₄ receptors in the NA, neurochemical studies do not support a role for these receptors in the regulation of the mesoaccumbens DA pathway. Systemic treatment with 5-HT₄ ligands did not affect the basal, morphine-, or haloperidol-stimulated firing of DA neurons in the VTA (Lucas et al., 2001; Porrás et al., 2002a). Likewise, no effects were observed on basal or stimulated *in vivo* DA release. However, a role for NA 5-HT₄ receptors in cocaine-induced hyperactivity has been reported (McMahon and Cunningham, 1999). To date, 5-HT₄ receptors have not yet been implicated in the regulation of mesocortical DA activity.

5-HT5

There are two subtypes of the 5-HT₅ receptor: 5-HT_{5A} and 5-HT_{5B} (Nelson, 2004). While these receptors are distributed in the CNS, there is no known role in the regulation of DA neurons.

5-HT6

Localization

Activation of the 5-HT₆ receptor in artificial expression systems (Ruat et al., 1993) and striatal tissues (Boess et al., 1998) enhances adenylate cyclase activity. *In situ* hybridization (Gerard et al., 1996) and immunohistochemical studies (Gerard et al., 1997) demonstrate that 5-HT₆ receptors are abundant in DA terminal areas including the striatum, NA, hippocampus, and frontal cortex. Lower levels are also found in the SN. Within the striatum, 5-HT₆ mRNA is colocalized with enkephalin, dynorphin, and Substance P mRNA, indicating localization on medium spiny GABAergic neurons which project to the pallidum and SN.

Modulation of Dopamine Systems

Interest in the 5-HT₆ and 5-HT₇ receptors as modulators of DA transmission was initially sparked because of the high affinities of several antipsychotic and antidepressant drugs for these sites (Roth et al., 1994). Systemic administration of the selective 5-HT₆ receptor antagonist SB-271046 increased dialysate levels of DA, but not 5-HT in the rat prelimbic/infralimbic portions of the PFC (Lacroix et al., 2004). This same group previously found a non-significant increase in DA in the frontal (motor) cortex (Dawson et al., 2001). Treatment with this 5-HT₆ receptor antagonist and another (SB 258510A) did potentiate amphetamine-induced DA release in the frontal cortex (Frantz et al., 2002). This latter study also found that 5-HT₆ antagonism enhanced the locomotor activating and reinforcing effects of amphetamine. While there is data indicating that 5-HT₆ receptors modulate cognition through actions on cholinergic neurons (see Mitchell and Neumaier, 2005 for review), there is little evidence at the present time for the modulation of cognitive processes by 5-HT₆ receptor/DA interactions.

5-HT₇

Activation of the 5-HT₇ receptor stimulates cAMP accumulation (Eglen et al., 1997). *In situ* hybridization and immunohistochemical studies show that the mRNA and receptor protein have a similar distribution in discrete regions of the CNS including the cortex, hippocampus, and amygdala (Neumaier et al., 2001). As previously mentioned, several antipsychotic drugs have high affinity for these 5-HT₇ receptors (Roth et al., 1994). However, work investigating modulation of DA by 5-HT₇ receptors has been hampered by a lack of selective ligands. One study examined the effects of the putative selective antagonist DR4004 on exploratory activity and monoamine tissue content (Takeda et al., 2005). DR4004 administration decreased exploration but not spontaneous locomotion. These decreases in exploration were correlated with decreases in DA and 5-HT turnover in the amygdala and were reversed by coadministration of the DA transporter blocker GBR12909 or the SSRI fluvoxamine. Clearly, more selective ligands must be developed and tested.

Summary and Implications

This review has summarized the evidence supporting roles for several 5-HT receptor subtypes in regulating dopaminergic activity. From this summary, commonalities emerge. With the exception of the constitutively active 5-HT_{2C} receptor, the 5-HT receptor subtypes do not appear to tonically modulate DA, as evidenced by the lack of effect of antagonist treatments alone. The 5-HT receptors are nearly all, however, capable of regulating DA activity when 5-HT tone is elevated (e.g. in response to stress or blockade of the 5-HT transporter by cocaine or SSRIs), or when they are stimulated by exogenous agonists. For the receptor subtypes that have mechanisms of regulating DA that are more understood, the effects are often indirect and mediated by complex neuronal circuitry involving other transmitters. For example, as previously detailed, 5-HT_{2A} and 5-HT_{1A} receptors are thought to be localized to pyramidal glutamatergic neurons in the PFC, and to regulate DA through “long-loop” feedback to the VTA. Likewise, there is evidence that 5-HT_{2C} and 5-HT_{1B} receptors in the VTA regulate mesocorticolimbic DA neurons indirectly by influencing GABA release from their host cells. Thus, the complexities of these circuits are significant. Future research must employ a variety of techniques to determine the precise cellular and subcellular localization of each receptor in individual brain regions and the circuitry involved in their regulation of DA release from each pathway. With the development of molecular techniques, specific ligands for receptor subtypes, and improved immunochemistry tools, these complicated circuits are becoming possible to elucidate.

As previously detailed, 5-HT receptor subtype-mediated regulation of DA has been implicated in the etiology and treatment of a number of clinical disorders and syndromes. Thus, the further

elucidation of these interactions may result in the development of improved therapeutics. One such area is the development of medications to treat Parkinson's disease and other extrapyramidal motor disorders. Inverse agonism or antagonism of 5-HT_{2C} receptors may contribute to the lack of extrapyramidal side effects observed with atypical antipsychotic drugs. Studies demonstrate that the 5-HT_{2C} antagonist SB 200646A and the inverse agonist SB 206553 can be beneficial in animal models of Parkinson's disease (Fox et al., 1998; Fox and Brotchie, 2000). Whether these effects reflect 5-HTC actions on nigrostriatal DA function remains to be determined.

Antidepressants act to elevate the extracellular concentration of 5-HT in the brain, presumably resulting in stimulation of all 5-HT receptor subtypes. While the specific receptor(s) linked to clinical efficacy are not known, studies in animal models of depression suggest that 5-HT_{2C} receptor binding may play a role in antidepressant treatment (Cryan et al., 2000; Dremencov et al 2005). 5-HT_{2C} receptors undergo RNA editing that generates different isoforms of the receptor (Burns et al., 1997). Specific patterns of 5-HT_{2C} mRNA editing in the PFC have been observed in human suicide victims, although the patterns varied between studies (Niswender et al., 2001; Gurevich et al., 2002). 5-HT_{2C} receptors have also been implicated in anxiety. Both 5-HT_{2C} antagonists (SB 242084) and inverse agonists (SB 206553) possess anxiolytic-like properties in animal models of anxiety (Kennett et al., 1996, 1997). 5-HT_{2C} receptor down-regulation following chronic exercise (Broocks et al., 1999), and desensitization in response to SSRI-treatment (Questad et al., 1997), have been proposed as the mechanisms by which these two treatments are anxiolytic.

Several 5-HT receptor subtypes have been implicated in the actions of drugs of abuse. It is well known that release of DA from the mesolimbic pathway is associated with drug and natural reward. By actions at relevant 5-HT receptor subtypes, endogenous 5-HT (or potential therapeutics) may regulate this pathway and thus facilitate or attenuate the rewarding effects of these drugs. For example, 5-HT₃ receptors have been shown to play a permissive role in the effects of both morphine and ethanol and thus 5-HT₃ receptor antagonism may be a desired property in drugs designed to treat their abuse. 5-HT_{1B} receptor agonists potentiate both the rewarding effects of cocaine and the cocaine-induced increase in mesolimbic DA release. In contrast, 5-HT_{2C} receptor *antagonists* potentiate these effects as well as cocaine-induced hyperlocomotion. These studies suggest that 5-HT_{1B} receptor antagonism and/or 5-HT_{2C} receptor agonism could be beneficial in treating psychostimulant abuse. 5-HT_{2A} and 5-HT_{1A} receptor subtypes have also been implicated in modulating responses to psychostimulants and may play a role in their rewarding effects. These data have important implications not only for the management and prevention of drug abuse, but also for the treatment of reduced motivation and response to reward, such as the anhedonia that is characteristic of withdrawal from drugs of abuse as well as disorders such as schizophrenia and depression. In fact, studies suggest that antidepressant efficacy at treating lack of motivation and anhedonia may involve increased DA release in the NA (Zangen et al., 2001).

5-HT receptor regulation of DA systems has also been implicated in the mechanism of action of atypical antipsychotic drugs. There has been particular interest in the 5-HT_{1A} and 5-HT_{2A} and, to some extent, the 5-HT_{2C} receptor sub-types. All three subtypes appear to play a prominent role in the modulation of PFC DA with 5-HT_{1A} and 5-HT_{2A} receptors stimulating DA release by actions in the cortex whereas 5-HT_{2C} receptor sites inhibit DA, perhaps by actions in the VTA. A combination of these properties, in concert with binding to other non-5-HT receptor sites (e.g. D₂ receptors), may stabilize DA systems. Administration of 5-HT_{2C} receptor antagonists or inverse agonists boosts extracellular DA levels in laboratory animals. In contrast, selective 5-HT_{2A} receptor antagonists do not alter basal DA levels but decrease stimulated DA release such as that observed following stress (Pehek et al., 2006). A combination of these properties in an antipsychotic drug could elevate tonic DA release while

blocking phasic release. A hallmark of schizophrenia is impaired cognition such as deficits in working memory. Low dopaminergic tone, which has been associated with schizophrenia (Weinberger, 1987), results in cognitive deficits in animals (Jentsch and Roth, 1999). Supranormal DA tone, such as that produced during stress, has also been associated with cognitive impairments (Zahrt et al., 1997; Arnsten and Goldman-Rakic, 1998). This has led to the belief that an optimal balance of dopaminergic tone in the PFC is necessary for normal cognitive function (Williams and Goldman-Rakic, 1995). A combination of 5-HT receptor blocking properties may normalize DA tone and thus improve cognitive dysfunction. There is recent data indicating that 5-HT_{2A} antagonists may function as cognitive enhancers. In a five-choice serial reaction time task in rats, microinjections of M100907 into the PFC reversed impairments in attentional functioning and anticipatory responding induced by intra-PFC infusions of a NMDA antagonist (Carli et al., 2005). In monkeys, the 5-HT_{2A} antagonist EMD 281014 improved delayed matching performance (Terry et al., 2005). However, it is not known if these effects are mediated by alterations in DA systems.

In conclusion, much work remains to be done. This area of research could benefit greatly from the study of alterations in DA systems of specific 5-HT receptor knock-out and overexpressing mice. Except for a few notable exceptions (e.g. Allan et al., 2001; Neumaier et al., 2002; Rocha et al., 2002; De Groote et al., 2003; Díaz-Mataix et al., 2005), this strategy has not been employed. These studies need to be performed in parallel with pharmacological studies employing selective ligands. In order for the latter to be accomplished, more selective receptor subtype ligands need to be developed, especially for the 5-HT_{1D/E/F}, 5-HT₅, 5-HT₆, and 5-HT₇ receptors. The physiological significance of mRNA editing of 5-HT receptor subtypes must also be examined by investigating the potential differential regional distribution of isoforms and the development of mouse mutants and pharmacological agents to assess function. These tools also need to be utilized in the further elucidation of the neuronal circuits underlying 5-HT receptor regulation of DA systems. For example, evidence implicates pyramidal cells projecting to subcortical sites in the enhancement of mesocortical DA following either 5-HT_{1A} or 5-HT_{2A} receptor stimulation. However, these receptors have opposite effects on pyramidal cell firing (inhibition and excitation, respectively, Araneda and Andrade, 1991). Thus, the underlying neural pathways must differ. Elucidation of these and other circuits will aid our understanding of complex brain function and the design of novel therapeutics.

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Abbreviations

BAY x 3702

R-(–)-2-[4-[(chroman-2-ylmethyl)-amino]-butyl]-1,1-dioxo-benzo[d]isothiazol one HCl

CP 93129

	3-(1,2,5,6-tetrahydro-4-pyridyl)-5-propoxy-pyrrolo[3,2-b]pyridine,
DA	dopamine
DAT	dopamine transporter
DAU 6215	(3- α -tropanyl)1H-benzimidazolone-3-carboxamide chloride
DOI	($\pm$)-2,5-Dimethoxy-4-iodoamphetamine hydrochloride
DR4004	2a-[4-(4-phenyl-1,2,3,6-tetrahydropyridyl)butyl]-2a,3,4,5-tetrahydrobenzo(c,d)indol-2-(1H)-one
EMD 281014	7-{4-[2-(4-fluoro-phenyl)-ethyl]-piperazine-1-carbonyl}-1H-indole-3-carbonitrile
GABA	γ -aminobutyric acid
GBR 12909	1-{2-[bis-(4-fluorophenyl)methoxy]ethyl}-4-(3-phenylpropyl)piperazine
GR 118303	(1,2-methylsulphonyl)aminoethyl-4-piperidiny-methyl-1-methyl-1H-indole-3-carboxylate)
GR 125487	{[1-[2-(methylsulfonylamino)ethyl]-4-piperidiny]methyl-5-fluoro-2-methoxy-1- <i>H</i> -indole-3-carboxylate sulphamate}
GR 127935	[4-(5-methoxy-3-(4-methyl-piperazin-1-yl)-phenyl)amide
5-HT	serotonin
ICS 205930	3-tropanyl-indole-3-carboxylate
K+	potassium
KO	knock-out
M100907	<i>R</i> -(+)-4-[1-hydroxy-1-(2,3-dimethoxyphenyl)methyl]- <i>N</i> -2-(4-flouro-phenylethyl)piperidine
mCPBG	1-(<i>m</i> -chlorophenyl)biguanide
mCPP	

m-chlorophenylpiperazine

MDL 11,939

alpha-phenyl-2-(2-phenylethyl)-4-piperidinemethanol

MDL 72222

3-tropanyl-3,5-dichlorobenzoate

MDMA

3,4-methylenedioxymethamphetamine

NA

nucleus accumbens

8-OHDPAT

8-hydroxy-2-(di-*n*-propylamino)tetralin

PFC

prefrontal cortex

p-MPPF

4-(2'-methoxy-)-phenyl-1-[2'-(*N*-2"-pyridinyl)-*p*-fluorobenzamido-]ethyl-piperazine

RS 39604

1-[4-amino-5-chloro-2-(3,5-dimethoxyphenyl)methoxy]-3-[1-[2-methylsulfonylamino]piperidin-4-yl]propan-1-one

SB 206553

5-methyl-1-(3-pyridylcarbonyl)-1,2,3,5-tetrahydropyrrolo[2,3-*f*]indole, Ro 60-0175,((*S*)-2-(chloro-5-fluoroindol-1-yl)-1-methylethylamine)

SB 207710

(1-*n*-butyl-4-piperidinyl) methyl-8-amino-7-iodo-1,4-benzodioxane-5-carboxylate

SB 242084

(6-chloro-5-methyl-1-[2-(2-methylpyridyl-3-oxy)pyrid-5-yl carbonyl]indoline)

SB 258510A

N-[4-Methoxy-3-(4-methyl-1-piperazinyl)-phenyl]-5-chloro-3-methylbenzo-thiophene-2-yl sulphonamide monohydrochloride

SB 271046

5-Chloro-3-methyl-benzo[*b*]thiophene-2-sulphonic acid (4-methoxy-3-piperazin-1-yl-phenyl)-amide monohydrochloride

SN

substantia nigra

SNpc

substantia nigra pars compacta

SNpr

substantia nigra pars reticulata

SR 46349B

{*trans*-4-[(3*Z*)3-[(2-dimethylaminoethyl)oxyimino]-3-(2-fluorophenyl)propen-1-yl]phenol hemifumarate}}

SSRI

selective serotonin reuptake inhibitor

TH

tyrosine hydroxylase

TTX

tetrodotoxin

VTA

ventral tegmental area

WAY 100,635

N-(2-(4-(2-methoxyphenyl)-1-piperazinyl)ethyl)-N-(2-pyridyl)cyclohexanecarboxamide

Fig.1. 5-HT_{1B} receptors potentiate cocaine-induced dopamine release in the nucleus accumbens

A: In the absence of cocaine, serotonin (5-HT) binding to 5-HT_{1B} receptors in the ventral tegmental area (VTA) does not alter basal dopamine (DA) release in the nucleus accumbens (NA).

B: In the presence of systemic or intra-VTA cocaine, 5-HT transporters are blocked by cocaine causing an increase in extracellular 5-HT in the VTA, and increased stimulation of 5-HT_{1B} receptors on the terminals of GABAergic projections from the NA. GABA release from these terminals is decreased in response to 5-HT_{1B} receptor stimulation, resulting in a disinhibition of the mesolimbic pathway and increased DA release in the NA.

Fig.2. Putative neuronal circuitry mediating the regulation of mesocortical dopamine release by 5-HT_{2A} and 5-HT_{2C} receptors

The model assumes that 5-HT_{2A} or 5-HT_{2C} receptor agonism is excitatory.

A: As depicted, presynaptic 5-HT_{2A} receptors stimulate the release of glutamate which acts on AMPA receptors to stimulate corticotegmental projections that regulate mesocortical dopamine (DA) cell activity in B. Alternatively, stimulation of 5-HT_{2A} receptors localized directly on pyramidal neurons may stimulate those that project to the ventral tegmental area.

B: 5-HT_{2C} receptors localized on γ -aminobutyric acid (GABA) interneurons stimulate the release of GABA which inhibits mesocortical DA cells. 5-HT_{2A} receptors stimulate DA neurons directly. This is attenuated by a concomitant stimulatory action of 5-HT_{2A} receptors on GABA interneurons which inhibit DA cells.

Table I

Serotonergic ligands employed to assess role of those serotonin receptors regulating dopamine function.

Receptor	Agonists	Antagonists/Inverse agonists
5-HT1A	8-OHDPAT, flesinoxan, S 15535, BAY X3702	WAY 100,635, pMPPF
5-HT1B	CP 93129, CP 94253, RU 24969	GR 127935, GR 55562
5-HT2A	DOI	M100907, SR46349B, ritanserin, ketanserin
5-HT2C	Ro 60-0175, mCPP, MK-212, SDZ SER-082	SB 242084, SB206553, ritanserin
5-HT3	2-methyl-5-HT, mCPBG, phenylbiguanide	MDL72222, ondansetron, ICS 205930, metoclopramide, DAU 6215, zatosetron, zacopride
5-HT4	zacopride	GR118303, SB207710, GR 125487, RS 39604
5-HT6		SB-271046, SB258510A
5-HT7		DR4004