REVIEW

# Presynaptic control of serotonin on striatal dopamine function

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**Abstract**

*Rationale* The influences of the serotonergic system on dopamine (DA) neuron activity have received considerable attention during the last three decades due to the real opportunity to improve disorders related to central DA neuron dysfunctions such as Parkinson's disease, schizophrenia, or drug abuse with serotonergic drugs. Numerous biochemical and behavioral data indicate that serotonin (5-HT) affects dopaminergic terminal function in the striatum.

*Objective* The authors propose a thorough examination of data showing controversial effects induced by striatal 5-HT on dopaminergic activity.

*Results* Inhibitory and excitatory effects of exogenous 5-HT have been reported on DA release and synthesis, involving various striatal 5-HT receptors. 5-HT also promotes an efflux of DA through reversal of the direction of DA transport. By analogy with the mechanism of action described for amphetamine, the consequences of 5-HT entering DA terminals might explain both the excitatory and inhibitory effects of 5-HT on presynaptic DA terminal activity, but the physiological relevance of this mechanism is far from clear. The recent data suggest that the endogenous 5-HT system affects striatal DA release in a state-dependent manner associated with the conditional involvement of various 5-HT receptors such as 5-HT$_{2A}$, 5-HT$_{2C}$, 5-HT$_3$, and 5-HT$_4$ receptors.

*Conclusion* Methodological and pharmacological issues have prevented a comprehensive overview of the influence of 5-HT on striatal DA activity. The distribution of striatal 5-HT receptors and their restricted influence on DA neuron activity suggest that the endogenous 5-HT system exerts multiple and subtle influences on DA-mediated behaviors.

## Introduction

The study of the interaction between serotonin (5-HT) and dopamine (DA) systems in the brain is crucial to understanding of the mechanisms of action of several psychoactive drugs. For instance, atypical antipsychotics, drugs able to reduce psychosis with minimal extrapyramidal side effects, block more efficiently 5-HT$_{2A}$ receptors than DA-D$_2$ receptors (Deutch et al. 1991; Meltzer 1999; Meltzer and Nash 1991). This property has contributed to highlighting the involvement of the 5-HT system in the efficacy of DA drugs in humans. Similarly, the 5-HT system may directly and indirectly participate in the mechanisms of action of L-DOPA, the metabolic precursor of DA and the gold standard medication of Parkinson's disease, and numerous data have shown that 5-HT drugs may ameliorate the motor and psychotic side effects induced by L-DOPA (Carta et al. 2007; 2008; Jenner et al. 1983; Melamed et al. 1996; Pact and Giduz 1999; Zoldan et al. 1995). The 5-HT drugs constitute a real hope for improving current DA therapies to treat extrapyramidal symptoms and knowledge of the influence of 5-HT in the control of DA neuron activity appears as a critical point.

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The striatum is part of the basal ganglia, a group of subcortical structures involved in the control of motor behavior. The striatum receives a substantial DA innervation coming from midbrain DA cell bodies mainly located in the substantia nigra pars compacta (Lindvall and Björklund 1978; Gerfen 1987) and, to a lesser extent, a 5-HT innervation coming from midbrain 5-HT cell bodies located in the dorsal raphe nucleus (DRN) (Azmitia and Segal 1978; Steinbusch 1984). Several behavioral, electrophysiological, and biochemical studies have shown that 5-HT may affect striatal DA transmission. However, 40 years after the discovery by Besson et al. (1969) that 5-HT enhances DA release from rat striatal slices, the mechanisms elicited by 5-HT in the control of DA neuron activity are still mysterious. Several factors may account for the inconsistent results. First, a major difficulty in studying such an interaction comes from the existence of multiple receptor subtypes for 5-HT as revealed by molecular biology or retrograde pharmacological approaches. Most of these receptors have been described in the striatum (Barnes and Sharp 1999). Selective pharmacological agents for particular 5-HT receptor subtype(s) were lacking until recently, and it is still difficult to assess their respective roles in the control of nigrostriatal DA function. Besides the pharmacological overlap of 5-HT drugs on 5-HT receptors, numerous studies have also shown that 5-HT and some 5-HT compounds may directly act within DA terminals to enhance DA release in a powerful fashion. This action, similar to that described for amphetamine, relies on the release of DA by plasmalemmal DA transporters. Such a mechanism of action is not observed when endogenous 5-HT is released in the striatum, raising the issue of its physiological relevance. Finally, as postulated many years ago, the influence of 5-HT system on DA function could change when central DA transmission is altered.

The purpose of this review is to present a thorough examination of the biochemical material published until now. This review will briefly explore the anatomical basis of the 5-HT system as it relates to the action of 5-HT in the striatum. We will then review biochemical data showing that 5-HT modifies striatal DA function. Excitatory and inhibitory effects will be discussed as well as the 5-HT receptors thought to mediate these effects. Then, we will focus on evidence indicating that 5-HT, by entering DA terminals, may elicit a carrier-mediated release of DA or inhibit enhanced DA release. Based on evidence obtained in the last few years using in vivo methods, we will discuss the physiological relevance of such a mechanism. Finally, we will present the hypothesis that striatal endogenous 5-HT and 5-HT receptors operate in a state-dependent manner to modulate DA function. This work extends the reviews by Alex and Pehek (2007) and Fink and Göthert (2007).

## 5-HT system in the neostriatum

### 5-HT nerve terminals

The 5-HT neurons originating from the dorsal (DR) and median raphe (MR) nuclei represent the major afferents to DA systems at both somato-dendritic and nerve terminal regions (Azmitia and Segal 1978). The 5-HT innervation of mammalian neostriatum arises primarily from the dorsal raphe nucleus (Azmitia and Segal 1978; Bobillier et al. 1976). The presence of 5-HT terminals in these regions has been confirmed by autoradiographic studies assessing the binding distribution of [$^3$H]-imipramine or [$^3$H]-citalopram, two 5-HT uptake site ligands (D'Amato et al. 1987; Dewar et al. 1991), as well as antibodies directed against 5-HT (Steinbusch et al. 1981; Steinbusch 1984), 5-HT reuptake sites (Hrdina et al. 1990), or tryptophan hydroxylase (Saavedra 1977). Consistently, post-mortem studies have shown that the striatum contains a substantial amount of tissue 5-HT or its main metabolite 5-hydroxyl-indolacetic acid. More recent studies have provided evidence for a functional release of 5-HT from striatal 5-HT terminals in vivo (Kalén et al. 1988; Kreiss et al. 1993).

Serotonergic axon terminals are closely apposed to a variety of structures including axon terminals, dendritic spines, and shafts, but rarely neuronal somata. The incidence of direct contact between DA and 5-HT axon terminals is lower than that found in the nucleus accumbens (Soghomonian et al. 1989; Van Bockstaele and Pickel 1993). Based on synaptic and apposition features of 5-HT axon terminals in the striatum and also in various brain regions, it has been proposed that 5-HT may exert its various effects on striatal neurons through diffusion processes (Descarries et al. 1991; Descarries and Mechawar 2000; Umbriaco et al. 1995). It may be hypothesized that 5-HT alters the function of striatal DA terminals through both direct and indirect mechanisms.

### 5-HT receptors present in the striatum

Serotonin, released in the striatum, may act on a variety of 5-HT receptors. To date, 16 5-HT receptors have been described and several of those have been described in the striatum with the use of different anatomical techniques: 5-HT$_{1A}$, 5-HT$_{1B}$, 5-HT$_{1E}$, 5-HT$_{2A}$, 5-HT$_{2C}$, 5-HT$_3$, 5-HT$_4$, 5-HT$_6$, and 5-HT$_7$ (Barnes and Sharp 1999; Hoyer et al. 2002; Zifa and Fillion 1992). Generally, 5-HT can affect most of the intracellular second messenger pathways by acting on various receptor subtypes. The distribution and the relative expression of 5-HT receptors are different for each receptor in the striatum and the basal ganglia.

*5-HT$_{1A}$ receptors*

The striatum displays very few binding sites for 5-HT$_{1A}$ radioligands such as [$^{3}$H]-8-OH-DPAT or [$^{3}$H]-WAY100635 (Gozlan et al. 1983; Hall et al. 1997; Laporte et al. 1994). Moreover, mRNAs encoding 5-HT$_{1A}$ receptor are almost undetectable in the rat striatum or the substantia nigra (SN) (Pompeiano et al. 1992). Although some biochemical data have suggested their presence on DA terminals (Johnson et al. 1993; see below), it has been shown that the binding of 8-OH-DPAT persisted in rats after lesion of DA neurons (Gozlan et al. 1983). In addition, using immunocytochemistry, some 5-HT$_{1A}$ receptor-labeled cells were also positive for the gliosis factor-associated protein, suggesting that a proportion of striatal 5-HT$_{1A}$ receptors are produced by glial cells (Whitaker-Azmitia et al. 1993). Using another immunohistochemical approach, Frechilla et al. (2001) have described labeling of interneurons that were not calbindin-positive in the striatum of primates. Some investigators have postulated the presence of 5-HT$_{1A}$ receptors on some terminals of corticostriatal fibers (Antonelli et al. 2005; Mignon and Wolf 2007), but the anatomical description of this hypothesis is still lacking. Thus, 5-HT$_{1A}$ receptors are poorly expressed in the striatum and are likely not located on DA neurons.

*5-HT$_{1B}$ receptors*

5-HT$_{1B}$ receptors have been well described in the basal ganglia of mammals. 5-HT$_{1B}$ receptor mRNA is highly concentrated in the striatum and the nucleus accumbens (Bonaventure et al. 1998; Boschert et al. 1994; Hen 1992; Varnas et al. 2005). Although presenting a two- to threefold-lower density of binding sites than in the SN, ventral tegmental area (VTA), or globus pallidus, 5-HT$_{1B}$ receptors have been detected in the striatum, the nucleus accumbens, and the cortex using various radioligands (Doménech et al. 1997; Hamon et al. 1990; Radja et al. 1991) or immunohistochemistry (Sari et al. 1997; 1999). Their expression is higher in the ventral striatum (Compan et al. 1998; Varnas et al. 2001).

5-HT$_{1B}$ receptors could be expressed at several striatal sites. Usually found at presynaptic terminals, they could be present on GABAergic collateral fibers of striatofugal neurons (Sari et al. 1999). They are likely present on 5-HT terminals as 5-HT autoreceptors modulating the release of 5-HT (Engel et al. 1986; see Hen 1992; Kreiss et al. 1993) although the contribution of this labeling appears to be extremely low compared to the total labeling of 5-HT$_{1B}$ receptors in the striatum (Vergé et al. 1986). The presence of 5-HT$_{1B}$ receptors on thalamostriatal and/or corticostriatal neurons has also been suggested (Bonaventure et al. 1998). On the other hand, numerous anatomical studies have reported that 5-HT$_{1B}$ receptors are not located on central DA neurons. Indeed lesions of DA neurons do not alter the density of [$^{3}$H]-5-HT striatal binding sites whereas kainic acid lesion of striatal neurons decreases density (>80%) (Quirion and Richard 1987). In addition, a loss of density of these receptors was observed in the post-mortem analysis of striata from Huntington's disease patients, a degenerative disease associated with destruction of striatal neurons, but not from parkinsonian patients (Waeber and Palacios 1989). Furthermore, mRNAs encoding 5-HT$_{1B}$ receptor are not found in the SNc (Bonaventure et al. 1998). These data suggest that 5-HT$_{1B}$ receptors could be placed to control the neuronal activity of some striatal efferent neurons.

Notably, the 5-HT$_{1D}$ receptors that have for a long time been confused with 5-HT$_{1B}$ receptors from a pharmacological point of view are present in the striatum. Their mRNA and binding sites have been clearly identified in the striatum. Their pattern of expression is almost the same as that described for 5-HT$_{1B}$ receptors, but their density is lower (Bruinvels et al. 1994; Mengod et al. 1996; Waeber and Moskowitz 1995).

*Other 5-HT$_1$ receptors*

The 5-HT$_{1E}$ receptors were described by Lovenberg et al. (1993). This receptor is negatively coupled to adenylyl cyclase activity (Lovenberg et al. 1993). It has been shown, using northern blot analysis, that striatum expresses detectable levels of 5-HT$_{1E}$ mRNA. In addition, it has been shown that 5-HT binds to a site sensitive to various 5-HT$_1$ receptor ligands, with the exception of 5-carboxytryptamine (5-CT), a non-selective 5-HT$_{1/7}$ agonist (Bruinvels et al. 1993). For these authors, this 5-HT$_{non1Anon1Bnon2C}$ receptor corresponds to the 5-HT$_{1E}$ site and is expressed by striatal neurons (Bruinvels et al. 1993). 5-HT$_{1F}$ receptors are poorly expressed in the striatum (Waeber and Moskowitz 1995).

*5-HT$_2$ receptor family*

Three 5-HT receptors, namely, 5-HT$_{2A}$, 5-HT$_{2B}$, and 5-HT$_{2C}$ receptors, are coupled to G proteins, leading to an intracellular increase in IP$_3$ through the stimulation of phospholipase C. On the basis of the pharmacological and molecular similarities of 5-HT$_2$ and 5-HT$_{1C}$ receptors, the 5-HT$_2$ receptor has been renamed as the 5-HT$_{2A}$ subtype, while the 5-HT$_{1C}$ subtype was renamed 5-HT$_{2C}$ (Hoyer et al. 1994). The 5-HT$_{2F}$, first described in the stomach fundus, corresponds to the 5-HT$_{2B}$ subtype. These three receptors are present in the brain (for reviews, see Barnes and Sharp 1999; Saudou and Hen 1994).

## 5-HT$_{2A}$ receptors

The presence of 5-HT$_{2A}$ receptors has been revealed by autoradiographic procedures using different radioligands such as [$^3$H]-ketanserin (Pazos et al. 1985), [$^3$H]-RP62203 (Malgouris et al. 1993), [$^3$H]-DOI (Waeber and Palacios 1994; Compan et al. 1998), and more recently with [$^3$H]-M100907 (López-Giménez et al. 1998). Typically, the density is maximal in the ventrocaudal region and the dorsomedial (periventricular) parts of the striatum. The density of 5-HT$_{2A}$ binding sites is higher in rodents compared to primates and humans (Lopez-Gimenez et al. 1999, 1998, 2001). In agreement with this, mRNA encoding 5-HT$_{2A}$ receptors is found in the striatum of rodents (Pompeiano et al. 1994; Ward and Dorsa 1996) while their expression appears to be low and even undetectable in human caudate putamen (Burnet et al. 1995; López-Giménez et al. 2001; Pasqualetti et al. 1996).

In rodents, some immunocytochemical and in situ hybridization studies indicate that 5-HT$_{2A}$ receptors are present mostly in the extrastriosomal "matrix" compartment of the striatum, though striosomal labeling has been reported in humans (Lopez-Gimenez et al. 1999). The striosomes, or "patches", and the extrastriosomal "matrix" represent a functional organization of the striatum, with the striosomes being low in acetylcholinesterase, rich in mu opioid receptors, and containing the cell bodies of the GABAergic neurons projecting to the SNc (Gerfen 1984, 1985; Graybiel 1991). The 5-HT$_{2A}$ receptors are localized on striatal efferent GABAergic neurons (Morilak et al. 1993; Ward and Dorsa 1996), on striatal interneurons (Morilak et al. 1993) in low density (Bonsi et al. 2007), as well as on afferents putatively of cortical origin (Bubser et al. 2001). Both striatopallidal and striatonigral neurons express 5-HT$_{2A}$ receptors (Laprade et al. 1996; Ward and Dorsa 1996) mostly at the level of proximal dendrites (Cornea-Hébert et al. 1999). Their presence on DA neuron terminals remains unclear. In some studies, the binding of 5-HT$_{2A}$ receptors in the striatum is not modified in the striatum of rats with a lesion of DA neurons (Leysen et al. 1988; Muramatsu et al. 1988). Conversely, it has been shown that destruction of nigrostriatal DA neurons in rats as neonates increased 5-HT$_{2A}$ binding sites (Radja et al. 1993), and this effect is paralleled by an increase in the levels of the mRNA encoding this receptor in the striatum (Laprade et al. 1996).

## 5-HT$_{2B}$ receptors

The presence of 5-HT$_{2B}$ receptors in the brain has been uncertain for several years (Loric et al. 1992; Pompeiano et al. 1994). Using an antibody directed against the receptor and in situ hybridization, it has been shown that 5-HT$_{2B}$ receptors are expressed in the central nervous system (Duxon et al. 1997). Whereas the expression of both the mRNA and the protein has been consistently detected in the hippocampus, the amygdala, and the cortex, the striatum and structures related to basal ganglia function are devoid of 5-HT$_{2B}$ receptors (Duxon et al. 1997).

## 5-HT$_{2C}$ receptors

The distribution of 5-HT$_{2C}$ receptors in the striatum was described in 1985 by studying the binding of [$^3$H]-mesulergine (Pazos et al. 1985). This study shows that 5-HT$_{2C}$ sites were located throughout the striatum, with the ventrolateral part being more enriched. The distribution has been found to be similar in other species (Saudou and Hen 1994). It is noteworthy that a patchy distribution of [$^3$H]-DOI and [$^3$H]-mesulergine has been reported in the striatum of humans and monkeys, but not rodents (Waeber and Palacios 1994). The presence of 5-HT$_{2C}$ receptors has been confirmed by immunocytochemistry and by in situ hybridization (Abramowski et al. 1995; Clemett et al. 2000; Eberle-Wang et al. 1997; Mengod et al. 1990; Molineaux et al. 1989; Pompeiano et al. 1994). Most neurons expressing 5-HT$_{2C}$ receptor mRNA are medium-sized spiny neurons of striato-pallidal and striatonigral pathways (Ward and Dorsa 1996). Recent reverse transcriptase polymerase chain reaction (RT-PCR) studies have shown that 5-HT$_{2C}$ receptor mRNA is present in cholinergic interneurons and that it shows an interesting patchy distribution (Ward and Dorsa 1996).

The 5HT$_{2C}$ receptors are presumably not located on DA terminals. Indeed it has been shown that SN neurons that synthesized mRNA encoding 5-HT$_{2C}$ receptors coexpress glutamic acid decarboxylase, the rate-limiting step of GABA synthesis, but not tyrosine hydroxylase, the rate-limiting step of DA biosynthesis (Eberle-Wang et al. 1997). Similar conclusions have been recently proposed from studies performed on human brain tissues (Pasqualetti et al. 1999). More recent techniques of laser capture micro-dissection allow the determination of mRNA expression in selected cell populations with quantitative PCR, a technique that is much more sensitive than in situ hybridization histochemistry. With this approach, 5HT$_{2C}$ receptor mRNA can be detected in tyrosine hydroxylase-positive neurons of the SNc (Mortazavi and Chesselet, unpublished observations). These data are compatible with results from a recent study reporting immunostaining with an antibody raised against 5-HT$_{2C}$ receptors in both GABAergic and DA neurons of the VTA (Bubar and Cunningham 2007). Even though such a colocalization appears to exist in the SN based on the PCR data, it is not known whether a small proportion of the receptors are found on terminals of DA neurons. This proportion should be extremely low because the lesion of DA neurons does not decrease the densities of

mRNA encoding 5-HT$_{2C}$ receptors or [$^3$H]-mesulergine binding along the nigrostriatal axis (Fox and Brotchie 2000; Numan et al. 1995; Radja et al. 1993).

## 5-HT$_3$ receptors

The 5-HT$_3$ receptor differs from the other 5-HT receptors by the efferent intracellular coupling system. Indeed this receptor is a Ca$^{2+}$/K$^+$/Na$^+$ channel similar to the nicotinic receptors (Davies et al. 1999; Maricq et al. 1991). The first distribution of 5-HT$_3$ receptors was provided in 1987 by Kilpatrick et al. who described the binding of the preferential 5-HT$_3$ antagonist [$^3$H]-zacopride throughout the brain. These authors found that the striatum was poor in 5-HT$_3$ receptor sites, in contrast to the cortex, the hippocampus, or the amygdala. These data have been confirmed later with several [$^3$H]-ligands, antibodies raised against the receptor, or in situ hybridization (Barnes et al. 1989; 1990; Kilpatrick et al. 1989; Miyake et al. 1995; Morales et al. 1996; Perry 1990; Tecott et al. 1993; Waeber and Palacios 1989). The density of binding sites is dependent on the radioligands used and varies among species, with the human striatum displaying higher densities of 5-HT$_3$ receptor binding sites to the rat striatum (Barnes et al. 1990).

Notably, two subunits have been cloned (Davies et al. 1999), namely, the 5-HT$_{3A}$ and 5-HT$_{3B}$ subunits, and their association can lead to 5-HT$_3$ receptors with distinct functional and pharmacological properties. The 5-HT$_{3A}$ receptor subunit is highly expressed in the brain compared to the 5-HT$_{3B}$ (Doucet et al. 2000), with the striatum of rodents being devoid of the 5-HT$_{3B}$ subunit (Morales and Wang 2002).

The 5-HT$_3$ receptors are likely not present on DA terminals in the striatum. In humans, the binding of 5-HT$_3$ receptors is markedly reduced in putamen homogenates from patients with Huntington's disease, but not those with Parkinson's disease (Steward et al. 1993). Similarly, it has been shown that the binding of [$^3$H]-(r,s)-zacopride disappeared in rats with a lesion of striatal neurons but persisted in rats with a lesion of DA neurons (Kidd et al. 1993). It has been suggested that 5-HT$_3$ receptors are expressed by interneurons in the brain (Barnes et al. 2009; Mikics et al. 2009; Morales and Bloom 1997; Morales et al. 1996), which is in agreement with the assumption that they are located on GABAergic interneurons in the striatum (Waeber and Palacios 1989).

## 5-HT$_4$ receptors

The 5-HT$_4$ receptors were discovered in 1988 by Dumuis et al. (1988) on mouse colliculus slices. In particular, it was the first described 5-HT receptor positively linked to adenylyl cyclase activity with a unique pharmacology (Bockaert et al. 1990; Dumuis et al. 1989). Using the 5-HT$_4$ antagonist [$^3$H]-GR113808, Grossman et al. (1993) reported that 5-HT$_4$ receptors are concentrated in human basal ganglia, especially in the striatum, the nucleus accumbens, and the olfactory tubercles. This distribution has been largely confirmed and, to some extent, is quite similar in several species (Jakeman et al. 1994; Schiavi et al. 1994). An increasing gradient of binding site density from the ventrolateral to the dorsolateral striatum has been reported in rodents (Vilaró et al. 1996; Waeber et al. 1994), but not in primates or humans (Bonaventure et al. 2000; Vilaro et al. 2005). The 5-HT$_4$ receptor was cloned in 1995 (Gerald et al. 1995). From this date, several splice variants (5-HT$_{4a,b,c,d,e,f,g, and h}$) diverging in the sequence encoding the C-terminal region of the receptor have been described (Bender et al. 2000; Blondel et al. 1998; Gerald et al. 1995). Although both the structure and the efficiency to adenylyl cyclase coupling are modified, no major difference in the affinity of several 5-HT$_4$ ligands has yet been noticed between the different products.

Whatever the isoform considered, mRNAs of 5-HT$_4$ receptors are expressed by efferent striatal neurons (Bender et al. 2000; Vilaró et al. 1996). These data suggest that the 5-HT$_4$ receptor binding sites in the globus pallidus or the SN are due to striatal efferent neurons (Compan et al. 1996). In addition, the binding of [$^3$H]-GR113808 is abolished by an exocytotic lesion of striatal neurons with kainic acid, but not by a 6-hydroxydopamine lesion of nigrostriatal DA neurons (Compan et al. 1996; Patel et al. 1995). In line with these data, the binding of [$^3$H]-GR113808 is strongly diminished in the striatum in Huntington's disease, but not in Parkinson's disease (Reynolds et al. 1995). Despite the recent report that the 5-HT$_{4a}$ subunit mRNA is expressed by neurons in the SN (Vilaro et al. 2005), it is far from clear if the expression is related to DA neurons. Consequently, 5-HT$_4$ receptors are likely not present on DA neurons in the striatum.

## 5-HT$_5$ receptors

The 5-HT$_5$ receptors were discovered in 1993 and two subtypes, namely, the 5-HT$_{5A}$ and the 5-HT$_{5B}$, have been distinguished on the basis of their primary sequence (Erlander et al. 1993). These receptors, highly concentrated in cortical areas, are, however, barely expressed in the striatum of various species (Saudou and Hen 1994; Barnes and Sharp 1999) as reported by in situ hybridization and binding studies (Rees et al. 1994; Thomas 2006; Waeber and Moskowitz 1995; Wesolowska 2002). Nonetheless, a faint immunohistochemical labeling has been reported in the rat striatum that could be associated with medium-sized spiny neurons (Oliver et al. 2000).

## 5-HT$_6$ receptors

The 5-HT$_6$ receptor was first described from its cloning from rat striatal slices cDNA (Monsma et al. 1993; Ruat et al. 1993a). The 5-HT$_6$ receptor has been shown to stimulate adenylyl cyclase activity in both HEK-293 cells (Monsma et al. 1993), pig caudate membranes (Schoeffter and Waeber 1994), and mouse embryonic striatal neurons (Sebben et al. 1994). The highest level of 5-HT$_6$ receptor mRNAs are detected in the olfactory tubercles, nucleus accumbens, striatum, and hippocampus (Gérard et al. 1996; Monsma et al. 1993; Ruat et al. 1993a; Ward et al. 1995). In the striatum, the mRNA encoding 5-HT$_6$ receptors is synthesized by GABAergic neurons expressing both dynorphin and enkephalin and may colocalize with either 5-HT$_{2A}$ or 5-HT$_{2C}$ receptor mRNA (Ward and Dorsa 1996). The distribution and the high quantitative expression have been confirmed in the striatum using various [$^3$H]-ligands such as [$^3$H]-SB258584 (Roberts et al. 2002). Gérard et al. (1997) raised polyclonal antibodies against a synthetic peptide corresponding to part of the C-terminal domain of the receptor. They confirmed that 5-HT$_6$ receptors were present in the striatum and showed that this receptor was expressed on dendritic shafts of striatal neurons (Gérard et al. 1997; Hamon et al. 1999).

Although 5-HT$_6$ receptor mRNAs have not been detected in the SN in prior studies using RT-PCR on nigral tissue (Bourson et al. 1998; Monsma et al. 1993), other studies provide evidence for the expression of 5-HT$_6$ receptors by some nigral neurons (Gérard et al. 1996). The presence of the protein in the SN was further confirmed by immunohistochemistry (Gérard et al. 1997). Nevertheless, the presence of 5-HT$_6$ receptors on DA neurons remains doubtful because the binding of [$^3$H]-SB258585 is not affected by a 6-hydroxydopamine lesion of nigral DA neurons (Roberts et al. 2002).

## 5-HT$_7$ receptors

5-HT$_7$ receptors are poorly expressed in the striatum. The study by Ruat et al. (1993b) reporting an undetectable level of 5-HT$_7$ receptor mRNA in the striatum has been challenged by the use of [$^3$H]-5-CT in the presence of the cold 5-HT$_1$ ligands sumatriptan and (−)pindolol in order to label selectively 5-HT$_7$ receptors (To et al. 1995) or by the use of [$^3$H]-mesulergine in a specific procedure (Martín-Cora and Pazos 2004). Using the more specific ligand [$^3$H]-SB269970, the density of binding sites appears to be extremely low in the striatum and could be species dependent (Varnas et al. 2004). An immunohistochemical study also reports the weak labeling of 5-HT$_7$ receptors in the striatum (Neumaier et al. 2001). The failure to detect mRNA for 5-HT$_7$ receptors in the striatum (Mengod et al.

1996; Ruat et al. 1993b) has been challenged because of the later discovery of distinct splice variants encoding this receptor. It has been reported that the 5-HT$_7$ (a) isoform, common in humans and rats, could be present in the striatum (Heidmann et al. 1997). According to Muneoka and Takigawa (2003), the expression of 5-HT$_7$ receptors in the striatum appears in the early stage of development and tends to disappear in adults.

Concluding remarks

In conclusion, the presence of a variety of 5-HT receptors in the striatum has been demonstrated repeatedly and Fig. 1 summarizes these findings. Taken together, most of the anatomical data aimed at determining the distribution of 5-HT receptors with respect to nigrostriatal DA neurons conclude that the 5-HT receptors are not located on DA terminals. The receptors are rather expressed by striatal neurons, including GABAergic striatofugal neurons and
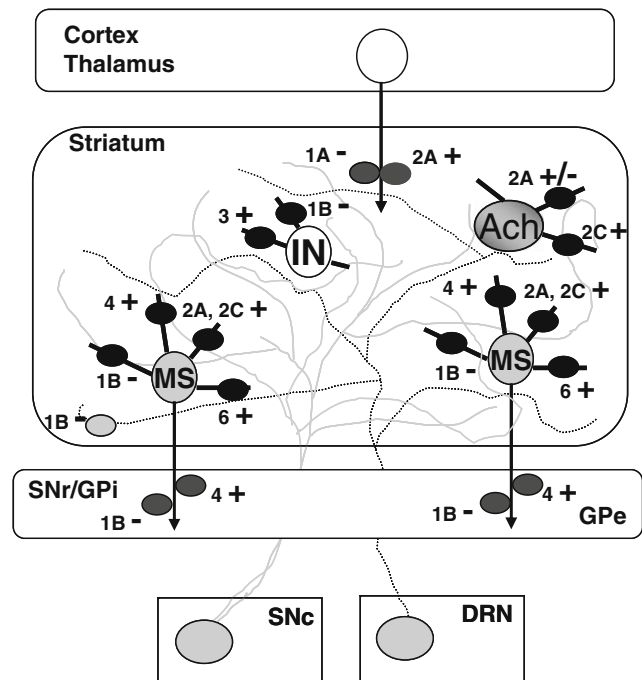


**Fig. 1** Drawing representing the expression of the different 5-HT receptor subtypes in the striatum. The *plus* and *minus symbols* refer to their putative influence on their cellular targets. Several 5-HT receptors are expressed by striatal cells including the medium-sized spiny neurons (*MS*), the cholinergic interneurons (*Ach*), and the other interneurons (*IN*). 5-HT receptors are also postulated to be present on thalamo- and corticostriatal fibers. Some 5-HT receptors (5-HT$_{1B}$/5-HT$_4$) are addressed at extrastriatal regions. Their presence on 5-HT fibers coming from the dorsal raphe nucleus (*DRN*) or DA fibers coming from the substantia nigra pars compacta (*SNc*) is not established anatomically. Of note, several 5-HT receptors are present also in the substantia nigra (for reviews, see Di Giovanni et al. 2008; Di Matteo et al. 2008). *GPi* and *GPe*, internal and external globus pallidus; *SNr*, substantia nigra pars reticulata

interneurons, and cholinergic interneurons as well as afferents. The use of immunohistochemistry using powerful antibodies or laser capture microdissection in selected cell populations of the SNc coupled to Q-PCR might challenge this first assumption. For instance, using this latter approach, $5HT_{2C}$ receptor mRNA can be detected in tyrosine hydroxylase-positive neurons of the SNc (Mortazavi and Chesselet, unpublished observations). These data are compatible with results from a recent study reporting immunostaining with an antibody raised against $5-HT_{2C}$ receptor in both GABAergic and DA neurons of the VTA (Bubar and Cunningham 2007). In any case, however, it appears that the hypothetical presence of 5-HT receptors on DA terminals in the striatum or the nucleus accumbens would be extremely low compared to their total expression in the striatum. This is important to consider when looking at the biochemical data.

## Effect of 5-HT on striatal DA terminal function

The study of the influence of 5-HT system on DA terminals has been undertaken by applying 5-HT itself (exogenous) or agonists able to target 5-HT receptors in various models. One of the most complex features of the 5-HT–DA interaction is that both excitatory and inhibitory effects have been reported.

Excitatory and inhibitory effects of 5-HT

### Excitatory effects

Several in vitro studies have reported an excitatory influence of exogenous 5-HT on basal DA release in the striatum (Andrews et al. 1978; Besson et al. 1969; Jacocks and Cox 1992; Yi et al. 1991; Zhou et al. 2005). This effect has also been observed in the nucleus accumbens (Jacocks and Cox 1992; Nurse et al. 1988), the olfactory tubercle (Zazpe et al. 1994), the SN (Williams and Davies 1983), and the VTA (Beart and McDonald 1982). The excitatory effect of 5-HT on basal DA release occurs either on striatal slices or on synaptosomes, a model allowing the study of the presynaptic regulation of synthesis and release (De Belleroche and Bradford 1980). It has been also reported that 5-HT further enhances preloaded $[^3H]$-DA or endogenous DA release in rat striatal slices or synaptosomes stimulated electrically or with high $K^+$ concentration (Blandina et al. 1989; De Belleroche and Bradford 1980; Kamal et al. 1983; Zhou et al. 2005), a depolarizing stimulus mostly involving exocytotic processes (Table 1).

The excitatory effect of 5-HT on striatal DA release has been observed in vivo by using intracerebral microdialysis. This in vivo technique permits the application of pharma-

cological compounds through the microdialysis probe to the site at which the neurotransmitter is measured (Di Chiara 1990). Using this pharmacological approach, it has been consistently shown that striatal infusion of 5-HT enhances striatal DA release in a concentration-dependent manner in the rat (Benloucif and Galloway 1991; Benloucif et al. 1993; Bonhomme et al. 1995; Yadid et al. 1994) (Fig. 2). Similar results have been also reported in rat nucleus accumbens (Parsons and Justice 1993; Zangen et al. 2001), cortex (Iyer and Bradberry 1996), and SN (Cheramy et al. 1981; Thorré et al. 1998). Striatal DA release is enhanced above the threshold concentration of 0.5–1 μM 5-HT in vivo (Benloucif and Galloway 1991; Bonhomme et al. 1995; Zangen et al. 2001) and may reach the huge enhancement of 2,000% of baseline values when 5-HT is infused at 100 μM (Benloucif and Galloway 1991). The increase in DA release induced by a 10-μM 5-HT concentration progressively diminishes during its perfusion (West and Galloway 1996).

### Inhibitory effects on DA release

The inhibitory effects of 5-HT on DA release have also been reported in vitro. Among all in vitro approaches employed, the inhibitory effect of 5-HT has been essentially observed on the stimulated release of $[^3H]$-DA in $[^3H]$-DA-preloaded preparations. Thus, 5-HT is able to negatively modulate the electrical- or $K^+$-stimulated striatal $[^3H]$-DA release in striatal slices or synaptosomes (Ennis et al. 1981; Muramatsu et al. 1988; Nurse et al. 1988; Sarhan et al. 1999; Westfall and Tittermary 1982). The inhibitory effect of 5-HT appears at concentrations of 5-HT lower or equal to 1 μM (Sarhan et al. 1999) and its maximal magnitude usually reaches 50% inhibition of $[^3H]$-DA released by the depolarizing stimulus (Ennis et al. 1981; Muramatsu et al. 1988). Using cyclic voltammetry on mice striatal slices, an inhibitory effect of 5-HT on endogenous DA release has been observed in the presence of a DA uptake blocker (Zhou et al. 2005).

### Inhibitory effects on DA synthesis

It has been shown that 5-HT inhibited DA synthesis in vitro on rat brain synaptosomes (Andrews et al. 1978; De Belleroche and Bradford 1980; Johnson et al. 1993). This effect can occur independently of a decrease of $[^3H]$-DA release (De Belleroche and Bradford 1980). It is observed with low concentrations of 5-HT.

### Concluding remarks

The excitatory effect of 5-HT on basal DA release has been reported in all studies in vitro or in vivo, including those

**Table 1** Effect of DA releasers and various 5-HT compounds on different parameters of DA terminal function in vitro and in vivo

| Compounds/ parameter | Preloaded [³H]-DA | Stimulated preloaded [³H]-DA | DA synthesis | Neosynthesized [³H]-DA | Endogenous DA in vitro | Endogenous DA in vivo |
|---|---|---|---|---|---|---|
| DA releaser | | | | | | |
| Amphetamine | + | +/− | + | + | + | + |
| Tyramine | + | +/− | + | + | + | + |
| Non-selective 5-HT agonists | | | | | | |
| 5-HT | + | +/− | − | + | + | + |
| 5-MT | 0 | − | NA | + | | + |
| 5-HTP | + | + | − | + | + | + |
| Tryptamine | NA | − | NA | + | NA | NA |
| 5-HT$_{1A}$ agonists | | | | | | |
| 8-OHDPAT | 0 | 0 | − | NA | NA | + |
| 5-HT$_{1B}$ agonists | | | | | | |
| CP93129 | + | − | NA | NA | 0 | + |
| CGS220602 | | | | | | + |
| 5-HT$_{2A/2C}$ agonists | | | | | | |
| DOI | 0 | 0 | 0 | 0 | 0 | +/0 |
| 5-HT$_3$ agonists | | | | | | |
| 2-Me-5-HT | + | + | NA | NA | + | + |
| 1-Phenylbiguanide | + | + | NA | NA | + | + |
| 5-HT$_4$ agonists | | | | | | |
| BIMU 8 | + | + | NA | NA | + | + |
| Renzapride | + | + | NA | NA | + | + |
| Cisapride | + | + | NA | NA | NA | + |
| Zacopride | | | | | | |

+ excitatory effects, − inhibitory effects, *NA* not available, *0* no effect, *+/−* both excitatory and inhibitory effects have been reported

reporting an inhibitory effect of 5-HT on stimulated [³H]-DA released for in vitro preparations preloaded with [³H]-DA (Ennis et al. 1981; Sarhan et al. 1999). In general, the inhibitory effect of 5-HT can be observed at lower concentrations compared to the excitatory effects. These effects can occur concomitantly at higher concentrations of 5-HT, depending on the experimental parameter used to reveal their occurrence.

**5-HT receptors involved in the excitatory effects of 5-HT on DA release**

Several researchers have attempted to determine the 5-HT receptors involved in the excitatory effects of exogenous 5-HT using 5-HT agonists and antagonists directed to 5-HT receptor subtypes. Despite the availability of a growing number of selective pharmacological tools, a clear picture concerning the 5-HT receptors involved in the excitatory effect of 5-HT on striatal DA release is lacking. To date, the involvement of 5-HT$_{1B}$, 5-HT$_{2A/2C}$, 5-HT$_3$, and 5-HT$_4$ receptors has been proposed. Some of the data in the literature are summarized in Table 1.

*5-HT$_{1A}$ receptors*

Some data have shown that the intrastriatal infusion of high concentrations of the 5-HT$_{1A/7}$ agonist 8-OHDPAT enhanced striatal DA release in vivo (Benloucif and Galloway 1991; Santiago et al. 1998). However, a role for 5-HT$_{1A/7}$ receptors in the effects of 8-OHDPAT remains unlikely given that 5-HT$_{1A}$ antagonists did not reduce this effect (Benloucif and Galloway 1991; Santiago et al. 1998).

*5-HT$_{1B}$ receptors*

The involvement of 5-HT$_{1B}$ receptors in the facilitatory control exerted by 5-HT was postulated 20 years ago by the finding that the striatal application in vivo of several non-selective 5-HT$_{1B}$ agonists such as RU 24969, TFMPP, and *m*-CPP enhanced striatal DA (Benloucif and Galloway 1991). More recently, similar results have been observed following the application of the 5-HT$_{1B}$ agonists CP93129 and CGS20654 or the non-selective 5-HT$_{1/7}$ agonist 5-CT in vitro and in vivo (Bentué-Ferrer et al. 1998; Galloway et al. 1993; Ng et al. 1999; Sarhan et al. 1999; Yadid et al.
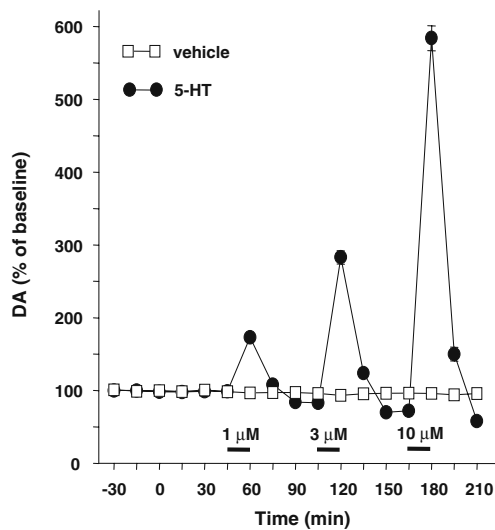
**Fig. 2** Effect of the intrastriatal application of 5-HT on striatal DA release. 5-HT has been applied at 1, 3, or 10 μM by reverse microdialysis in the striatum of anesthetized rats (adapted from De Deurwaerdère et al. 1996; courtesy of the International Society of Neurochemistry)

1994). This effect has been reported in vivo in various structures such as the cortex (Iyer and Bradberry 1996), the nucleus accumbens (Hållbus et al. 1997), or the SN (Thorré et al. 1998). Some 5-HT$_{1B}$ antagonists such as (−)pindolol, at high concentrations only (100 μM), are able to reduce the facilitatory effect of 5-HT or 5-HT$_{1B}$ agonists (Benloucif and Galloway 1991). Also, high concentrations of the 5-HT$_{1B}$ antagonist isamoltane reduced the excitatory effects of 5-CT (Ng et al. 1999). In the nucleus accumbens or the cortex, the mixed 5-HT$_{1B/1D}$ antagonist GR127935 infused at 10 μM reduced 5-HT-induced DA release (Hållbus et al. 1997; Iyer and Bradberry 1996). Nevertheless, some 5-HT antagonists able to block 5-HT$_{1B}$ receptors, such as methiotepine, did not affect the release of striatal DA induced by 5-HT (De Deurwaerdère et al. 1997). In addition, lower concentrations of (−)pindolol, although blocking efficiently the decrease in endogenous 5-HT release elicited by 5-HT$_{1B}$ agonists (Thorré et al. 1998), are unable to affect the excitatory effect of 5-HT or CP 93129 (10 μM) on DA release in the striatum and the SN (Bonhomme et al. 1995, personal communication; Thorré et al. 1998). The excitatory effect of CP 93129 was also not affected in 5-HT$_{1B}$ receptor knock-out mice (De Groote et al. 2003). Recently, it has been reported that the intrastriatal administration of CP 93129 reduced jaw movements induced by apomorphine, but this effect was not blocked by the 5-HT$_{1B}$ antagonist GR55562 (Fujita et al. 2008), confirming that CP 93129 has multiple sites of action other than solely 5-HT$_{1B}$ receptors. These data show that 5-HT$_{1B}$ antagonists lost their selectivity toward 5-HT$_{1B}$ receptors at high concentrations and, in fact, their perfusion at high concentrations increased DA release

(Benloucif and Galloway 1991; Bonhomme et al. 1995; Thorré et al. 1998). These results detract from the hypothesis that striatal 5-HT$_{1B}$ receptors are critically involved in an excitatory control of striatal DA release.

### 5-HT$_{2A/2C}$ receptors

The influence of striatal 5-HT$_{2A}$ and 5-HT$_{2C}$ receptors in the control of striatal DA release still remains enigmatic. This is attributable in part to the long period during which 5-HT$_2$ compounds overlapped on both receptors (Baxter et al. 1995) and the absence of selective agonists for each subtype. Thus, local infusion of the 5-HT$_{2A/2C}$ agonist DOI by reverse microdialysis has been shown to slightly enhance striatal DA release in some studies (Balcioglu and Wurtman 1998; Lucas and Spampinato 2000) but not in others (Benloucif et al. 1993; Ng et al. 1999). DOI did not modulate [$^3$H]-DA release in striatal slices (Jacocks and Cox 1992). The facilitatory effect of 1 μM DOI in vivo is blocked by the 5-HT$_{2B/2C}$ receptor antagonist SB 206553 but not by the 5-HT$_{2A}$ receptor antagonist SR46349 (Lucas and Spampinato 2000), suggesting a preferential role of striatal 5-HT$_{2C}$ receptors in this effect. Intrastriatal infusion of SB 206553 has been shown to effect per se striatal DA release in vivo but the data are contradictory, reporting either an inhibitory (Lucas and Spampinato 2000) or an excitatory effect (Alex et al. 2005; Navailles and De Deurwaerdère 2011). In the nucleus accumbens, the infusion of SB 206553 induced an increase in DA release (Navailles et al. 2006) while 5-HT$_{2C}$ antagonists enhance the expression of the proto-oncogene c-fos in the striatum (De Deurwaerdère et al. 2010). It is noteworthy, however, that 5-HT$_2$ antagonists such as ritanserin, methiotepine, ketanserin, or cinanserin did not reduce the facilitatory effect of 5-HT on striatal DA release in vitro and in vivo (Benloucif et al. 1993; Bonhomme et al. 1995; De Belleroche and Bradford 1980; De Deurwaerdère et al. 1997; Jacocks and Cox 1992).

It has been well established for almost 15 years that 5-HT$_{2A}$ receptors enhance both DA release and DA synthesis (Schmidt et al. 1992). Indeed selective 5-HT$_{2A}$ antagonists such as MDL100907 or SR 46349B, mixed 5-HT$_{2A/2C}$ antagonists, but not 5-HT$_{2B/2C}$ antagonist, are able to reduce the enhancement of DA release induced by MDMA or amphetamine (Porras et al. 2002b; Schmidt et al. 1992; Yamamoto et al. 1995). Similar findings have been observed with the non-selective DA antagonists haloperidol and raclopride (Andersson et al. 1995; Lucas et al. 2000b). On the one hand, the facilitatory effect of MDMA or haloperidol in vivo can be reduced by the intrastriatal administration of 5-HT$_{2A}$ antagonists (Lucas and Spampinato 2000; Schmidt et al. 1994; Yamamoto et al. 1995). These data strongly suggested that striatal 5-HT$_{2A}$ receptors stimulate striatal DA

release. On the other hand, the effect elicited by the intrastriatal administration of MDMA was not reduced by the systemic administration of ketanserin (Nash and Brodkin 1991). Furthermore, on rat striatal slices in vitro, MDL 100907 did not affect the excitatory effect of MDMA on DA release (Schmidt et al. 1994). Koch and Galloway (1997) have reported also that the MDMA-induced DA release was sensitive to endogenous 5-HT only when MDMA was administered peripherally. These data, in apparent contradiction, are however in perfect agreement with the fact that the intrastriatal application of 5-HT elicited an increase in DA release independently of 5-HT$_2$ receptor stimulation (Benloucif et al. 1993; Bonhomme et al. 1995). These data add a higher level of complexity in the interaction between 5-HT and DA systems in which the involvement of 5-HT receptors in the control of striatal DA function is dependent on extrastriatal influences (see the paragraph on the state-dependent involvement of striatal 5-HT receptors).

### 5-HT$_3$ receptors

Blandina et al. (1989) have found that the enhancement of endogenous DA elicited by 5-HT or the 5-HT$_3$ agonist 2-methyl-5-HT in rat striatal slices was suppressed by the 5-HT$_3$ antagonist ICS205930. These data, suggesting the involvement of 5-HT$_3$ receptors in the control of striatal DA release, were soon contradicted. Indeed an action of the 5-HT$_3$ agonists 2-methyl-5-HT, 1-phenylbiguanide, or methyl-chlorophenylbiguanide on DA uptake sites has been shown to contribute to the excitatory effects of these agonists on basal DA release in vitro (Benuck and Reith 1992; Schmidt and Black 1989; Zazpe et al. 1994) and in vivo (Santiago et al. 1995). In line with this possibility, selective 5-HT$_3$ antagonists failed to reduce the effect of 5-HT on DA release in vitro and in vivo in several studies (Bonhomme et al. 1995; Jacocks and Cox 1992; Yi et al. 1991; Zazpe et al. 1994). Given that ICS205930 is able to block 5-HT$_4$ receptors (Dumuis et al. 1989), it was already postulated in 1991 by Deutch and colleagues that the facilitatory effect of 5-HT reported by Blandina et al. (1989) could be attributable to 5-HT$_4$ receptor stimulation (see below).

It is noteworthy to mention that the facilitatory effects of exogenous 5-HT or 2-methyl-5-HT described by Blandina et al. (1989), which were partially direct on striatal DA terminals, were studied in the continuous presence of the DA uptake blocker nomifensine. However, the excitatory effect of 5-HT on DA release in synaptosomes that persist in the presence of nomifensine is not affected by the co-administration of the 5-HT$_{3/4}$ antagonist DAU 6285 (De Deurwaerdère et al. 1997). In addition, a persisting effect of 5-HT or phenylbiguanide in the presence of nomifensine or cocaine on striatal DA release has been observed in several studies (Andrews et al. 1978;

Benuck and Reith 1992; De Deurwaerdère et al. 1997; Jacocks and Cox 1992; Zazpe et al. 1994). The remaining effects of 5-HT or 1-phenylbiguanide after blockade of the DA transporter, often representing a small contribution to their total effect, are insensitive to 5-HT$_3$ antagonists and are likely dependent on the conditions of nomifensine perfusion (Benuck and Reith 1992).

The ability of striatal 5-HT$_3$ receptors to affect striatal DA release has been reported in vivo but it has been associated with very restricted conditions (Porras et al. 2003; see the paragraph on the direct effects of 5-HT on DA terminals). Whether these conditions were met in the study of Blandina et al. (1989) remains an indefinable topic because of the concomitant loss of selectivity of 5-HT and 5-HT$_3$ agents to DA uptake sites. For Fink and Göthert (2007), the in vitro preparation could have included part of the nucleus accumbens or olfactory tubercle in which the control exerted by 5-HT$_3$ receptors might be more pronounced (Zazpe et al. 1994).

### 5-HT$_4$ receptors

Some non-selective 5-HT$_4$ agonists have been shown to sharply enhance DA release in vitro for a limited period of time (Steward et al. 1996). This effect occurs in rat striatal slices but not in rat striatal synaptosomes (De Deurwaerdère et al. 1997; Steward et al. 1996), suggesting that the effect exerted by some of these agonists is indirect with respect to the DA terminals. In vivo, striatal application of several 5-HT$_4$ receptor agonists such as BIMU8, 5-MT, renzapride, cizapride, or (s)-zacopride enhanced striatal DA release (Bonhomme et al. 1995; De Deurwaerdère et al. 1997; Steward et al. 1996). The effect of BIMU8 and 5-MT is partially blocked by 5-HT$_{3/4}$ antagonists (Benloucif et al. 1993; Bonhomme et al. 1995) while the effect elicited by (s)-zacopride is suppressed by the non-selective 5-HT$_4$ antagonist SDZ205557 (Steward et al. 1996). Further, the excitatory effect of 5-HT on DA release has been partly reduced by a variety of 5-HT antagonists sharing the property of blocking 5-HT$_4$ receptors such as DAU 6285, ICS 205930, GR 113808, or GR 125487 (Benloucif et al. 1993; Bonhomme et al. 1995; De Deurwaerdère et al. 1997; Suchowski and Galloway 1995; see Table 2).

The postsynaptic location of striatal 5-HT$_4$ receptors with respect to DA terminals implies that the excitatory influence of 5-HT on DA release via 5-HT$_4$ receptors is indirect. Tetrodotoxin (TTX), a blocker of fast sodium voltage-dependent channels, allows the determination of whether the effect elicited by 5-HT$_4$ receptor stimulation is indirect. Indeed given that action potentials are blocked by TTX, most indirect actions involving another neuronal system are suppressed, so that mainly direct effects on striatal DA terminals persist in the presence of TTX. Using

**Table 2** Pharmacological characterization of the effect of 5-HT on DA release and synthesis. Basal and stimulated effluxes of DA as well as DA synthesis have been separated. Their sensitivity to $Ca^{2+}$ and tetrodotoxin (TTX), 5-HT antagonists, and inhibitor of DA transporters has been reported

| Effects of 5-HT | $Ca^{2+}$-dependent/TTX-sensitive | 5-HT receptor antagonists | References | Inhibitor of DA transporters | References |
|---|---|---|---|---|---|
| Basal efflux of DA | | | | | |
| Excitatory in vitro | No/no–yes | Not sensitive | See references in the extreme right panel + de Belleroche and Bradford 1980 | Cocaine benztropine fluoxetine (> 1 μM) GBR 12909 nomifensine | Andrews et al. 1978 Nurse et al. 1988 |
| | | ICS 205930 | Blandina et al. 1989 | | Jacocks and Cox 1992 Zhou et al. 2005 |
| Excitatory in vivo | Partial/partial | (−)Pindolol | Benloucif and Galloway 1991 | Nomifensine | Suchowski and Galloway 1995 |
| | | DAU 6285 GR125487 | Bonhomme et al. 1995 De Deurwaerdère et al. 1997 | GBR 12909 | De Deurwaerdère et al. 1996 |
| | | ICS 205930 MDL72222 | Benloucif et al. 1993 | | |
| Stimulated efflux of DA | | | | | |
| Inhibitory in vitro | (Yes)/no | Methysergide | Westfall and Tittermary 1982 | Nomifensine | Nurse et al. 1988 |
| | | Ketanserin Mianserin SB 221485 | Muramatsu et al. 1988 Sarhan et al. 1999 | Benztropine | |
| | | (-) Pindolol | | | |
| Excitatory in vitro | (?)/(?) | Not sensitive | de Belleroche and Bradford 1980 | Nomifensine GBR 12909 | Kamal et al. 1983 Zhou et al. 2005 |
| DA synthesis: inhibitory effect in vitro | | | | | |
| Inhibitory in vitro | (?)/no | Methysergide | de Belleroche and Bradford 1980 | Cocaine | Andrews et al. 1978 |
| | | Various non-selective 5-HT$_{1A}$ antagonists | Johnson et al. 1993, 1996 | | |

such an approach, it has been reported that the facilitatory effects on the striatal DA release of (s)-zacopride in vivo or renzapride and cisapride in vitro were suppressed in the presence of TTX (De Deurwaerdère et al. 1997; Steward et al. 1996). The data concerning 5-HT are more complex. Indeed in vivo 5-HT-evoked striatal DA release is reduced by almost 50% in the presence of TTX, suggesting the involvement of mechanisms both pre- and postsynaptic with respect to DA terminals (De Deurwaerdère et al. 1996; see Fig. 3). However, the ability of 5-HT$_4$ antagonists to block the facilitatory effect of 5-HT on DA release was lost in the presence of TTX in vivo, suggesting that 5-HT$_4$ antagonists are able to prevent only the indirect but not the direct excitatory effects of 5-HT (De Deurwaerdère et al. 1997).

In conclusion, striatal 5-HT$_4$ receptors would be able to facilitate striatal DA release through an indirect mechanism involving other striatal neurotransmitters.

**Other 5-HT receptors**

Due to the lack of agonists and antagonists at 5-HT$_{1E}$, 5-HT$_6$, and 5-HT$_7$ receptors until recently (Barnes and Sharp 1999; Saudou and Hen 1994), no direct evidence is yet available concerning the influence of these receptors on DA release. The data showing that neither ritanserin nor methiotepine effect exogenous 5-HT-stimulated DA release in vivo (Benloucif and Galloway 1991; De Deurwaerdère et al. 1997) suggest indirectly that the 5-HT$_{6/7}$ receptors are not involved in this effect. Indeed ritanserin and methiotepine display a moderate to high affinity for 5-HT$_{6/7}$ receptors (Monsma et al. 1993). Whatever the situation concerning these 5-HT receptors, the available data suggest that several 5-HT receptors could contribute to the excitatory effects of exogenous 5-HT both in vivo and in vitro. It is noteworthy, however, that a complete blockade of the facilitatory effect of 5-HT has never been observed in vitro or in vivo,
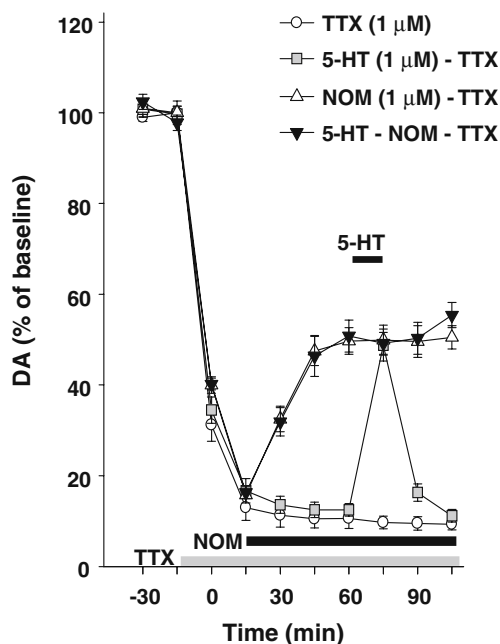
**Fig. 3** Evidence for a carrier-mediated release of striatal DA induced by the local infusion of 1 μM 5-HT. Tetrodotoxin (*TTX*) and nomifensine (*NOM*) were applied at 1 μM as indicated by the *gray* and the *black horizontal bars*, respectively. 5-HT was infused at 1 μM during 15 min. These results illustrate that TTX, which inhibits striatal DA release, does not completely prevent the effect of 5-HT ($p < 0.001$, Tukey's test after significant ANOVA). In these conditions, NOM induces a slight increasing effect on striatal DA release. When combining TTX+NOM, the TTX-insensitive effect of 5-HT on DA release is abolished. Notably, such an experiment could not be performed without TTX. Indeed 1 μM NOM enhanced DA release by about 660% of baseline, preventing an accurate study of the effect of 1 μM 5-HT (about 160% of baseline values). Results are expressed in percent (%) of baseline (adapted from De Deurwaerdère et al. 1996; courtesy of the International Society of Neurochemistry)

whatever the receptor subtypes considered. Another mechanism underlying the excitatory effect of 5-HT on striatal DA release has to be considered.

### 5-HT receptors involved in the inhibitory effects of 5-HT on DA release

The inhibitory effect of 5-HT appears sensitive to various 5-HT antagonists although a clear picture concerning the 5-HT receptor subtype(s) involved is also lacking.

#### *5-HT$_{1A}$ receptors*

Striatal 5-HT$_{1A}$ receptors have not been directly involved in the inhibitory effect elicited by 5-HT on striatal DA release, but they have been claimed to mediate the inhibitory effect of 5-HT on striatal DA synthesis. Indeed several 5-HT$_{1A}$ agonists including 8-OHDPAT are able to reduce DA synthesis in vitro on rat brain synaptosomes (Johnson et al. 1993, 1996). In addition, the inhibitory effect of 5-HT as

well as some 5-HT$_{1A}$ agonists on tyrosine hydroxylase activity was blocked by methysergide (de Belleroche and Bradford 1980) or by non-selective 5-HT$_{1A}$ antagonists (Johnson et al. 1993, 1996). In this latter study, however, each non-selective 5-HT$_{1A}$ antagonist induced an inhibitory effect (Johnson et al. 1993). In addition, the EC$_{50}$ of 5-HT$_{1A}$ agonists or 5-HT to inhibit tyrosine hydroxylation was almost a thousand times higher than their Kd for 5-HT$_{1A}$ receptors (Zifa and Fillion 1992). Finally, 5-HT$_{1A}$ receptors are not located on DA terminals and the inhibitory effect of 5-HT$_{1A}$ drugs on striatal DA synthesis may not involve a specific action at 5-HT$_{1A}$ receptors.

#### *5-HT$_{1B}$ receptors*

Non-selective 5-HT agonists such as 5-MT, 5-*N,N*-dimethyl-5-HT or tryptamine have been shown to mimic the inhibitory effect of exogenous 5-HT on [$^3$H]-DA release in striatal slices (Ennis et al. 1981). More recently, the 5-HT$_{1B}$ agonist CP93129 and the non-selective 5-HT$_1$ agonist 5-CT, but not the 5-HT$_{1A}$ agonist 8-OHDPAT, have been shown to decrease [$^3$H]-DA released by 20 mM K$^+$ in rat brain synaptosomes (Sarhan et al. 1999). Although the concentration of these compounds required to inhibit stimulated [$^3$H]-DA release is very high (>300 nM) with respect to their respective Kd for 5-HT$_{1B}$ receptors (1–10 nM), it has been postulated that the efficacy of 5-HT$_{1B}$ agonists on postsynaptic 5-HT$_{1B}$ receptors is lower compared to presynaptic 5-HT$_{1B}$ receptors controlling 5-HT release (Sarhan and Fillion 1999). The inhibitory effect elicited by 5-HT, CP 93129, and 5-CT is also reduced by the 5-HT$_{1B}$ antagonist SB 224289 in rat striatal synaptosomes (Sarhan et al. 1999; Sarhan and Fillion 1999). Finally, the effect of CP93129 or 5-CT is reduced in mutant mice lacking 5-HT$_{1B}$ receptors (Sarhan et al. 2000). These data suggest the involvement of 5-HT$_{1B}$ receptors in the inhibitory effect of 5-HT.

As for the situation described for the 5-HT$_4$ receptor-dependent excitatory control, one may expect that the inhibitory control exerted by 5-HT$_{1B}$ receptors on DA release is indirect because 5-HT$_{1B}$ receptors are not present on DA terminals. Nevertheless, the inhibitory effects of 5-HT on [$^3$H]-DA release are direct on striatal DA terminals. Indeed the ability of 5-HT to inhibit electrical- or K$^+$-stimulated striatal [$^3$H]-DA and DA synthesis occurs on synaptosomes or on striatal slices in the presence of TTX (Sarhan et al. 1999; Westfall and Tittermary 1982). This finding has been reported with several 5-HT agonists including CP 93129 (Ennis et al. 1981; Sarhan et al. 1999). Therefore, due to the anatomical findings all supporting a postsynaptic location of 5-HT$_{1B}$ receptor with respect to striatal DA terminals, the involvement of 5-HT$_{1B}$ receptors in the inhibitory control of enhanced striatal DA release is

not clear. It is possible that the loss of selectivity of these 5-HT$_1$ ligands may dramatically interfere with DA terminals function (see below).

### 5-HT$_2$ receptors

A role for 5-HT$_2$ receptors was originally postulated to explain the inhibitory effect of 5-HT on striatal DA release. Indeed non-selective 5-HT antagonists such as methysergide or methiotepine (Ennis et al. 1981; Westfall and Tittermary 1982) and non-selective 5-HT$_2$ antagonists such as ketanserin or mianserin (Ennis et al. 1981; Muramatsu et al. 1988) are able to reduce the inhibitory effect of 5-HT or 5-MT on K$^+$-stimulated [$^3$H]-DA release. These compounds are unfortunately not selective toward 5-HT$_2$ receptors.

Pehek and colleagues (Alex and Pehek 2007; Alex et al. 2005) have shown that the intrastriatal infusion of the 5-HT$_{2B/2C}$ receptor antagonist SB 206553 enhances striatal DA release in vivo, suggesting that striatal 5-HT$_{2C}$ receptors may participate in the ability of peripheral 5-HT$_{2C}$ antagonists to unmask the tonic inhibitory control of 5-HT$_{2C}$ receptors on in vivo striatal DA release (De Deurwaerdère et al. 2004; Di Giovanni et al. 1999; Navailles and De Deurwaerdère 2011). An inhibitory action of 5-HT$_{2C}$ receptors is further supported by data reporting an excitatory effect of local infusion of the 5-HT$_{2C}$ antagonist RS 102221 into the nucleus accumbens (Dremencov et al. 2005).

### Concluding remarks

Several receptors have been altogether proposed to mediate the effects of 5-HT on striatal DA function (Fig. 4). The absence of complete blockade of 5-HT-induced DA release with any of several 5-HT antagonists suggests that another mechanism is likely involved in the excitatory effects elicited by 5-HT on DA release. In addition, despite the biochemical evidence supporting a direct inhibitory role of 5-HT$_{1B}$, 5-HT$_2$, or 5-HT$_{1A}$ receptors on striatal DA function, anatomical data lessens this possibility.

## Direct effects of 5-HT on DA terminals: involvement of DA reuptake sites

### Involvement of DA transporters

The involvement of DA transporters, a protein located on the plasma membrane of DA terminals and involved in the high rate of extracellular DA clearance in normal conditions (Luthman et al. 1993), has been proposed to explain the excitatory effect of 5-HT on DA release. Briefly, such a mechanism is direct on striatal DA terminals and is non-exocytotic. Thus, as opposed to an exocytotic release, the output of DA from the cytosol to the extracellular space occurs independently of the extracellular Ca$^{2+}$ ions via the reversal of the direction of DA transport (Levi and Raiteri 1993). The release of DA induced through DA transporters is sensitive to all DA uptake blockers. Amphetamine and tyramine are two well-described DA releasers (Seiden et al. 1993; Sulzer et al. 1995) (Fig. 5).

To be operational, a carrier-mediated release of DA requires the entry of the releaser inside DA terminals. It has been shown for many years that 5-HT is a substrate of DA uptake sites (Shaskan and Snyder 1970) and may be transported inside DA neurons (Feuerstein et al. 1986; Kelly et al. 1985; Ternaux et al. 1977; Zhou et al. 2005). The "false labeling" of DA terminals by 5-HT in in vitro caudate preparations of rodents occurs for concentrations of [$^3$H]-5-HT likely lower than 0.1 μM in the presence of a 5-HT uptake blocker (Feuerstein et al. 1986; Kelly et al. 1985). It requires to some extent functional DA reuptake sites since the false labeling of DA neurons with 5-HT is dramatically reduced in the presence of nomifensine (Feuerstein et al. 1986; Lupp et al. 1992; Zhou et al. 2002, 2005 for functional aspects). These data indicate that 5-HT can enter DA terminals.

### Presynaptic versus postsynaptic effect

Several studies have attempted to determine whether 5-HT acts directly on DA terminals (presynaptic) or indirectly, involving another neurotransmitter system (postsynaptic). The fact that 5-HT enhanced DA on striatal synaptosomes suggested the existence of mechanisms occurring directly at
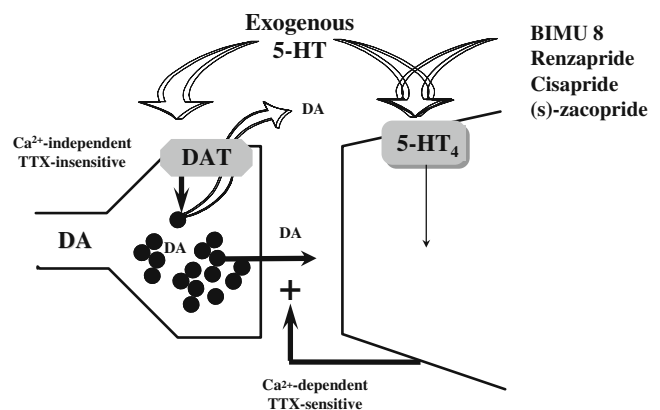


Fig. 4 Drawing representing the influences of exogenous 5-HT on striatal DA release in vivo. Exogenous 5-HT, applied in the striatum, triggers both a Ca$^{2+}$-independent/TTX-insensitive (directly on DA terminals) and Ca$^{2+}$-dependent/TTX-sensitive mechanisms (indirect with respect to DA terminals). The direct effect elicits a non-exocytotic release of DA that is abolished by DA reuptake blockers, but not by 5-HT$_4$ antagonists. The putative indirect effect is sensitive to 5-HT$_4$ antagonists. Various 5-HT$_4$ agonists are able to increase DA release in a TTX-sensitive manner via 5-HT$_4$ receptor stimulation
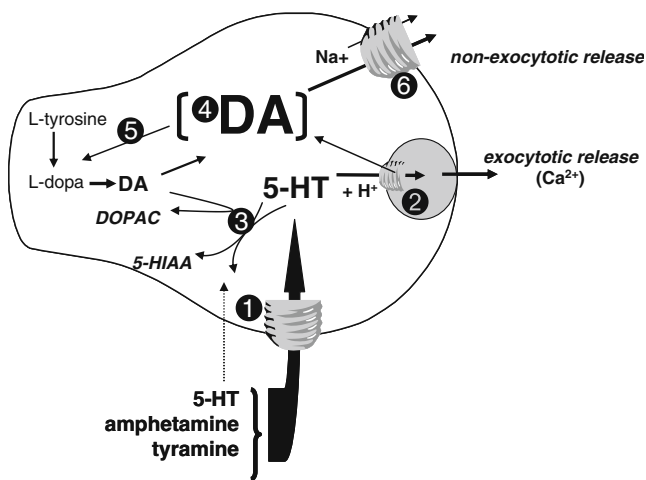
**Fig. 5** Drawing representing the influences by steps of 5-HT entry into striatal DA terminals. (*1*) Serotonin enters DA terminals by DA transporters. Other molecules such as amphetamine are known to enter DA terminals by DA transporters but may also enter by other mechanisms (small target). (*2*) Cytosolic 5-HT competes with DA to enter the exocytotic vesicles on VMAT. In this case, 5-HT can be released from DA terminals by exocytosis. (*3*) Cytosolic 5-HT is metabolized by monoamine oxydase A in the cytosol. (*4*) Cytosolic DA is dramatically increased by less metabolism and less entry in exocytotic vesicles. (*5*) The increase in cytosolic DA inhibits tyrosine hydroxylase activity. (*6*) Via a mechanism depending on the releaser, the functioning of the DA transporter is inverted and DA is released by a non-exocytotic process. *5-HT*, 5-hydroxytryptamine; *DA*, dopamine; *DOPAC*, dihydroxyphenylacetic acid; *5-HIAA*, 5-hydroxyindolacetic acid

the level of DA terminals (Andrews et al. 1978; De Deurwaerdère et al. 1997; Yi et al. 1991). As mentioned above, it has been shown that 5-HT still enhances/inhibits DA release on rat striatal slices completely (Ennis et al. 1981; Jacocks and Cox 1992; Zazpe et al. 1994) or partly (Blandina et al. 1989) in the presence of TTX. In vivo, half of the 5-HT-evoked striatal DA release persists in the presence of TTX and this remaining effect is insensitive to 5-HT$_{3/4}$ antagonists (De Deurwaerdère et al. 1996, 1997; see Table 2).

*Exocytotic versus non-exocytotic mechanism*

Studies have provided evidence for both an exocytotic and non-exocytotic mechanism of action mediated by 5-HT regarding its excitatory and inhibitory effects on striatal DA release. First, numerous in vitro and ex vivo data have suggested that 5-HT or its metabolic precursor 5-hydroxytryptophan (5-HTP) elicit a non-exocytotic release of DA (Andrews et al. 1978; Awazi and Gulberg 1978; Butcher et al. 1972; Ng et al. 1972). It has been shown that the release of [$^3$H]-DA or endogenous DA elicited by 5-HT in rat striatal slices or synaptosomes did not depend on the presence of extracellular $Ca^{2+}$ (Jacocks and Cox 1992; Yi et

al. 1991; Zazpe et al. 1994). In vivo, the effect of 5-HT was reduced by half following the removal of $Ca^{2+}$ ions from the perfusion medium, indicating that 5-HT is able to elicit a non-exocytotic release of DA (De Deurwaerdère et al. 1996). Given that a TTX-sensitive effect is also $Ca^{2+}$ dependent (Westerink et al. 1987), the similar reduction observed with TTX and with the removal of $Ca^{2+}$ ions indirectly suggested that the TTX/$Ca^{2+}$-insensitive mechanism of 5-HT is entirely non-exocytotic in vivo (De Deurwaerdère et al. 1996, 1997). The contribution of this mechanism might be even higher in the total effect of 5-HT in vivo. Indeed the consequence of the entry of 5-HT into DA terminals is necessarily associated with the fact that DA reuptake is impeded. That part, which would be similar to a DA reuptake blocker, is a TTX-sensitive mechanism. Consequently, a small contribution of other mechanisms such as 5-HT$_4$ receptors might have been magnified simply because DA reuptake sites were less efficient in the presence of 5-HT.

At variance, the inhibitory effect of 5-HT or 5-HT agonists on stimulated [$^3$H]-DA release in striatal slices or synaptosomes is dependent on the extracellular presence of $Ca^{2+}$ (Sarhan et al. 1999). This approach is, however, subject to caution given that the $K^+$-stimulating effect on DA release is also suppressed in the absence of $Ca^{2+}$ and reduced in the presence of $Ca^{2+}$ channel blockers (El Ayadi et al. 2001). Therefore, the fact that 5-HT or 5-HT agonists are unable to affect [$^3$H]-DA release in the absence of $Ca^{2+}$ does not necessarily imply that their ability to reduce $K^+$-induced [$^3$H]-DA release is a receptor-mediated mechanism.

*Influence of DA reuptake site blockers in the facilitatory effect of 5-HT*

The evidence for a non-exocytotic process elicited by 5-HT on DA release is compatible with an effect mediated by DA transporters (Levi and Raiteri 1993). As discussed above, in vitro, the excitatory effect of 5-HT on basal or stimulated DA release is reduced by various DA uptake blockers (Andrews et al. 1978; Benuck and Reith 1992; De Deurwaerdère et al. 1997; Jacocks and Cox 1992; Kamal et al. 1983; Nurse et al. 1988; Zazpe et al. 1994; Zhou et al. 2005) (see Table 2). In vivo, a concentration of the DA uptake blocker nomifensine as low as 100 nM was able to reduce the release of DA induced by 3 μM 5-HT (De Deurwaerdère et al. 1996). To better address the role of DA reuptake sites, the effect of 5-HT was studied in the presence of TTX and nomifensine. This procedure further reduces the effect of nomifensine itself since, in the presence of TTX, the effect of DA reuptake inhibitors is strongly attenuated (Westerink et al. 1987, 1989). In these conditions, the TTX-resistant release of DA elicited by low 5-HT concentrations was suppressed in the presence of 1 μM nomifensine (Fig. 3).

Behavioral data also support the involvement of a DA carrier-mediated release of DA induced by 5-HT. Indeed it has been reported that the local administration of 5-HT (20 μg/μl) in the ventral striatum elicits orofacial stereotypies in rats (Yeghiayan and Kelly 1995). This effect, insensitive to various 5-HT antagonists, disappeared in rats with a lesion of DA neurons, administering the non-selective DA receptor antagonist haloperidol or the DA uptake blocker GBR12909 (Yeghiayan et al. 1997). These authors conclude that the behavioral effect elicited by the local administration of 5-HT in the striatum is primarily attributable to a carrier-mediated release of DA elicited by 5-HT.

In conclusion, 5-HT is capable of inducing a carrier-mediated release of striatal DA. This mechanism is consistent among all studies (in vitro or in vivo) reporting an excitatory effect of 5-HT on basal DA release.

### Influence of DA reuptake site blockers in the inhibitory effects of 5-HT

The rationale for studying the influence of DA reuptake sites in the inhibitory effect of 5-HT is to prevent the entry of 5-HT inside DA terminals. Indeed it is known that amphetamine and tyramine may inhibit stimulated $[^3H]$-DA release from $[^3H]$-DA preloaded striatal slices and synaptosomes (Bowyer et al. 1987; de Langen et al. 1979; Kamal et al. 1983). This effect occurs at concentrations unable to induce a basal efflux of DA through DA transporters and is $Ca^{2+}$ dependent. At higher concentrations of amphetamine or tyramine, this mechanism is concomitant to the DA carrier-mediated release of DA (Bowyer et al. 1987; Kamal et al. 1983). The inhibitory effect of amphetamine on stimulated $[^3H]$-DA release from striatal slices is blocked by DA reuptake blockers (Kamal et al. 1983).

Concerning 5-HT, Westfall and Tittermary (1982) have described the inhibitory effect of 5-HT on the electrically stimulated release of $[^3H]$-DA in the presence of the DA uptake blocker benztropine, but these authors have not studied the effect of 5-HT without benztropine. On the other hand, the inhibitory effect of 5-HT on $K^+$-stimulated release of $[^3H]$-DA was suppressed by nomifensine and benztropine (Nurse et al. 1988) (Table 2). For these authors, 5-HT is displacing preloaded $[^3H]$-DA from the vesicular pool in the cytoplasm so that less $[^3H]$-DA is available when inducing a depolarizing stimulation (Nurse et al. 1988). This hypothesis is supported by in vivo data showing that 5-HT can be released by DA neurons in rats bearing a lesion of 5-HT neurons and receiving an acute administration of 5-HTP (Jackson and Wightman 1995). Studies conducted by Ng et al. (1972) have shown by fluorometry that 5-HTP enters DA neurons and is converted to 5-HT inside DA terminals by endogenous L-aromatic

acid decarboxylase. They showed that an inhibitor of decarboxylase blocked the facilitatory effect of 5-HTP on $[^3H]$-DA in $[^3H]$-DA preloaded striatal slices. These results indicated that the ability of 5-HTP to elicit an efflux of DA is dependent on its conversion to 5-HT inside DA terminals. More importantly, Feuerstein et al. (1986) have clearly shown in vitro that $[^3H]$-5-HT, loaded in DA terminals, can be released by high $K^+$ stimulation while Zhou et al. (2005) have reported that 5-HT can be co-released with DA provided that 5-HT is able to enter DA terminals via DA reuptake sites. These data are compatible with the fact that vesicular transporters (VMAT2), ATPase pumps coupling the co-transport of the monoamine with two protons, are identical for all monoamines (Fig. 5) (Adam et al. 2008). Similarly, brain 5-HT terminals are responsible for the release of DA induced by an injection of its metabolic precursor L-DOPA in hemiparkinsonian rats (Navailles et al. 2010).

This mechanism, proposing that a drug can dilute the quantity of DA available for release, has also been used to explain the inhibitory effects of amphetamine on DA release in vitro and in vivo (Jones et al. 1998; Kamal et al. 1983; Kuhr et al. 1985; Schmitz et al. 2001). In addition, the inhibitory effects of 5-HT on DA synthesis have also been blocked by cocaine (Andrews et al. 1978). For these authors, the displacement of DA from its storage vesicle enhances free DA in the cytosol and, consequently, inhibits tyrosine hydroxylase activity (Fig. 5; Table 2).

### Influence of DA mechanisms in the inhibitory effects of 5-HT agents

The data are more complex with 5-HT agonists because their putative direct or indirect interaction with DA transporters is not evident and even less studied. Nonetheless, 5-HT-related compounds that are able to inhibit stimulated $[^3H]$-DA release from $[^3H]$-DA preloaded in rat brain preparations have their own stimulatory effects in the same studies or in others. In particular, CP 93129 produces a non-exocytotic release of $[^3H]$-DA on striatal synaptosomes when applied at high concentrations (>1 μM) (Sarhan et al. 1999), implying that at lower concentrations (300 nM) CP 93129 has already reached the cytosol of the DA terminal. Similarly, 5-MT (De Deurwaerdère et al. 1997), 5-NN-MeOT (Berge et al. 1983; Yeghiayan et al. 1997), and 5-CT (Ng et al. 1999) have been shown to enhance DA transmission (Table 2). The data are not clear for tryptamine although this compound is a releaser of 5-HT and noradrenaline in the myenteric plexus while its affinity for 5-HT receptors is very low (Takaki et al. 1985). In addition, it enters DA terminals (Zhou et al. 2005). Therefore, the entry of 5-HT and 5-HT agonists into DA terminals has to be considered to explain their inhibitory effects on

stimulated [$^3$H]-DA release. Unfortunately, there is not one signature for a DA releaser to modify DA parameters from DA terminals. For instance, to the best of our knowledge, 5-HT$_3$ agonists have never been reported to decrease K$^+$-stimulated [$^3$H]-DA release though they have clearly been involved in a carrier-mediated release of DA. Thus, the effects of all these agents are critically dependent on their pharmacological properties and the in vitro experimental procedures employed (see Herdon et al. 1985 and Kamal et al. 1983 for comparison between amphetamine and 5-HT; Fink and Göthert 2007).

### Concluding remarks

The displacement of DA by 5-HT from its vesicle is a satisfactory alternative to explain the inhibitory effects of 5-HT in vitro. Indeed, as mentioned earlier, this effect is direct on DA terminals whereas 5-HT receptors thought to mediate these effects, namely, 5-HT$_{1A}$, 5-HT$_{1B}$, and 5-HT$_{2A/2C}$ receptors, are not present on DA terminals. Obviously, this hypothesis implies that 5-HT antagonists lose their selectivity for 5-HT receptors at the concentrations used and that they directly act inside DA terminals. Additional studies are warranted to further evaluate this pharmacological issue.

### Conclusion

Although the involvement of 5-HT receptors has been proposed, the inhibitory effect of 5-HT on striatal DA release has been described mainly in one type of in vitro study (stimulated [$^3$H]-DA release from [$^3$H]-DA preloaded preparations) that relies on the integrity of the releasable pool (Herdon et al. 1985). In any case, due to the concentration of 5-HT used (>100 nM), the presence of 5-HT inside DA terminals and vesicles has to be considered. Thus, both the excitatory and inhibitory effects of 5-HT on striatal DA release and synthesis might have the same origin: the entry of 5-HT into DA terminals.

The concomitant action of 5-HT inside DA terminals warns further studies concerning the striatal 5-HT mechanisms elicited by exogenous 5-HT in the control of DA release. For instance, the data accumulated lately concerning the contribution of 5-HT$_4$ receptors in the control of striatal DA release does not match the findings obtained with 5-HT$_4$ agonists and antagonists. Indeed, it has been hypothesized that 5-HT$_4$ receptors stimulate only the impulse-dependent striatal DA release (Porras et al. 2003; Pozzi et al. 1995). In their recent review, Fink and Göthert (2007) discuss the possibility that the conditions to highlight presynaptic influence of 5-HT$_4$ receptors on striatal DA release have not been completely addressed, in particular in the presence of concomitant and depolarizing triggering stimuli. Indeed,

the excitatory effect of exogenous 5-HT on DA release is not an impulse-dependent release of DA. Thus, one may question the extent to which the mechanisms described in vitro or in vivo by directly applying 5-HT or 5-HT agonists occur in physiological conditions (Gallager et. al 1975). An important point seems to address the putative ability of endogenous 5-HT to enter DA neurons.

### Effect of Endogenous 5-HT on striatal DA function: Significance and physiological relevance of a carrier-mediated release of DA elicited by 5-HT

The important question coming from these studies is to determine the extent to which 5-HT may enter DA terminals as a basic physiological process regulating DA release and synthesis. In the following section, the ability of endogenous 5-HT to induce a carrier-mediated release of DA will be mainly considered although, as illustrated before, inhibitory effects of 5-HT on stimulated striatal DA release in vitro, even if they are independent of 5-HT receptors, occur at lower 5-HT concentrations.

It has been shown in mice lacking monoamine oxidase that 5-HT may be found in DA terminals, suggesting that 5-HT may be accumulated over a long period of time in DA terminals. However, such an accumulation is not necessarily associated with acute effects such as the above-mentioned inhibitory or excitatory effects on DA release and synthesis. The limiting factor for eliciting such mechanisms in vivo should be the concentration of endogenous 5-HT reached in the vicinity of DA terminals. This concentration could be close to 100 nM (probably lower) to enter DA terminals through DA transporters (Feuerstein et al. 1986; Zhou et al. 2005). It remains to be determined whether endogenous 5-HT, released from striatal 5-HT terminals, can reach approximately a 100 nM concentration at nearby DA terminals.

### Extracellular concentration of 5-HT

The basal extracellular concentration of 5-HT, determined in microdialysis experiments in vivo, is extremely low in the striatum, ranging from 0.5 to 2 nM (Ferré et al. 1994; Kalén et al. 1988; Kreiss et al. 1993). Moreover, given that 5-HT terminals are rarely in close apposition to DA terminals in this region (Soghomonian et al. 1987), it seems difficult for 5-HT to enter striatal DA terminals and, *a fortiori*, trigger a carrier-mediated mechanism in resting conditions.

### Mobilization of endogenous 5-HT

Methods to enhance endogenous 5-HT release have been tried by increasing 5-HT nerve activity or impair-

ing 5-HT reuptake with pharmacological manipulations (Table 3).

### Dorsal raphe electrical stimulation

DRN electrical stimulation has been shown to increase endogenous 5-HT release from 5-HT nerve terminals (Sharp et al. 1989). This effect is of small magnitude with respect to other pharmacological-based treatments (see below) since it elicits an increase of 2 to 5 times basal extracellular levels of 5-HT. In these conditions, DRN electrical stimulation failed to enhance DA release in the striatum (De Deurwaerdère et al. 1998; De Simoni et al. 1987). These data suggest that a carrier-mediated release of DA elicited by endogenous 5-HT cannot be induced by simply increasing 5-HT nerve activity. It is not likely that a concentration of 100 nM is obtained following such a procedure. This hypothesis is consistent with in vitro data

performed at the level of the SN, a region that displays a dense 5-HT innervation (Moukhles et al. 1997), in which repeated pulse stimulation enhanced extracellular 5-HT concentration to about 65 nM (Bunin and Wightman 1998).

### Pharmacological manipulations

Pharmacological manipulations of 5-HT nerve terminal activity in the striatum represent another way to elicit an increase of endogenous 5-HT extracellular levels. It is usually achieved by infusing selective 5-HT reuptake inhibitors (SSRI) through the dialysis probe of the microdialysis system. The major drawback of such an approach is that these molecules may display a non-negligible affinity for DA reuptake sites and may directly act inside DA terminals (Lupp et al. 1992). Most of them display an affinity ranging from 5 to 50 nM for 5-HT reuptake sites while their affinity for DA uptake sites is close to

**Table 3** Effect of systemic or intrastriatal administration of 5-HT agents on basal or activated DA release. The global magnitude of effect of these agents on DA release has been reported. The involvement of endogenous 5-HT in their effect has been directly studied in rats bearing a lesion of 5-HT neurons or, indirectly, in rats receiving a 5-HT antagonist. The influence of some of these agents combined with DA drugs has been reported at the right side to illustrate the "state-dependent" action of endogenous 5-HT. Some references have been included

| 5-HT transporters agents | Regimen | Effect on basal DA release | Involvement of endogenous 5-HT | Effect on activated DA release | References |
|---|---|---|---|---|---|
| Systemic administration | | | | | |
| Fluoxetine | 5 mg/kg | None | / | +(Amphetamine) | Lucas et al. 2000a |
| | 10 mg/kg | None, + | nd | +(Haloperidol) | Balcioglu and Wurtman 1998 |
| | 20 mg/kg | None, − | nd | | Nash and Brodkin 1991 |
| Citalopram | 1, 5 mg/kg | None/none | | + | De Deurwaerdère et al. 1995; 1998 |
| Clomipramine | 10 mg/kg | | / | nd | Schmidt et al. 1993; 1994 |
| | | | / | | Santiago et al. 1998 |
| D-Fenfluramine | 1, 2.5 mg/kg | 0 | / | +(Phentermine) | |
| | 5, 10 mg/kg | + | nd/yes (5-HT$_{2A}$ receptors) | nd | |
| MDMA | 10, 20 mg/kg | + | Yes (5-HT$_{2A}$ receptors) | nd | |
| DRN electrical stimulation | 3, 5, 10 Hz | 0 | | +(Haloperidol) | De Simoni et al. 1987 |
| | 20 Hz | − | Yes | | |
| Instrastriatal application (μM) | | | | | |
| Fluoxétine | 1, 10 | / | / | +(Haloperidol) | Lucas et al. 2000b |
| | 100 | + 400% | Nd | | Yadid et al. 1994 |
| | | | | | Santiago et al. 1998 |
| Citalopram | 1 | 0 | / | +(Haloperidol) | De Deurwaerdère et al. 1995 |
| | 25, 100 | + 25%/+67% | No | | Koch and Galloway 1997 |
| | | | | | Nash 1990 |
| Alaproclate | 400 | +80% | Yes | | |
| Clomipramine | 5, 10, 100 | 30%, 120%, 280% | No | | |
| D-Fenfluramine | 5, 10, 25, 100 | 12%, 35%, 65%, 150% | No | | |
| MDMA | 10 | 148% | No | | |

micromolar concentrations (Thomas et al. 1987). Considering a relative probe membrane recovery of 10% in vivo, most of these compounds should not be infused above 10 μM to keep a relative selectivity for 5-HT uptake sites with respect to DA uptake sites. Each time a concentration higher than 10 μM has been used, 5-HT uptake inhibitors such as clomipramine (Santiago et al. 1998), fluvoxamine (Koch and Galloway 1997), citalopram (De Deurwaerdère et al. 1995), fluoxetine (Benloucif and Galloway 1991) or alaproclate (Yadid et al. 1994), enhanced striatal DA release. Confirming the loss of selectivity of high concentrations of these compounds, the excitatory effects elicited by 25 μM citalopram or 100 μM chlomipramine on striatal DA release were not affected by a lesion of 5-HT neurons (Lucas et al. 2000a; Santiago et al. 1998). At lower concentrations (1 μM), citalopram or fluoxetine failed to modify striatal DA release. At higher concentrations in vitro, fluoxetine behaved as DA transporter blocker (Izenwasser et al. 1990). Again, the enhancement of extracellular 5-HT in these conditions is relatively small and should not potentiate more than 5 times basal extracellular levels of 5-HT (Kreiss et al. 1993). Of note, the stimulatory effect of alaproclate has been suppressed by a 5,7-DHT lesion of dorsal raphe nucleus 5-HT neurons (Yadid et al. 1994). Given the poor selectivity of this compound that behaves as a voltage-gated potassium channels blocker or a noncompetitive antagonist of the NMDA receptor (see Wilkinson et al. 1994) and considering the very high concentrations used by Yadid et al. (400 μM), one may foresee methodological problems in this experiment. As a further comment, the DA effects elicited by high concentrations of these drugs may come from multiple sources including the blockade of DA uptake sites, their affinity for sigma receptors (Narita et al. 1996), known to affect striatal DA release (Moison et al. 2003), or their numerous other targets in the brain (for review see Millan 2006).

A strong enhancement of endogenous 5-HT release can be obtained by directly infusing 5-HT releasers such as fenfluramine (Kirby et al. 1995; Schwartz et al. 1989). Such an increase may reach over 1000% of basal levels of 5-HT (Schwartz et al. 1989). However, the facilitatory effect of 25 μM d-fenfluramine, a concentration known to enhance 5-HT release (Berger et al. 1992), was not reduced in rats bearing a quasi-total destruction of 5-HT neurons (De Deurwaerdère et al. 1995). These data indicated that intrastriatal infusion d-fenfluramine is not a good pharmacological approach to selectively address the role of striatal endogenous 5-HT. As discussed previously, the ability of the 5-HT releaser MDMA to affect striatal DA release via 5-HT-dependent mechanisms is obtained when it is peripherally administered (Nash, 1990), but not when it is directly applied in the striatum (Koch and Galloway 1997; Schmidt et al. 1994).

Altogether, these data suggest that intrastriatal manipulations of endogenous 5-HT barely affect striatal DA release in resting conditions (Table 3).

### Endogenous 5-HT and inhibitory effect on striatal DA release

The in vitro data indicated that the inhibitory effects of 5-HT on stimulated striatal DA release are observed at lower concentrations of 5-HT. Some inhibitory effects on striatal DA release have been reported when central 5-HT transmission is increased (De Deurwaerdère et al. 1998; Dewey et al. 1995). It is unlikely, however, that this inhibitory effect corresponds to the in vitro data because it has been observed in resting, but not in stimulated DA conditions. Rather, in conditions in which exocytotic release of DA is enhanced by haloperidol or electrical stimulation of the medial forebrain bundle, an enhancement of 5-HT extracellular levels either potentiated or did not affect stimulated striatal DA release (De Simoni et al. 1987; Dugast et al. 1994; Lucas et al. 2000a). Therefore, a direct effect of 5-HT in inhibiting stimulated striatal DA release seems unlikely.

The inhibitory effects induced by a global enhancement of endogenous 5-HT elicited by DRN stimulation or SSRI on striatal DA release could be due to the entry of 5-HT at the level of DA cell bodies. Indeed, 5-HT terminals are concentrated in the SN (Moukhles et al. 1997), and it has been reported that genetic or pharmacological impairment of 5-HT transporters induced 5-HT-immunoreactivity in DA cell bodies but not in the striatum (Zhou et al. 2002). Consequently, it cannot be excluded that the inhibitory effects elicited by DRN electrical stimulation or high doses of SSRI promotes an efflux of DA in the SN, indirectly inhibiting DA neuron impulse-flow via $D_2$ autoreceptors.

### Concluding remarks

Although a carrier-mediated release of DA induced by 5-HT can be elicited in vivo (De Deurwaerdère et al. 1996; Yeghiayan and Kelly 1995; Yeghiayan et al. 1997), it should probably not occur in physiological conditions when considering the anatomy and functional relationship between DA and 5-HT terminals in the striatum. The difference between exogenous and endogenous 5-HT is explainable by the fact that, when 5-HT is directly applied in the tissue, it spreads around striatal DA terminals independently of the anatomical substrate linking 5-HT and DA terminals. In contrast, the highest increase in 5-HT extracellular levels induced by SSRI, d-fenfluramine and DRN stimulation might be restricted to a limited area. This increase would not be sufficient to elicit a carrier-mediated release of DA.

The situation could be different in other brain areas where the density of 5-HT terminals is higher such as in the cortex. Numerous recent data have suggested that such an entry of monoamines in heterologous monoamine systems may participate in the mechanism of action of antidepressant or psychostimulant drugs (Di Chiara et al. 1992; Di Matteo et al. 2008; Rothman and Baumann 2006; Zhou et al. 2005) have brought up recent elements suggesting that, after a long-term treatment with fluoxetine and tryptophan to enhance 5-HT release, 5-HT and DA may be co-released from DA terminals. However, the concentrations of 5-HT were extremely low, probably because monoamine oxidase A, which is highly concentrated in DA terminals (Lupp et al. 1992; Westlund et al. 1988), has a better affinity for 5-HT than for DA (Youdim et al. 1986).

## The state-dependent involvement of striatal 5-HT in the control of striatal DA release and metabolism

Although all these studies minimize the influence of endogenous 5-HT and 5-HT receptors on striatal DA release, new elements have been discovered allowing us to better understand the subtleties of this interaction. Indeed, whereas the involvement of most 5-HT receptors seems silenced in resting conditions, various pharmacological treatments known to alter the activity of DA neurons lead to the involvement of striatal 5-HT receptors in the control of striatal DA release. The purpose of the following section is to present some of the conditional factors allowing striatal 5-HT receptors to control DA terminals nerve activity.

Alteration of DA neuron activity

Several agents such as amphetamine, MDMA, haloperidol, morphine, apomorphine or cocaine affect nigrostriatal DA nerve activity and striatal DA transmission. Interestingly, these agents trigger specific cellular mechanisms that recruit discrete 5-HT controls on striatal DA release. Of note, the intrastriatal administration of an SSRI, without effect by itself (see above), enhanced the output of striatal DA release induced by haloperidol (Lucas et al. 2000a). Given that 5-HT receptors are located on striatal neurons, it might be suggested that a modification of central DA transmission (not restricted to striatal cells) would increase the influence exerted by some 5-HT receptors on striatal cells.

Another key factor is that the different drugs able to modulate DA release trigger different 5-HT receptors in the control of DA neuron activity that may be localized in the striatum or elsewhere. In different studies, it has been proposed that 5-HT receptors (and the cells carrying these receptors) would preferentially affect one type of DA

release. Indeed, extracellular level of DA is an integrated parameter relying on various processes occurring in the regulation of DA terminal activity (firing, depolarization, synthesis, reuptake, etc.) (Fig. 6). Because the triggering drugs have to be peripherally administered, the control exerted by one 5-HT receptor may occur outside the striatal system. Yet, numerous data are available now to demonstrate the role of striatal 5-HT receptors in the state-dependent control of striatal DA release.

Nature of DA released

The most studied drugs to date are morphine, haloperidol, cocaine, amphetamine, MDMA. These drugs differ in their mechanism of action to release DA. Haloperidol and morphine are known to exert an impulse-dependent release of DA (Carboni et al. 1989; Di Chiara and Imperato 1988; Mereu et al. 1984). Cocaine, by blocking DA transporters, induces an increase in extracellular levels of DA associated with a decrease in DA neuron impulse-flow (Benwell et al. 1993; Bunney et al. 2000; Di Chiara and Imperato 1988; White 1997). Amphetamine and MDMA induce mainly a non-exocytotic release of DA (Di Chiara and Imperato 1988; Gudelsky and Yamamoto 2008; Pitts and Marwah 1988; Yamamoto et al. 1995). Moreover, the enhancement of striatal DA induced by haloperidol, amphetamine and
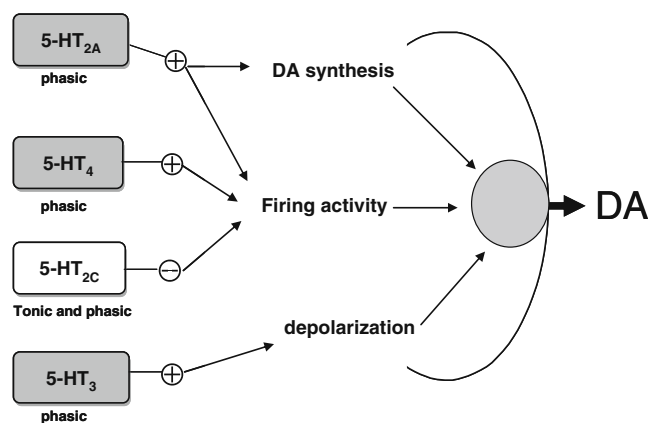
Fig. 6 Influence of 5-HT receptors on striatal DA release. Striatal DA release is supported by various cellular mechanisms including DA synthesis, firing activity of the neuron, or depolarization of the terminals. The different origin of release is important to consider as basal DA release is not critically dependent on DA synthesis in contrast to MDMA-induced DA release. 5-HT receptors affect DA release under certain restricted conditions. 5-HT$_{2A}$ receptors stimulate DA release in a phasic manner and act on DA firing rate and/or DA synthesis. 5-HT$_4$ receptors stimulate DA release in a phasic manner on an impulse-dependent release of DA. 5-HT$_{2C}$ receptors tonically inhibit the impulse-dependent release of DA. 5-HT$_3$ receptors exert a phasic excitatory control restricted to the impulse-dependent and/or depolarization-induced DA release. It is important to note that only 5-HT$_3$ receptors would require an increase in 5-HT levels

MDMA relies critically on DA synthesis (Lucas et al. 2000b; Millan et al. 1999; Patterson and Schenk 1991; Porras et al. 2003; Schmitz et al. 2001). Finally, a last criterion to consider is the ability or not of these drugs to enhance endogenous 5-HT tone at the same time (Andrews and Lucki 2001; Gudelsky and Yamamoto 2008; Lucas et al. 2001; Navailles et al. 2004; Porras et al. 2003; Tao and Auerbach 1994; 1995).

In these conditions, modifications of endogenous 5-HT tone have been shown to alter the enhancement of DA release and/or metabolism induced by these drugs. Thus, the preferential 5-HT$_{1A}$ agonist 8-OHDPAT reduced DA release induced by amphetamine (Ichikawa and Meltzer 1995) and haloperidol, depending on the dose administered (Lucas et al. 1997; 2000b). The administration of SSRI citalopram and fluoxetine have been shown to enhance DA release induced by haloperidol (Lucas et al. 2000a,b).

Involvement of striatal 5-HT receptors

5-HT$_{2A}$ receptors

As indicated above, intrastriatal administration of the 5-HT$_{2A}$ antagonists M100907 or SR46349B significantly reduced the increase in DA release induced by systemic administration of MDMA or haloperidol, respectively (Lucas and Spampinato 2000; Schmidt et al. 1994). Intrastriatal injection of the mixed agonist DOI enhanced striatal DA release induced by haloperidol (Lucas and Spampinato 2000). Additionally, the increase in DA release induced by amphetamine was reduced by the systemic administration of SR46349B (Egerton et al. 2008; Porras et al. 2002a) while that of the mixed agonist DOI further enhanced the effect of amphetamine (Ichikawa and Meltzer 1995). These data indicate that 5-HT$_{2A}$ receptors play a permissive role on striatal DA function. Given that systemic administration of these antagonists did not affect DA release stimulated by morphine or cocaine, and that 5-HT$_{2A}$ receptors exert a state-dependent increase in DA synthesis (Sorensen et al. 1993; Waldmeier and Delini-Stula 1979), it has been proposed that 5-HT$_{2A}$ receptors stimulate the release of DA that relies on DA synthesis (Lucas et al. 2000b; Schmidt et al. 1993).

5-HT$_{2C}$ receptors

Among 5-HT receptors, the 5-HT$_{2C}$ subtype is the only receptor able to affect striatal DA release in resting conditions but its involvement on activated DA transmission also requires specific conditions. 5-HT$_{2C}$ antagonists are able to increase striatal DA release induced by morphine, haloperidol, cocaine, but not amphetamine while 5-HT$_{2C}$ agonists decrease striatal DA release induced by haloperidol, morphine, nicotine but not cocaine and

amphetamine (Di Matteo et al. 2004; Lucas et al. 2000b; Navailles et al. 2004, 2006; Porras et al. 2002a; Willins and Meltzer 1998). These data suggest that 5-HT$_{2C}$ receptors exert an inhibitory control of exocytotic DA release, and preferentially on the impulse-dependent release of DA by acting at the level of nigrostriatal DA neuron activity (Navailles et al. 2004; 2006). Nevertheless, the site of action of 5-HT$_{2C}$ receptors has not been elucidated.

5-HT$_3$ receptors

Against the proposal that 5-HT$_3$ receptors are not able to modulate striatal DA release, it seems that, in very restricted conditions, 5-HT$_3$ receptors exert a state-dependent excitatory control of striatal DA release. Thus, the stimulated release of DA induced by haloperidol, low-dose morphine, amphetamine, or cocaine is not affected by 5-HT$_3$ antagonism. However, 5-HT$_3$ antagonism reduced the increase in DA release induced by a high dose of morphine and by the cocktail haloperidol plus citalopram (Porras et al. 2003). More interestingly, local infusion of ondansetron mimicked the effect of systemic ondansetron, confirming previous data showing that the involvement of 5-HT$_3$ receptors may occur under very particular conditions (De Deurwaerdère et al. 2005). These results indicate that 5-HT$_3$ receptors can stimulate DA release provided that the stimulated release of DA relies on depolarized terminals and that the endogenous 5-HT tone is increased.

Thus, 5-HT$_3$ receptors are not selectively involved in the control of neurons along the mesocorticolimbic DA pathways as previously shown (Bachy et al. 1993; Frankel et al. 1998). The preferential influence in the mesoaccumbal DA pathway is likely related to another population of 5-HT$_3$ receptors located at the level of the VTA and able to initiate an increase in the impulse-dependent DA release in the nucleus accumbens (De Deurwaerdère et al. 2005; Imperato and Angelucci 1989).

5-HT$_4$ receptors

The 5-HT$_4$ receptors exert a state-dependent facilitatory control of DA release stimulated by morphine and haloperidol, but not cocaine or amphetamine (Lucas et al. 2001; Porras et al. 2002b; Pozzi et al. 1995). The role of striatal 5-HT$_4$ receptors is not clear. On the one hand, intrastriatal infusion of GR113808 did not modify the effect of morphine (Pozzi et al. 1995). On the other hand, intrastriatal infusion of GR 125487 reduced the effect of haloperidol (Lucas et al. 2001). In this latter case, however, it is not determined whether this effect is related to the local decrease in endogenous 5-HT tone induced by 5-HT$_4$ antagonists (Ge and Barnes 1996; Lucas et al. 2001) or to a more direct mechanism toward DA neuron activity.

## Concluding remarks

These data indicate that the 5-HT system may affect striatal DA function in conditions in which central DA transmission is modified. The conditional involvement of the numerous 5-HT receptors in the control of striatal DA function depends on the nature of the DA released and the level of DA transmission. Among the receptors described in the striatum, 5-HT$_{2A}$, 5-HT$_3$, and 5-HT$_4$ receptors may enhance striatal DA release in restricted conditions (Fig. 6). Complementary studies are needed to determine the status of 5-HT$_{1B}$ and 5-HT$_6$ receptors.

In this context, it is important to mention that numerous 5-HT receptors are able to control the firing activity of nigrostriatal DA neurons, conditioning the activity of DA terminals and participating in the recruitment of striatal 5-HT receptors in the control of striatal DA release. Several 5-HT receptors are known to affect the electrical activity of DA neurons by acting in the SNc or centrally. For instance, DA neuron activity is indirectly decreased by 5-HT$_{2C}$ receptors (Di Giovanni et al. 1999, 2008), thereby acting against the ability of striatal 5-HT receptors to enhance the impulse-dependent DA release. In contrast, DA neuron activity is activated by 5-HT$_4$ receptors in specific conditions (Porras et al. 2002a). The control of DA nerve activity by 5-HT receptors has been the purpose of a well-documented review (Di Giovanni et al. 2008).

## Concluding remarks

The study of the influence of exogenous 5-HT on DA terminal activity has led to conflicting results. The origin of these discrepancies is primarily attributable to the ability of 5-HT and several related compounds to enter DA terminals. Inside DA terminals and depending on the activity of the molecules in the cytosol, various pathways involved in the synthesis or release of DA might be affected. At high concentrations of 5-HT, a carrier-mediated release of DA predominates. In these conditions, it appears difficult to determine the influence of concomitant 5-HT receptors involved in the control of striatal DA release in vivo and in vitro. These actions have to be taken into account when using these approaches to study the influence of the 5-HT system on other neurotransmitter systems in the vicinity of DA neurons.

The striatum participates in sensorimotor integration, procedural memory, formation of habits, and behavioral automatisms (Graybiel 2005; Mink 1996). DA plays a fundamental role in all these functions. Physiologically, several 5-HT receptors can participate in the control of the activity of striatal DA terminals. It seems that striatal 5-HT, through various 5-HT receptors, exerts excitatory effects on striatal DA release with the exception of the 5-HT$_{2C}$ receptor.

Most of the excitatory 5-HT controls occur in a state-dependent manner. These findings are not incompatible with the functional "inhibitory" role of 5-HT on DA-mediated behavior (Spoont 1992; Soubrié 1986). Indeed by acting on the effector neurons of DA, the 5-HT system limits the efficacy of striatal DA transmission (Giambalvo and Snodgrass 1978; Waldmeier and Delini-Stula 1979). This would indirectly lead to adjust the release of DA via the modulatory influence of 5-HT on striatal neurons. In this context, DA release might not be an accurate index of the changes of DA-dependent behaviors triggered by 5-HT drugs. For instance, the reversal of haloperidol-induced catalepsy by 5-HT$_2$ antagonists occurs independently from changes in DA release (Lucas et al. 1997). Conversely, while 5-HT$_4$ antagonists reduce morphine- or haloperidol-induced striatal DA release, 5-HT$_4$ antagonists do not affect haloperidol-induced catalepsy and morphine-induced catatonia (De Deurwaerdère et al. 2002; Ward and Dorsa 1999). Thus, although various striatal 5-HT receptors are able to affect behaviors related to striatal DA dysfunction such as dyskinesia, catalepsy, stereotypies, locomotor activity, or even addiction, the picture is still unclear (Di Matteo et al. 2008; Soubrié et al. 1984). In light of the biochemical and anatomical data, it is becoming evident that each 5-HT receptor interacts in a specific manner in the striatum, either by acting indirectly on striatal DA function or even independently from DA function, as suggested by the available literature concerning striatal 5-HT$_6$ receptors (Pouzet et al. 2002; Svenningsson et al. 2002). It is likely that, functionally, each 5-HT receptor will affect a specific component of behaviors associated with the striatum. The availability of selective pharmacological agents will permit the determination of the role of the various 5-HT receptors in the control of striatal neuron activity and function.

Overall, the studies available to date represent a major endeavor to better understand the various modalities of control exerted by the numerous 5-HT receptors on DA neuron activity within the striatum and provide critical data to envision 5-HT drugs as potential therapeutic tools to improve treatments of numerous disorders associated with chronic alteration of DA transmission, such as Parkinson's disease, schizophrenia, and addiction.

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