

REVIEW

Presynaptic regulation of dopaminergic neurotransmission

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Abstract

The development of electrochemical recordings with small carbon-fiber electrodes has significantly advanced the understanding of the regulation of catecholamine transmission in various brain areas. Recordings *in vivo* or in slice preparations monitor diffusion of catecholamine following stimulated synaptic release into the surrounding tissue. This synaptic 'overflow' is defined by the amount of release, by the activity of reuptake, and by the diffusion parameters in brain tissue.

Such studies have elucidated the complex regulation of catecholamine release and uptake, and how psychostimulants and anti-psychotic drugs interfere with it. Moreover, recordings with carbon-fiber electrodes from cultured neurons have provided analysis of catecholamine release and its plasticity at the quantal level.

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Dopaminergic transmission is characterized by transmitter 'spill-over', i.e. dopamine (DA) released by a presynaptic terminal can diffuse beyond the synaptic cleft to reach multiple postsynaptic targets (for review see Vizi 1982; Zoli *et al.* 1999; Gonon *et al.* 2000; Nicholson 2000; Rice 2000). Accordingly, ultrastructural immunohistochemical studies have demonstrated that both DA receptors and uptake transporters are located extrasynaptically (Sesack *et al.* 1994; Yung *et al.* 1995; Nirenberg *et al.* 1997). Another argument supporting 'spill-over' DA neurotransmission is that carbon-fiber electrodes (Kissinger *et al.* 1973; Gonon *et al.* 1980; Ewing *et al.* 1983; Millar *et al.* 1985; Marsden *et al.* 1988; Kawagoe *et al.* 1993; Michael and Wightman 1999) detect synaptically released DA at micromolar concentration, although the diffusion distance to the electrode comprises several microns.

An important aspect of this type of 'social' synapse is the impact of presynaptic regulation on transmitter release and reuptake. If release is enhanced and/or uptake reduced, the number of postsynaptic binding targets increases. In contrast, there has been a long debate about the physiological impact of presynaptic plasticity in fast excitatory or inhibitory synapses, traditionally thought of as point-to-point (or

'private') synapses enwrapped by glial processes that prevent transmitter diffusion out of the synaptic cleft. In recent studies, the concept of physiologically relevant transmitter 'spill-over' has been extended to GABAergic and glutamatergic synapses (Kullmann and Asztely 1998; Jahr 2003), although its role and the conditions under which it may occur remain controversial.

In this review, we discuss the role of presynaptic DA transporters, autoreceptors, and heteroreceptors in the regulation of DA neurotransmission and mechanisms by which drugs of abuse and anti-psychotic drugs interfere with this regulation. We focus mostly on DAergic axon terminals, but

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Abbreviations used: DA, dopamine; DAT, DA transporter; GDNF, glial-derived neurotrophic factor; N.acc, nucleus accumbens; NET, norepinephrine transporter; PPD, paired pulse depression; SERT, serotonin transporter; SN, substantia nigra; TH, tyrosine hydroxylase; VTA, ventral tegmental area.

also discuss some issues concerning somatodendritic DA release.

The DA transporter

The DA transporter (DAT) is a member of the family of biogenic amine transporters with 12 putative transmembrane domains (for recent reviews see Blakely and Bauman 2000; Torres *et al.* 2003). In brain regions densely innervated by DAergic terminals (e.g. dorsal striatum, nucleus accumbens, olfactory tubercle), DA reuptake is the most important mechanism of DA inactivation (Jones *et al.* 1998b; Benoit-Marand *et al.* 2000). The DAT is a major target of psychostimulant drugs, particularly cocaine and amphetamine, which induce dramatic increases in extracellular DA concentrations. The DAT is localized on somata, dendrites, axons, and axon terminals of dopaminergic midbrain neurons (Nirenberg *et al.* 1996). Ultrastructurally, DAT immunolabel is mostly present on extrasynaptic plasma membranes (Nirenberg *et al.* 1997), supporting the idea of extrasynaptic transmission. Quantitative descriptions of the diffusion of DA in the brain's extracellular microenvironment and its restriction by uptake have been obtained by injecting defined amounts of DA solution into brain slice preparations and recording DA signals at a distance from the injection site (Rice *et al.* 1985; Nicholson 1995). A comparison of somatodendritic regions [substantia nigra (SN) and ventral tegmental area (VTA)] and axon terminal regions (striatum) revealed that the amplitude and time course of DA signals are predominantly determined by uptake in the striatum and by diffusion in the SN and VTA (Cragg *et al.* 2001).

DA uptake

DA uptake follows Michaelis–Menten kinetics where the apparent affinity of uptake, K_m , is a reciprocal measure of the affinity of a substrate for the uptake site, and V_{max} is the maximal uptake velocity. V_{max} is dependent on the number of uptake sites and is decreased by noncompetitive uptake inhibitors. K_m is independent of the number of uptake sites and is increased by competitive uptake inhibitors (Horn 1979). Tissue-specific parameters of DA uptake were initially derived from measurements of [³H]DA uptake in synaptosome preparations (for review see Horn 1990), and later from electrochemical measurements with rotating disk electrode voltammetry in striatal tissue suspensions (McElvain and Schenk 1992; Earles and Schenk 1998). Recent studies have estimated uptake parameters in brain slices by either recording DA diffusion from injection sites (Nicholson 1995; Sabeti *et al.* 2002), or by recording evoked endogenous DA overflow (Wightman and Zimmerman 1990; Jones *et al.* 1995b; Schmitz *et al.* 2001; Schonfuss *et al.* 2001; Wu *et al.* 2001b).

Estimates for the K_m of DA uptake range from 0.2 to 2 μM . A K_m of 0.2 μM was determined for striatal

synaptosome preparations (Near *et al.* 1988; Ross 1991). Rotating disk voltammetry provided values between 0.6 and 1.2 μM for striatal tissue suspensions (McElvain and Schenk 1992; Earles and Schenk 1998), and $\sim 2 \mu\text{M}$ for cell lines expressing the DAT (Wu and Gu 1999). The studies using simulation models of stimulated DA overflow in the striatum derived K_m values of 0.16 μM (Wu *et al.* 2001a), 0.22 μM (Schonfuss *et al.* 2001), and 0.8 μM (Schmitz *et al.* 2001), respectively. V_{max} expressed as $\mu\text{M/s}$ can be calculated from the initial slope of the falling phase of DA overflow recordings, provided the evoked DA release is sufficiently high (Kawagoe *et al.* 1992). The peak of DA overflow in response to a single electrical stimulation in the dorsal striatum *in vitro* is $\sim 1 \mu\text{M}$ DA, as measured by cyclic voltammetry. This translates into an initial (immediately after release) DA concentration of $\sim 2\text{--}4 \mu\text{M}$ according to simulation models that account for the filtering of the signal caused by diffusion to the electrode. V_{max} values between 4 and 6 $\mu\text{M/s}$ have been determined for dorsal striatum from simulation of DA overflow recorded in response to single stimulation *in vitro*, and to multiple stimulation *in vivo* (Wightman *et al.* 1988; Wightman and Zimmerman 1990; Jones *et al.* 1995b; Cragg *et al.* 2000; Schmitz *et al.* 2001; Schonfuss *et al.* 2001; Wu *et al.* 2001b). There are regional variations in V_{max} within the dorsal striatum that may reflect different functional domains (Cragg *et al.* 2002). DA uptake in the ventral striatum (Nucleus accumbens, N. acc.) was reported to be less efficient than in the dorsal striatum (Stamford *et al.* 1988b; Cass *et al.* 1992; Suaud-Chagny *et al.* 1995), with estimates for V_{max} of 2 $\mu\text{M/s}$ and 0.6 $\mu\text{M/s}$ in the N. acc. core and shell, respectively (Jones *et al.* 1996b). DA uptake in the prefrontal cortex and amygdala appears to be very low (Garris and Wightman 1994; Sesack *et al.* 1998) with V_{max} values around 0.05 $\mu\text{M/s}$ and 0.5 $\mu\text{M/s}$, respectively (Jones *et al.* 1995b; Mundorf *et al.* 2001). In areas with low DAT activity, the norepinephrine transporter (NET) and the serotonin transporter (SERT) may participate in DA uptake (Yamamoto and Novotney 1998; Miner *et al.* 2000; Cragg *et al.* 2001; Moron *et al.* 2002). In addition, enzymatic breakdown by catechol-*O*-methyltransferase plays a role in DA clearance in these brain regions (Wayment *et al.* 2001; Matsumoto *et al.* 2003).

The role of DA uptake in DA transmission

DAergic neurons exhibit two kinds of discharge activity. In the rodent, these correspond to single spikes at a mean frequency below 5 Hz and bursts of two to six action potentials with an intraburst frequency of 15–30 Hz (Grace and Bunney 1984a,b). Individual DAergic neurons can switch from one pattern to another and in unrestrained rats the bursting pattern is favored in response to sensory stimuli (Freeman and Bunney 1987). In monkeys, midbrain neurons respond to an appetitive or conditioned stimulus by a single burst (Schultz *et al.* 1997).

Grace and Bunney (1984a,b) hypothesized that 'bursting may be as important as firing frequency in affecting DA release' and this hypothesis was supported by early studies (Gonon and Buda 1985; Gonon 1988). More recently, it has been shown that the main mechanism subserving the high extracellular DA level evoked by stimulations mimicking the bursting activity is not facilitation of DA release *per se*, but accumulation of the released DA as a result of saturated DA uptake (Chergui *et al.* 1994). During tonic activity, the DA released by single spikes is cleared before the next spike. In contrast, during a burst, released DA accumulates in the extracellular space. This accumulation is more obvious in the nucleus accumbens and olfactory tuberculum than in the dorsal striatum because DA reuptake is more potent in the dorsal striatum than in the other regions (Chergui *et al.* 1994; Suaud-Chagny *et al.* 1995). Therefore, due to reuptake, tonic activity and bursting activity result in different extracellular DA levels.

Accordingly, in mice lacking the DAT, the released DA accumulates during tonic activity with no further enhancement during burst activity (Benoit-Marand *et al.* 2000). Interestingly, these mice are hyperactive, due to their high basal extracellular level, but show an impairment in spatial learning and 'difficulties in suppressing inappropriate responses' (Gainetdinov *et al.* 1999). These cognitive deficits might occur because these mice are not able to translate bursting activity involved in learning into phasic changes in extracellular DA (Benoit-Marand *et al.* 2000). The extracellular accumulation of DA elicited by bursts is required to significantly activate D2 autoreceptors (Benoit-Marand *et al.* 2001) and to stimulate postsynaptic D1 receptors (Chergui *et al.* 1996; Chergui *et al.* 1997; Gonon 1997). All these data point out the importance of DA reuptake in the differential expression of bursts and single spike discharge activity of DAergic neurons.

Finally, DA uptake has been suggested to play a role in refilling intracellular DA stores, particularly during prolonged DA release (Gainetdinov *et al.* 1998). In accordance with this hypothesis, DA release is more dependent on DA synthesis, and the rate of DA synthesis is doubled, in mice lacking the DAT (Jones *et al.* 1998b; Benoit-Marand *et al.* 2000).

DAT functions beyond uptake

The DAT, in addition to uptake, also elicits ion channel-like currents in response to substrates such as DA and amphetamine (Khoshbouei *et al.* 2003). In cultured rat DA neurons, transport of DA, at concentrations lower than necessary for D2 receptor activation, stimulated an anion conductance causing an excitatory response (Ingram *et al.* 2002). The authors suggested that under conditions of low extracellular DA, depolarization due to DAT activity facilitates DA release. With higher extracellular DA concentrations this effect would be suppressed by the activation of inhibitory autoreceptors.

Another recent study suggested that the DAT may mediate DA release directly via the reversal of transport, a mechanism previously only associated with the action of amphetamine (see section on Amphetamine). In a slice preparation, DA release was elicited from dendrites and somata in the SN reticulata by stimulation of the glutamatergic projection from the subthalamic nucleus and was abolished by DAT inhibitors. The authors suggested that stimulation-dependent reverse transport of DA may occur if dendrites are depolarized beyond the reversal potential for DA transport. This nonvesicular DA release would cause feedback inhibition of the DA neuron via autoreceptor activation, thereby shaping the firing response (Falkenburger *et al.* 2001).

Cocaine

The first indication that cocaine may act as an amine uptake inhibitor came from Burn and Rand, who suggested 'the action of cocaine may be to arrest the release of the noradrenaline-like substance from the store' (Burn and Rand 1958). Later work demonstrated neuronal binding sites for [³H]cocaine (Reith *et al.* 1980), and that DAT binding sites were related to self-administration of the drug (Ritz *et al.* 1987). The effects of cocaine on motor activity and reward systems have been well documented. While blockade of DA reuptake by cocaine appears a sufficient explanation for its locomotion-inducing effect, the reinforcing effects of cocaine may involve several amine transporters (Uhl *et al.* 2002). Thus, cocaine maintains reinforcing properties in mice lacking the DAT (Giros *et al.* 1996; Rocha *et al.* 1998; Sora *et al.* 1998), and elevates DA levels in the N. acc. of these animals (Carboni *et al.* 2001). This effect of cocaine in DAT knockout mice is not mediated by the blockade of the NET and the SERT in the N. acc., and is most likely located outside of this structure (Budygin *et al.* 2002). In mice lacking both the DAT and the SERT, cocaine place preference is eliminated (Sora *et al.* 2001).

The uptake inhibition by cocaine has been variously reported to follow competitive (Calligaro and Eldefrawi 1987; Krueger 1990; Jones *et al.* 1995a; Chen and Justice 1998; Wu *et al.* 2001a), noncompetitive, or uncompetitive kinetics (McElvain and Schenk 1992; Wheeler *et al.* 1994; Povlock and Schenk 1997). Studies supporting competitive inhibition report a decrease in the apparent affinity, with a K_m ranging from 2.5 μM (Jones *et al.* 1995b; Jones *et al.* 1995a) to 11 μM (Wu *et al.* 2001a) for 10 μM cocaine. In any case, cocaine is not a substrate for the DAT and is not internally transported (Sonders *et al.* 1997).

The efficacy of cocaine depends on the ongoing release of DA. The increased extracellular DA levels resulting from cocaine uptake blockade, however, might eventually activate DA D2 autoreceptors and shut down subsequent DA release (see section on The D2 autoreceptor). Accordingly, an *in vitro* study on axon terminal DA release reported that there was an acute autoreceptor response in the presence of uptake

blockade resulting in a reduction of DA release in the N. acc., although not in the dorsal striatum (Wieczorek and Kruk 1994a). Consistent with this idea, extracellular DA levels in response to cocaine assessed by *in vivo* microdialysis were higher in mice lacking D2 receptors than in wild-type mice (Rouge-Pont *et al.* 2002). Nevertheless, even in the presence of D2 autoreceptors, the net result of DA uptake inhibition by cocaine is an elevation of extracellular DA levels.

Many studies have addressed the question whether chronic cocaine treatment and withdrawal alters the activity/expression of D2 autoreceptors and the DAT itself in different brain regions (for review (Kuhar and Pilotte 1996; White and Kalivas 1998; Zahniser and Doolen 2001)). While somatodendritic D2 autoreceptors in the VTA become subsensitive during cocaine treatment (Henry *et al.* 1989; Ackerman and White 1990; Lee *et al.* 1997; Henry *et al.* 1998), results from studies on axon terminal autoreceptors are contradictory. One important factor appears to be the regimen of cocaine administration. Intermittent cocaine treatment may lead to subsensitivity, and continuous cocaine treatment to supersensitivity of axon terminal D2 autoreceptors (Yi and Johnson 1990; Jones *et al.* 1996a; Howard *et al.* 1997; King *et al.* 1999; Davidson *et al.* 2000). In the case of a developmental absence of DAT-mediated uptake, as in DAT knockout mice, D2 autoreceptor expression is reduced to less than half of wild-type level, and autoreceptor activity is virtually absent (Jones *et al.* 1999b).

Recent studies indicate that acute cocaine treatment blocks the turnover and mobilization of the DAT so that more DAT protein is expressed in the plasmalemmal membrane (Daws *et al.* 2002; Little *et al.* 2002). With chronic cocaine treatment, most evidence points to a decrease in DAT expression following a sufficient withdrawal period (Kuhar and Pilotte 1996), although both decreased and increased mRNA/protein levels have been reported (for a recent review of the literature see Kimmel *et al.* 2003).

Amphetamine

Amphetamine (AMPH), in contrast to cocaine, is a substrate for both the DAT and the NET and is a competitive inhibitor of DA uptake (Heikkila *et al.* 1975; Wieczorek and Kruk 1994b; Sonders *et al.* 1997; Jones *et al.* 1999a; Khoshbouei *et al.* 2003). Based on results from electrochemical recordings, it was estimated that AMPH (10 μM) decreases the apparent affinity of the DAT from a K_m value of 0.8 to $\sim 30 \mu\text{M}$ (Schmitz *et al.* 2001). In addition, AMPH and its derivatives promote DA efflux by reverse transport through monoamine uptake transporters (Heikkila *et al.* 1975; Fischer and Cho 1979; Raiteri *et al.* 1979; Parker and Cubeddu 1986; Sulzer *et al.* 1993; Sulzer *et al.* 1995; Jones *et al.* 1998a; Schmitz *et al.* 2001). The DA efflux caused by AMPH activates D2 autoreceptors and thereby inhibits stimulation-dependent DA release (Wieczorek and Kruk

1994b; Irvani and Kruk 1995; Schmitz *et al.* 2001). Vesicular DA release is further decreased by AMPH as it promotes the redistribution of DA from synaptic vesicles to the cytosol (Sulzer *et al.* 1995; Mosharov *et al.* 2003) by collapsing the vesicular pH gradient (Sulzer and Rayport 1990). Thus, the overall effect of AMPH is a reduction of activity-dependent, vesicular DA release, inhibition of DA uptake, and an induction of continuous DA efflux by reverse transport. The effects of cocaine and AMPH on dopaminergic transmission differ significantly, for cocaine enhances and prolongs activity-dependent, exocytotic DA signals, whereas AMPH causes continuous DA efflux independently from firing activity while dampening but prolonging synaptically released DA.

Acute AMPH treatment has been shown to cause DAT internalization in *in vitro* and *in vivo* studies (Saunders *et al.* 2000; Gulley *et al.* 2002), although not in all systems (Daniels and Amara 1999). In fact, cocaine and other DA uptake blockers (mazindol and nomifensine) inhibited AMPH-induced internalization of the DAT (Saunders *et al.* 2000) suggesting that inhibitors stabilize DAT expression in the membrane, whereas DAT substrates such as AMPH and DA itself induce internalization. This process most likely involves PKC-dependent pathways (Sandoval *et al.* 2001; Gulley *et al.* 2002), as numerous studies have shown that PKC activation results in DAT internalization (Copeland *et al.* 1996; Huff *et al.* 1997; Vaughan *et al.* 1997; Zhang *et al.* 1997; Zhu *et al.* 1997; Pristupa *et al.* 1998; Daniels and Amara 1999; Melikian and Buckley 1999). A direct phosphorylation of the DAT by PKC does not appear to be required in the pathway (Granás *et al.* 2003). The effects of chronic treatment with AMPH on DAT expression are not as well characterized, and the results thus far are not conclusive. Some studies reported no changes in DAT mRNA (Kula and Baldessarini 1991; Persico *et al.* 1993; Mintz *et al.* 1994), whereas other studies reported an up-regulation of DAT mRNA in response to several days of AMPH injections followed by several days of withdrawal (Lu and Wolf 1997; Shilling *et al.* 1997).

The DA autoreceptor

The term 'autoreceptor' was coined in 1975 by Arvid Carlsson for DA autoreceptors (Carlsson 1975; Starke 2001). Although doubts have been expressed about the physiological significance of autoreceptor regulation in certain transmitter systems (Kalsner 2001), it is clear that DA autoreceptors provide the DA midbrain neuron with a complex feedback system at the soma and the axon terminal.

DA autoreceptors belong to the D2-family (D2, D3, D4) of DA receptors that are coupled to inhibitory G proteins and modulate ion channel activity and/or depress adenylyl cyclase. D2 receptors are expressed by somata and dendrites of SN and VTA neurons, as well as by their axon terminals in

the striatum and N. acc. (Sesack *et al.* 1994). Studies on D2 receptor knockout mice reported no detectable autoreceptor response to D2-class receptor agonists with respect to regulation of firing rates, DA release and DA synthesis. These results implicated the D2 receptor as the only functional autoreceptor in the D2-family (Mercuri *et al.* 1997; L'hirondel *et al.* 1998; Benoit-Marand *et al.* 2001; Schmitz *et al.* 2002). There exists, however, evidence for a contribution of D3 receptors to autoreceptor function. In the SN and VTA, some DA neurons appear to express D3 receptor immunoreactivity, whereas the axons and axon terminals in N. acc. and striatum lack D3 receptor label (Diaz *et al.* 2000). Studies on transfected cells demonstrated that D3 receptors can modulate the same ion channels (G protein-activated inwardly rectifying potassium channels, GIRKs) as D2 receptors (Kuzhikandathil and Oxford 1998; Kuzhikandathil and Oxford 1999, 2000), and have the potential to affect DA release and synthesis (Tang *et al.* 1994; O'Hara *et al.* 1996). This was not confirmed, however, by a recent study on acutely dissociated midbrain neurons from D2 receptor knockout mice that did not find any evidence for D3 receptor-mediated activation of GIRK currents (Davila *et al.* 2003). Several pharmacological *in vivo* studies support a role for D3 receptors as autoreceptors (Rivet *et al.* 1994; Aretha *et al.* 1995; Kreiss *et al.* 1995; Lejeune and Millan 1995; Gainetdinov *et al.* 1996), although this evidence is weakened by the poor selectivity of available DA receptor agonists and antagonists. An earlier study on a mouse line lacking D3 receptors reported no alterations in autoreceptor function, but a role of D3 receptors in the circuit regulating DA levels (Koeltzow *et al.* 1998). In contrast, a recent study on another D3 receptor knockout mouse line provided evidence that D3 receptors may participate directly in regulating DA secretion (Joseph *et al.* 2002). A study on rats treated with D3 receptor antisense oligodeoxynucleotides suggested a role for D3 receptors in regulating firing rates (Tepper *et al.* 1997).

There is little evidence supporting a role of D4 receptors as autoreceptors beyond a recent immunohistochemistry study that demonstrated presynaptic D4 receptor localization in a subset of mesoaccumbal terminals in the N. acc. shell (Svingos *et al.* 2000). D4 antagonists have been reported to affect DA levels in the N. acc. in a microdialysis study (Broderick and Piercey 1998), and in D4 receptor knockout mice, DA synthesis and turnover are increased, a possible indication for altered autoreceptor function. Given the weak evidence for D4 autoreceptors, the authors of the latter study argued that the observed change in DA metabolism in D4 knockout mice might rather be due to indirect circuit effects involving glutamatergic afferents (Rubinstein *et al.* 1997). In accordance with a lack of an autoreceptor role for D4 receptors, studies on transfected dopaminergic cell lines reported that D4 receptor expression did not regulate DA release and synthesis (Tang *et al.* 1994; O'Hara *et al.* 1996).

In summary, it appears that DA autoreceptor function is predominantly carried out by D2 receptors, with a putative minor contribution from D3 receptors. In recent studies, it has been suggested that the two isoforms of the D2 receptor generated by alternative splicing, D2S and D2L, may serve different pre- and postsynaptic functions (Khan *et al.* 1998). It was reported that the D2 receptor agonist quinpirole was still able to inhibit DA release in D2L knockout mice (Usiello *et al.* 2000; Wang *et al.* 2000). Moreover D2 receptor agonist effects on membrane potential were preserved in D2L knockout mice (Centonze *et al.* 2002). These results indicate that D2L receptors may act mostly as postsynaptic receptors and D2S receptors as presynaptic autoreceptors. While this hypothesis will need further experimental support, it could potentially lead to the development of specific antagonists and agonists for pre versus postsynaptic D2 receptors that may be useful to improve pharmacological treatment of neuropsychiatric and movement disorders.

Firing rate

It is well established that D2 autoreceptors modulate the membrane potential of DAergic mesencephalic neurons. D2 receptor activation elicits a hyperpolarization and decreases the firing rate (Bunney *et al.* 1973; Silva and Bunney 1988; Rayport *et al.* 1992; Mercuri *et al.* 1997) due to activation of a GIRK conductance (Lacey *et al.* 1987; Kim *et al.* 1995; Cathala and Paupardin-Tritsch 1999). The firing pattern that DA midbrain neurons exhibit *in vivo*, either single spike firing or burst firing (Grace and Bunney 1984a,b), depends mainly on the excitatory and inhibitory afferent inputs (Kitai *et al.* 1999), which are in turn modulated by DA release (Paladini *et al.* 2003). Treatment with D2 receptor antagonists *in vivo* increases the proportion of spontaneously firing DA cells, increases the firing rate, and shifts the firing pattern from single spike discharge to burst firing. Repeated administration of D2 receptor antagonists can eventually lead to a depolarization block of DA neurons in anaesthetized animals. The degree to which D2 autoreceptor blockade contributes to these responses, however, is not clear (Bunney and Grace 1978; Grace *et al.* 1997), and whether depolarization activation may be related to the type of anesthesia remains controversial (Melis *et al.* 1998).

DA release

D2 autoreceptor activation inhibits axon terminal (Seeman and Lee 1975; Starke *et al.* 1978; Cubeddu and Hoffmann 1982; Gonon and Buda 1985; Dwoskin and Zahniser 1986; Mayer *et al.* 1988; Stamford *et al.* 1988a; May and Wightman 1989; Palij *et al.* 1990; Suaud-Chagny *et al.* 1991; Kennedy *et al.* 1992; Cragg and Greenfield 1997) and somatodendritic DA release (Cragg and Greenfield 1997). Patch clamp studies on DA midbrain neurons *in vitro* have revealed a D2 receptor regulation of voltage-gated calcium

currents (Cardozo and Bean 1995), and axon terminal DA release has been shown to be dependent on N and P/Q type calcium channels (Phillips and Stamford 2000). Given the dependence of transmitter release on calcium influx, modulation of calcium channels appears to be a reasonable mechanism for D2 receptor-mediated DA release inhibition. This has not been proven directly, however, and a recent study on autapses (i.e. synapses that a cell makes with itself) of midbrain neurons in culture found no evidence for a D2 autoreceptor regulation of calcium influx (Congar *et al.* 2002). Instead, the authors presented evidence that D2 receptor-mediated release inhibition may involve 4-aminopyridine-sensitive K⁺ channels that act downstream from calcium influx. A drawback of this study is that the autapses of cultured DA neurons are glutamatergic (Sulzer *et al.* 1998), and it is not known whether this finding can be extrapolated to DA release. Finally, while somatodendritic DA release is also calcium-dependent (Kalivas and Duffy 1991; Rice *et al.* 1997), it exhibits, in contrast to the typically nonlinear dependence of release on extracellular calcium, a linear dependence in very low extracellular calcium concentrations, saturating around 1 μM (Chen and Rice 2001).

While there is no disagreement that D2 receptors inhibit DA release, estimates of the time of onset and the duration of release autoinhibition have been considerably variable. The estimated duration of axon terminal release autoinhibition in different preparations ranges from tens of milliseconds up to several seconds (Mayer *et al.* 1988; Limberger *et al.* 1991; Kennedy *et al.* 1992; Dugast *et al.* 1997; Benoit-Marand *et al.* 2001; Phillips *et al.* 2002; Schmitz *et al.* 2002). Possible reasons for this divergence might be found in variations between *in vitro* and *in vivo* conditions or in species differences. A recent pharmacological *in vitro* study (Phillips *et al.* 2002), and two studies on D2 receptor knockout mice (Benoit-Marand *et al.* 2001; Schmitz *et al.* 2002) derived congruent estimates for the time course of the D2 effect on axon terminal DA release. In these studies, the onset of the D2 effect was between 50 ms and 100 ms, the maximum effect between 300 ms and 550 ms. The duration was about 800 ms in the *in vivo* study and less than 5 s in the two *in vitro* studies. The slightly longer time course determined in the *in vitro* studies is likely due to the larger amount of DA released per stimulation in slice preparations.

This timing of D2-mediated release autoinhibition might be suited to depress or enhance the DA signal in response to different firing patterns of midbrain neurons. The basal firing rate of midbrain neurons in the rat is 4 Hz, interrupted by burst firing of 2–6 pulses at 15 Hz (Grace and Bunney 1984a,b). Recordings of SN neurons in monkeys have shown that burst firing occurs in response to reward and after a learning period in response to the conditioning stimulus (Schultz *et al.* 1997). According to the time course of release autoinhibition, DA release is tonically depressed during basal firing, whereas less inhibition occurs during burst firing

(within the first three spikes). In addition, burst firing transiently attenuates subsequent DA release elicited by tonic discharge activity. In this way, autoinhibition of DA release may serve to enhance the signal-to-noise ratio of the DA signal in response to ‘meaningful’ burst firing versus baseline firing.

DA synthesis

With the exception of mesoprefrontal axon terminal autoreceptors (Chiodo *et al.* 1984; Galloway *et al.* 1986), there is accumulating evidence that D2 receptors modulate DA synthesis by decreasing tyrosine hydroxylase (TH) activity (Kehr *et al.* 1972; Roth *et al.* 1975; Kapatos and Zigmond 1979; Haubrich and Pflueger 1982; el Mestikawy and Hamon 1986; Strait and Kuczenski 1986; Wolf *et al.* 1986; Wolf and Roth 1990; O’Hara *et al.* 1996). The underlying pathway involves most likely inhibition of adenylyl cyclase and a cAMP-dependent change in phosphorylation of TH (Onali and Olanas 1989; Salah *et al.* 1989; Lindgren *et al.* 2001). A direct link between D2 receptor-mediated inactivation of DA synthesis and reduced DA release has been shown for PC12 cells, but not yet for neurons. Incubation of PC12 cell cultures with D2 receptor agonists resulted in decreased DA synthesis and a reduced frequency and size (molecules per vesicle) of quantal release (Pothos *et al.* 1998b). Thus, DA release can be regulated by D2 autoreceptors on two different time scales, a fast one lasting no longer than a few seconds likely involving ion channel modulation, and a slow one that may last for minutes to hours and involves regulation of DA synthesis.

Interaction with the vesicular transporter

Few studies have investigated the possibility that the expression of neuronal vesicular monoamine transporter (VMAT2) is regulated, either in general or by D2 autoreceptors specifically. An initial autoradiography study reported no change in VMAT2 label after repeated *in vivo* treatment with dopaminergic drugs (Vander Borgh *et al.* 1995). In contrast, two recent publications (Brown *et al.* 2001; Brown *et al.* 2002) suggested a regulation of the expression of VMAT2 by D2 autoreceptors. Cocaine treatment increased the uptake of DA into synaptic vesicles, an effect blocked by D2 receptor antagonists. Conversely, D2 receptor agonists increased vesicular DA uptake (Brown *et al.* 2001). In a subsequent study, a decrease in VMAT2 activity was induced by a single treatment with the DA releasing drug methamphetamine, which was also blocked by D2 receptor antagonists (Brown *et al.* 2002). A recent, ultrastructural immunogold label study (Pickel *et al.* 2002) also suggested that D2 receptors could in principle regulate dendritic VMAT2 expression, based on the close association between dendritic D2 receptors and VMAT2 containing vesicles. This pathway would present a third mechanism, in addition to regulation of ion channel conductance and DA synthesis, by which D2 autoreceptors regulate DA release.

Interaction with the plasmalemmal DA transporter

Several studies have provided evidence that D2 autoreceptors modulate DA reuptake (Meiergerd *et al.* 1993; Parsons *et al.* 1993; Cass and Gerhardt 1994; Wiczorek and Kruk 1994a; Batchelor and Schenk 1998; Dickinson *et al.* 1999; Kimmel *et al.* 2001; Mayfield and Zahniser 2001; Schmitz *et al.* 2002; Wu *et al.* 2002). Immediate regulation of DA uptake by D2 receptors may occur through the voltage dependence of uptake (Sonders *et al.* 1997; Hoffman *et al.* 1999), although this mechanism was not supported by studies utilizing midbrain cell cultures (Prasad and Amara 2001). D2 receptor-mediated changes in DAT activity may involve phosphorylation, trafficking, and/or expression of the DAT. The second messengers that may mediate these actions are not well characterized. PKC activation has been shown to reduce DAT activity through enhanced internalization and reduced delivery to the membrane (Copeland *et al.* 1996; Huff *et al.* 1997; Vaughan *et al.* 1997; Zhang *et al.* 1997; Zhu *et al.* 1997; Pristupa *et al.* 1998; Daniels and Amara 1999; Melikian and Buckley 1999). Although it is possible that D2 receptor activity is linked to PKC-mediated pathways (Iannazzo *et al.* 1997; Huff *et al.* 1998), there is thus far no direct evidence that D2 receptors affect the DAT via PKC. Several studies demonstrated that D2 receptor antagonists inhibit DAT activity, suggesting that D2 autoreceptor activation promotes DAT activity (Meiergerd *et al.* 1993; Cass and Gerhardt 1994; Rothblat and Schneider 1997; Benoit-Marand *et al.* 2001; Wu *et al.* 2002). The effect of D2 receptor agonists on DAT activity, however, is less clear. In striatal suspensions, quinpirole stimulated DA uptake by a PKA-dependent pathway possibly via transient enhancement of DAT insertion into the membrane (Batchelor and Schenk 1998). In striatal slice preparations, however, quinpirole does not appear to induce any detectable effect on DA uptake under normal conditions (Joseph *et al.* 2002).

The effect of chronic D2 receptor stimulation on DAT expression is also not clear. Chronic treatment with D2 receptor agonists was reported to result in increased DAT expression in the N. acc., and decreased DAT expression in the caudate putamen (Kimmel *et al.* 2001). Altered DAT levels have been reported in schizophrenic patients, although it is unknown if this represents a manifestation of the disease or a consequence of anti-psychotic drug treatment (Dean and Hussain 2001; Laakso *et al.* 2001).

Studies on three different mouse lines lacking D2 receptors also addressed potential alterations of DAT activity, with different outcomes. In a mouse line with a deletion mutation for the D2 receptor (i.e. a truncated form of the receptor is still expressed), DAT activity was decreased based on the kinetics of DA reuptake of injected DA solution into the striatum (Dickinson *et al.* 1999). In a D2 receptor knockout mouse line (Baik *et al.* 1995), an *in vivo* study using amperometric recordings of evoked DA release reported no apparent change in uptake based on the half-life of DA

overflow (Benoit-Marand *et al.* 2001). In contrast, immunostaining with antibodies against the DAT revealed an increased density of DAT-containing fibers in the striatum of this mouse line (Parish *et al.* 2001). In another knockout mouse line (Jung *et al.* 1999), a study on evoked DA overflow in striatal slices found an increase in DA uptake activity, based on the half life of evoked DA overflow and effects of DAT blockers (Schmitz *et al.* 2002).

To summarize, there is accumulating evidence that D2 receptors regulate DAT activity. The conditions under which autoreceptors activate or inhibit DA uptake, and the mechanisms that are involved in the regulation remain unclear and need to be delineated. An altered DAT expression in DA terminals in response to chronic autoreceptor activation may explain some of the characteristic responses seen with anti-psychotic drug treatment, such as the alleviation of the hyperdopaminergic state in schizophrenic patients, and the delay in the full response to treatment.

Heteroreceptors on nigrostriatal axon terminals

Most of the efforts in characterizing receptor-mediated presynaptic modulation of evoked DA release in the striatum have examined the D2 autoreceptor, but additional neurotransmitter receptors are present on nigrostriatal terminals. Electron microscopic demonstration of heteroreceptor immunolabel in DA terminals is clearly invaluable for establishing their presence, but there are relatively few studies in this area. One technical difficulty is that double staining with a marker for nigrostriatal terminals, such as tyrosine hydroxylase, is required. There are also technical obstacles to measuring terminal heteroreceptor effects on synaptic DA release. Synaptosomal preparations are useful for ascertaining if there is a response to a given agonist, but provide poor kinetic resolution. Numerous microdialysis studies have provided evidence for heteroreceptor regulation of DA release, however, with this technique it is not always possible to exclude circuit effects. We limit the discussion here to data obtained by real-time electrochemical recordings of electrically evoked axon terminal DA release *in vitro*, although this approach also has to consider circuit effects (Avshalumov *et al.* 2003).

A role for glutamate receptors on striatal DA terminals has been implicated in two studies that demonstrated attenuation of evoked DA release in response to the glutamate antagonist kynurenate and glutamate itself (Wu *et al.* 2000; Kulagina *et al.* 2001). It is unclear why agonists and antagonists have similar effects, and the role and even presence of presynaptic ionotropic glutamate receptors in DA terminals remains to be demonstrated (Bernard and Bolam 1998; Chen *et al.* 1998). A recent study suggested that the inhibitory effects of glutamate on striatal DA release are indeed indirect and are mediated by the AMPA receptor-dependent production of the diffusible messenger H₂O₂ (Avshalumov *et al.* 2003). In

contrast to ionotropic glutamate receptors, the metabotropic receptor mGluR1 has been observed by ultrastructural immunolabel in striatal DA terminals (Yoland Smith, personal communication), and a direct effect of metabotropic glutamate receptor activation in regulating evoked DA release is possible (Zhang and Sulzer, 2003).

The nicotinic acetylcholine receptor is presynaptic in a wide variety of neuronal synapses (McGehee *et al.* 1995) and there is immunohistochemical evidence for its presence on DA terminals (Wonnacott *et al.* 2000). Electrochemical studies demonstrated an inhibition of evoked DA release by muscarinic and nicotinic agonists (Kudernatsch and Sutor 1994). It may be that the acute effect of nicotine on DA release is excitatory, but the receptor is rapidly desensitized during the recordings (Zhou *et al.* 2001).

GABA_B receptor agonists inhibit evoked DA release measured electrochemically in the striatal slice with kinetic parameters similar to those of the D2 autoreceptor (Schmitz *et al.* 2002). There is ultrastructural evidence consistent with expression of GABA_B receptors on DA terminals (Charara *et al.* 2000). Thus, there are at least two G-protein-coupled receptors for classical neurotransmitters on DA terminals that produce similar effects.

Ultrastructural studies show that delta and kappa opioid receptors are present on striatal DA terminals (Svingos *et al.* 1999; Svingos *et al.* 2001). There are numerous additional ionotropic and G-protein-linked receptor candidates that may act as heteroreceptors on DA terminals, and elucidation of their effects is fundamental for understanding modulation of dopaminergic transmission.

A receptor complex for glial-derived neurotrophic factor (GDNF) appears to be present on nigrostriatal terminals (Araujo *et al.* 1997). GDNF delivery to the striatum, the SN, or the ventricles promoted axonal sprouting and enhanced TH activity and DA release *in vivo* (Gash *et al.* 1996; Hebert *et al.* 1996; Rosenblad *et al.* 1998; Grondin *et al.* 2003). In cultured midbrain neurons, GDNF increased the quantal size of DA release (see below (Pothos *et al.* 1998a). It may be that there is a developmental window during which GDNF, and likely other growth factors, can exert effects on nigrostriatal terminals.

Retrograde messengers

In glutamatergic synapses, several retrograde messengers have been identified that are released postsynaptically and feed back on to the presynaptic site to affect transmitter release. In DA synapses, no clear evidence for retrograde signaling has yet been reported. Destruction of the target neurons in the striatum by kainate injections had no effect on the presynaptic characteristics of DA transmission (Gonon 1986). Similarly, there was no effect on DA release and uptake in mice lacking endogenous inhibitors of protein phosphatase-1 (DARPP-32, or inhibitor-1, or both), which

participates in a major signaling pathway activated by postsynaptic DA receptors (Zachariou *et al.* 2002). Likewise, preliminary *in vivo* experiments with mice lacking the exclusively postsynaptic D1 DA receptor show no obvious alterations in the presynaptic regulation of evoked DA overflow (Mallet and Gonon, unpublished observations).

Quantal size

The term 'quantal size' was originally defined as the magnitude of miniature excitatory postsynaptic potentials in response to the exocytosis of single vesicles. This term was appropriated for the number of neurotransmitter molecules released during synaptic vesicle fusion which can be determined directly for catecholamine containing vesicles by electrochemical recordings (Sulzer *et al.* 1995; Pothos *et al.* 1996). Numerous interventions have now been reported to alter presynaptic quantal size, as discussed in a recent review (Sulzer and Pothos 2000). Only a few studies have been performed on neurons, and fewer still on cultured catecholamine containing neurons, although some preparations may be adapted for such experiments (Jaffe *et al.* 1998; Puopolo *et al.* 2001). Synaptic vesicle fusion in cultured ventral midbrain DA neurons typically releases ~3000 DA molecules per quantum during ~100 μs. A variety of interventions that decrease quantal size in chromaffin cells and other neurosecretory cells probably do so in DA midbrain neurons as well. For instance, reserpine decreases quantal size in chromaffin and PC12 cells (Kozminski *et al.* 1998; Colliver *et al.* 2000), and chronic activation of D2 autoreceptors decreases quantal size in the PC12 cell line (Pothos *et al.* 1998b). The lack of data on interventions that decrease quantal size in midbrain DA neurons is mostly due to the very small quantal size, which is more than 2–3 orders of magnitude smaller than in chromaffin cells. Thus, most of the reported modulation of quantal size in midbrain neurons is on interventions that increase quantal size.

Short-term incubation (30 min) of neuronal cultures with L-DOPA, a precursor for DA, rapidly increased quantal size by ~4-fold. Application of GDNF elevated quantal size to a similar extent, but the effect required several days to occur (Pothos *et al.* 1998a). Alterations in quantal size by drugs that alter PKC activity have recently been observed (Roland Staal, manuscript in submission). Another example of regulation of quantal size is the overexpression of the vesicular monoamine transporter VMAT2 in cultured midbrain neurons. VMAT2 overexpression increased not only the size but also the frequency of quantal events, apparently by converting the neurochemical phenotype of synaptic vesicles that did not formerly release DA (Pothos *et al.* 2000). Thus, it is possible for a single intervention to modulate both quantal size and the frequency of vesicle exocytosis. Aside from the evidence discussed in the section 'Interaction with the vesicular DA transporter', it is presently

unclear whether and how expression of VMAT2 is regulated under physiological conditions.

Releasable vesicular pool

DA release elicited in striatal slice preparations exhibits a pronounced and long lasting paired pulse depression (PPD), i.e. the amount of DA release elicited by the second stimulus is reduced compared to the DA release elicited by the first stimulus. Full recovery takes about 60 s, and is fitted by a double exponential function with time constants of ~ 5 s and ~ 25 s (Kennedy *et al.* 1992; Abeliovich *et al.* 2000; Phillips *et al.* 2002). The situation *in vivo* is quite different, however. The amplitude of DA overflow recorded in response to a single stimulation of the medial forebrain bundle is about 10 times smaller than the amplitude of DA overflow evoked by direct stimulation in the striatum *in vitro*. There appears to be no depression of DA release (apart from D2 receptor-mediated autoregulation) for stimulation frequencies from 4 to 100 Hz (Chergui *et al.* 1994; Garris *et al.* 1994; Dugast *et al.* 1997; Benoit-Marand *et al.* 2001). A careful re-examination, however, revealed that at least a moderate PPD may also exist *in vivo*, i.e. for an interstimulus interval of 1 s there is a PPD of $\sim 35\%$ (Benoit-Marand and Gonon, unpublished data). The reason for this difference in PPD of DA release *in vitro* and *in vivo* is not understood. One obvious difference between the *in vivo* and *in vitro* situation is the absence of spontaneous DA release in slice preparations, whereas *in vivo* there is a tonic activity of DAergic midbrain neurons and presumably tonic DA release from the terminals in the striatum. Stimulation of the slice with a regular pattern, however, does not emulate the release behavior found *in vivo*. Moreover, reducing the stimulation current *in vitro*, so that only half of the maximal DA release is elicited, does not accelerate the recovery rate but slows it even further (Schmitz, Benoit-Marand, Gonon, and Sulzer, unpublished data).

Two manipulations have been shown to accelerate the recovery of striatal DA release from PPD *in vitro*. An incidental finding was that in α -synuclein knockout mice recovery from PPD is accelerated, with time constants of 5 and 16 s (Abeliovich *et al.* 2000). α -synuclein is a presynaptic protein of unknown function, although it has been shown to affect the vesicular pool size (Murphy *et al.* 2000; Cabin *et al.* 2002). Elevated extracellular calcium (10 mM versus 2.4 mM) also accelerated the recovery rate of DA release (time constants of 2.5 and 18 s), while also enhancing the amount of DA released by the first stimulation, as expected from the dependence of vesicular release on calcium (Abeliovich *et al.* 2000).

More work is clearly required to understand the pronounced PPD of DA release *in vitro* and the behavior of these synapses *in vivo*. From the *in vitro* data, it appears as if releasable vesicular pools in DA synapses may be

up-regulated quickly after activity stops, and/or release probability may increase. So far, such plasticity has only been reported for glutamatergic synapses after several days of inactivity in cultured neurons (Murthy *et al.* 2001).

Summary

Released DA diffuses beyond the synaptic cleft and concentrations sufficient for receptor activation are reached even several microns from the release site, as termination of the DA signal by the DAT occurs at extrasynaptic sites. Both changes in the frequency as well as changes in the quantal size of vesicular release are expected to have an impact in this type of 'spill-over' (or social) synapse as saturation of postsynaptic receptors is less likely to occur than in a point-to-point (or private) synapse. Hence, dopaminergic transmission is highly regulated presynaptically by auto- and heteroreceptors and DATs. The mutual interaction between receptors and DATs provides a complex regulatory system that shapes the DA signal. The striking behavioral effects of psychostimulants, as well as many of the effects of anti-psychotic drugs, seem to result from their interference with this regulation.

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References

- Abeliovich A., Schmitz Y., Farinas I., Choi-Lundberg D., Ho W. H., Castillo P. E., Shinsky N., Verdugo J. M., Armanini M., Ryan A. *et al.* (2000) Mice lacking alpha-synuclein display functional deficits in the nigrostriatal dopamine system. *Neuron* **25**, 239–252.
- Ackerman J. M. and White F. J. (1990) A10 somatodendritic dopamine autoreceptor sensitivity following withdrawal from repeated cocaine treatment. *Neurosci. Lett.* **117**, 181–187.
- Araujo D. M., Hilt D. C., Miller P. J., Wen D., Jiao S. and Lapchak P. A. (1997) ret receptor tyrosine kinase immunoreactivity is altered in glial cell line-derived neurotrophic factor-responsive neurons following lesions of the nigrostriatal and septohippocampal pathways. *Neuroscience* **80**, 9–16.
- Aretha C. W., Sinha A. and Galloway M. P. (1995) Dopamine D3-preferring ligands act at synthesis modulating autoreceptors. *J. Pharmacol. Exp. Ther.* **274**, 609–613.
- Avshalumov M. V., Chen B. T., Marshall S. P., Pena D. M. and Rice M. E. (2003) Glutamate-dependent inhibition of dopamine release in striatum is mediated by a new diffusible messenger, H₂O₂. *J. Neurosci.* **23**, 2744–2750.

- Baik J. H., Picetti R., Saiardi A., Thiriet G., Dierich A., Depaulis A., Le Meur M. and Borrelli E. (1995) Parkinsonian-like locomotor impairment in mice lacking dopamine D2 receptors. *Nature* **377**, 424–428.
- Batchelor M. and Schenk J. O. (1998) Protein kinase A activity may kinetically upregulate the striatal transporter for dopamine. *J. Neurosci.* **18**, 10304–10309.
- Benoit-Marand M., Jaber M. and Gonon F. (2000) Release and elimination of dopamine *in vivo* in mice lacking the dopamine transporter: functional consequences. *Eur. J. Neurosci.* **12**, 2985–2992.
- Benoit-Marand M., Borrelli E. and Gonon F. (2001) Inhibition of dopamine release via presynaptic D2 receptors: time course and functional characteristics *in vivo*. *J. Neurosci.* **21**, 9134–9141.
- Bernard V. and Bolam J. P. (1998) Subcellular and subsynaptic distribution of the NR1 subunit of the NMDA receptor in the neostriatum and globus pallidus of the rat: co-localization at synapses with the GluR2/3 subunit of the AMPA receptor. *Eur. J. Neurosci.* **10**, 3721–3736.
- Blakely R. D. and Bauman A. L. (2000) Biogenic amine transporters: regulation in flux. *Curr. Opin. Neurobiol.* **10**, 328–336.
- Broderick P. A. and Piercey M. F. (1998) Clozapine, haloperidol, and the D4 antagonist PNU-101387G: *in vivo* effects on mesocortical, mesolimbic, and nigrostriatal dopamine and serotonin release. *J. Neural Transm.* **105**, 749–767.
- Brown J. M., Hanson G. R. and Fleckenstein A. E. (2001) Cocaine-induced increases in vesicular dopamine uptake: role of dopamine receptors. *J. Pharmacol. Exp. Ther.* **298**, 1150–1153.
- Brown J. M., Riddle E. L., Sandoval V., Weston R. K., Hanson J. E., Crosby M. J., Ugarte Y. V., Gibb J. W., Hanson G. R. and Fleckenstein A. E. (2002) A single methamphetamine administration rapidly decreases vesicular dopamine uptake. *J. Pharmacol. Exp. Ther.* **302**, 497–501.
- Budygin E. A., John C. E., Mateo Y. and Jones S. R. (2002) Lack of cocaine effect on dopamine clearance in the core and shell of the nucleus accumbens of dopamine transporter knock-out mice. *J. Neurosci.* **22**, RC222.
- Bunney B. S. and Grace A. A. (1978) Acute and chronic haloperidol treatment: comparison of effects on nigral dopaminergic cell activity. *Life Sci.* **23**, 1715–1727.
- Bunney B. S., Walters J. R., Roth R. H. and Aghajanian G. K. (1973) Dopaminergic neurons: effect of antipsychotic drugs and amphetamine on single cell activity. *J. Pharmacol. Exp. Ther.* **185**, 560–571.
- Burn J. H. and Rand M. J. (1958) The action of sympathomimetic amines in animals treated with reserpine. *J. Physiol.* **144**, 314–336.
- Cabin D. E., Shimazu K., Murphy D., Cole N. B., Gottschalk W., McIlwain K. L., Orrison B., Chen A., Ellis C. E., Paylor R. *et al.* (2002) Synaptic vesicle depletion correlates with attenuated synaptic responses to prolonged repetitive stimulation in mice lacking alpha-synuclein. *J. Neurosci.* **22**, 8797–8807.
- Calligaro D. O. and Eldefrawi M. E. (1987) High affinity stereospecific binding of [³H]cocaine in striatum and its relationship to the dopamine transporter. *Membr. Biochem.* **7**, 87–106.
- Carboni E., Spielewoy C., Vacca C., Nosten-Bertrand M., Giros B. and Di Chiara G. (2001) Cocaine and amphetamine increase extracellular dopamine in the nucleus accumbens of mice lacking the dopamine transporter gene. *J. Neurosci.* **21**, RC141: 141–144.
- Cardozo D. L. and Bean B. P. (1995) Voltage-dependent calcium channels in rat midbrain dopamine neurons modulation by dopamine and GABAB receptors. *J. Neurophysiol.* **74**, 1137–1148.
- Carlsson A. (1975) Dopaminergic autoreceptors, in: *Chemical Tools in Catecholamine Research*, Vol. II (Almgren O., Carlsson A. and Engel J., eds), pp. 219–225. North-Holland Publishing Co, Amsterdam.
- Cass W. A. and Gerhardt G. A. (1994) Direct *in vivo* evidence that D2 dopamine receptors can modulate dopamine uptake. *Neurosci. Lett.* **176**, 259–263.
- Cass W. A., Gerhardt G. A., Mayfield R. D., Curella P. and Zahniser N. R. (1992) Differences in dopamine clearance and diffusion in rat striatum and nucleus accumbens following systemic cocaine administration. *J. Neurochem.* **59**, 259–266.
- Cathala L. and Paupardin-Tritsch D. (1999) Effect of catecholamines on the hyperpolarization-activated cationic I_h and the inwardly rectifying potassium I (Kir) currents in the rat substantia nigra pars compacta. *Eur. J. Neurosci.* **11**, 398–406.
- Centonze D., Usiello A., Gubellini P., Pisani A., Borrelli E., Bernardi G. and Calabresi P. (2002) Dopamine D2 receptor-mediated inhibition of dopaminergic neurons in mice lacking D2L receptors. *Neuropharmacology* **27**, 723–726.
- Charara A., Heilman C., Levey A. I. and Smith Y. (2000) Pre- and postsynaptic localization of GABAB receptors in the basal ganglia in monkeys. *Neuroscience* **95**, 127–140.
- Chen N. and Justice J. B. Jr (1998) Cocaine acts as an apparent competitive inhibitor at the outward-facing conformation of the human norepinephrine transporter: kinetic analysis of inward and outward transport. *J. Neurosci.* **18**, 10257–10268.
- Chen B. T. and Rice M. E. (2001) Novel Ca²⁺ dependence and time course of somatodendritic dopamine release: substantia nigra versus striatum. *J. Neurosci.* **21**, 7841–7847.
- Chen Q., Veenman L., Knopp K., Yan Z., Medina L., Song W. J., Surmeier D. J. and Reiner A. (1998) Evidence for the preferential localization of glutamate receptor-1 subunits of AMPA receptors to the dendritic spines of medium spiny neurons in rat striatum. *Neuroscience* **83**, 749–761.
- Chergui K., Suaud-Chagny M. F. and Gonon F. (1994) Nonlinear relationship between impulse flow, dopamine release and dopamine elimination in the rat brain *in vivo*. *Neuroscience* **62**, 641–645.
- Chergui K., Nomikos G. G., Mathe J. M., Gonon F. and Svensson T. H. (1996) Burst stimulation of the medial forebrain bundle selectively increase Fos-like immunoreactivity in the limbic forebrain of the rat. *Neuroscience* **72**, 141–156.
- Chergui K., Svenningsson P., Nomikos G. G., Gonon F., Fredholm B. B. and Svensson T. H. (1997) Increased expression of NGFI-A mRNA in the rat striatum following burst stimulation of the medial forebrain bundle. *Eur. J. Neurosci.* **9**, 2370–2382.
- Chiodo L. A., Bannon M. J., Grace A. A., Roth R. H. and Bunney B. S. (1984) Evidence for the absence of impulse-regulating somatodendritic and synthesis-modulating nerve terminal autoreceptors on subpopulations of mesocortical dopamine neurons. *Neuroscience* **12**, 1–16.
- Colliver T. L., Pyott S. J., Achalabun M. and Ewing A. G. (2000) VMAT-mediated changes in quantal size and vesicular volume. *J. Neuroscience* **20**, 5276–5282.
- Congar P., Bergevin A. and Trudeau L. E. (2002) D2 receptors inhibit the secretory process downstream from calcium influx in dopaminergic neurons: implication of K(+) channels. *J. Neurophysiol.* **87**, 1046–1056.
- Copeland B. J., Vogelsberg V., Neff N. H. and Hadjiconstantinou M. (1996) Protein kinase C activators decrease dopamine uptake into striatal synaptosomes. *J. Pharmacol. Exp. Ther.* **277**, 1527–1532.
- Cragg S. J. and Greenfield S. A. (1997) Differential autoreceptor control of somatodendritic and axon terminal dopamine release in substantia nigra, ventral tegmental area, and striatum. *J. Neurosci.* **17**, 5738–5746.
- Cragg S. J., Hille C. J. and Greenfield S. A. (2000) Dopamine release and uptake dynamics within nonhuman primate striatum *in vitro*. *J. Neurosci.* **20**, 8209–8217.

- Cragg S. J., Nicholson C., Kume-Kick J., Tao L. and Rice M. E. (2001) Dopamine-mediated volume transmission in midbrain is regulated by distinct extracellular geometry and uptake. *J. Neurophysiol.* **85**, 1761–1771.
- Cragg S. J., Hille C. J. and Greenfield S. A. (2002) Functional domains in dorsal striatum of the nonhuman primate are defined by the dynamic behavior of dopamine. *J. Neurosci.* **22**, 5705–5712.
- Cubeddu L. X. and Hoffmann I. S. (1982) Operational characteristics of the inhibitory feedback mechanism for regulation of dopamine release via presynaptic receptors. *J. Pharmacol. Exp. Ther.* **223**, 497–501.
- Daniels G. M. and Amara S. G. (1999) Regulated trafficking of the human dopamine transporter: clathrin-mediated internalization and lysosomal degradation in response to phorbol esters. *J. Biol. Chem.* **274**, 35794–35801.
- Davidson C., Ellinwood E. H. and Lee T. H. (2000) Altered sensitivity of dopamine autoreceptors in rat accumbens 1 and 7 days after intermittent or continuous cocaine withdrawal. *Brain Res. Bull.* **51**, 89–93.
- Davila V., Yan Z., Cracium L. C., Logothetis D. and Sulzer D. (2003) D3 dopamine autoreceptors do not activate GIRK channel currents in substantia nigra dopamine neurons. *J. Neurosci.* **23**, 5693–5697.
- Daws L. C., Callaghan P. D., Moron J. A., Kahlig K. M., Shippenberg T. S., Javitch J. A. and Galli A. (2002) Cocaine increases dopamine uptake and cell surface expression of dopamine transporters. *Biochem. Biophys. Res. Commun.* **290**, 1545–1550.
- Dean B. and Hussain T. (2001) Studies on dopaminergic and GABAergic markers in striatum reveals a decrease in the dopamine transporter in schizophrenia. *Schizophr. Res.* **52**, 107–114.
- Diaz J., Pilon C., Le Foll B., Gros C., Triller A., Schwartz J. C. and Sokoloff P. (2000) Dopamine D3 receptors expressed by all mesencephalic dopamine neurons. *J. Neurosci.* **20**, 8677–8684.
- Dickinson S. D., Sabeti J., Larson G. A., Giardina K., Rubinstein M., Kelly M. A., Grandy D. K., Low M. J., Gerhardt G. A. and Zahniser N. R. (1999) Dopamine D2 receptor-deficient mice exhibit decreased dopamine transporter function but no changes in dopamine release in dorsal striatum. *J. Neurochem.* **72**, 148–156.
- Dugast C., Brun P., Sotty F., Renaud B. and Suaud-Chagny M. F. (1997) On the involvement of a tonic dopamine D2-autoinhibition in the regulation of pulse-to-pulse-evoked dopamine release in the rat striatum *in vivo*. *Naunyn Schmiedeberg's Arch. Pharmacol.* **355**, 716–719.
- Dwoskin L. P. and Zahniser N. R. (1986) Robust modulation of [3H]dopamine release from rat striatal slices by D-2 dopamine receptors. *J. Pharmacol. Exp. Ther.* **239**, 442–453.
- Earles C. and Schenk J. O. (1998) Rotating disk electrode voltammetric measurements of dopamine transporter activity: an analytical evaluation. *Anal Biochem.* **264**, 191–198.
- Ewing A. G., Bigelow J. C. and Wightman R. M. (1983) Direct *in vivo* monitoring of dopamine released from two striatal compartments in the rat. *Science* **221**, 169–171.
- Falkenburger B. H., Barstow K. L. and Mintz I. M. (2001) Dendro-dendritic inhibition through reversal of dopamine transport. *Science* **293**, 2465–2470.
- Fischer J. F. and Cho A. K. (1979) Chemical release of dopamine from striatal homogenates: evidence for an exchange diffusion model. *J. Pharmacol. Exp. Ther.* **208**, 203–209.
- Freeman A. S. and Bunney B. S. (1987) Activity of A9 and A10 dopaminergic neurons in unrestrained rats: further characterization and effects of apomorphine and cholecystokinin. *Brain Res.* **405**, 46–55.
- Gainetdinov R. R., Sotnikova T. D., Grekhova T. V. and Rayevsky K. S. (1996) *In vivo* evidence for preferential role of dopamine D3 receptor in the presynaptic regulation of dopamine release but not synthesis. *Eur. J. Pharmacol.* **308**, 261–269.
- Gainetdinov R. R., Jones S. R., Fumagalli F., Wightman R. M. and Caron M. G. (1998) Re-evaluation of the role of the dopamine transporter in dopamine system homeostasis. *Brain Res. Brain Res. Rev.* **26**, 148–153.
- Gainetdinov R. R., Wetsel W. C., Jones S. R., Levin E. D., Jaber M. and Caron M. G. (1999) Role of serotonin in the paradoxical calming effect of psychostimulants on hyperactivity. *Science* **283**, 397–401.
- Galloway M. P., Wolf M. E. and Roth R. H. (1986) Regulation of dopamine synthesis in the medial prefrontal cortex is mediated by release modulating autoreceptors: studies *in vivo*. *J. Pharmacol. Exp. Ther.* **236**, 689–698.
- Garris P. A. and Wightman R. M. (1994) Different kinetics govern dopaminergic transmission in the amygdala, prefrontal cortex, and striatum: an *in vivo* voltammetric study. *J. Neurosci.* **14**, 442–450.
- Garris P. A., Ciolkowski E. L., Pastore P. and Wightman R. M. (1994) Efflux of dopamine from the synaptic cleft in the nucleus accumbens of the rat brain. *J. Neurosci.* **14**, 6084–6093.
- Gash D. M., Zhang Z., Ovadia A., Cass W. A., Yi A., Simmerman L., Russell D., Martin D., Lapchak P. A., Collins F. *et al.* (1996) Functional recovery in parkinsonian monkeys treated with GDNF. *Nature* **380**, 252–255.
- Giros B., Jaber M., Jones S. R., Wightman R. M. and Caron M. G. (1996) Hyperlocomotion and indifference to cocaine and amphetamine in mice lacking the dopamine transporter. *Nature* **379**, 606–612.
- Gonon F. G. (1986) Control of dopamine release by dopamine receptors and by impulse flow as studied by *in vivo* voltammetry. *Ann. N Y Acad. Sci.* **473**, 160–169.
- Gonon F. G. (1988) Nonlinear relationship between impulse flow and dopamine released by rat midbrain dopaminergic neurons as studied by *in vivo* electrochemistry. *Neuroscience* **24**, 19–28.
- Gonon F. (1997) Prolonged and extrasynaptic excitatory action of dopamine mediated by D1 receptors in the rat striatum *in vivo*. *J. Neurosci.* **17**, 5972–5978.
- Gonon F. G. and Buda M. J. (1985) Regulation of dopamine release by impulse flow and by autoreceptors as studied by *in vivo* voltammetry in the rat striatum. *Neuroscience* **14**, 765–774.
- Gonon F., Buda M., Cespuoglio R., Jouvet M. and Pujol J. F. (1980) *In vivo* electrochemical detection of catechols in the neostriatum of anaesthetized rats: dopamine or DOPAC? *Nature* **286**, 902–904.
- Gonon F., Burie J. B., Jaber M., Benoit-Marand M., Dumartin B. and Bloch B. (2000) Geometry and kinetics of dopaminergic transmission in the rat striatum and in mice lacking the dopamine transporter. *Prog. Brain Res.* **125**, 291–302.
- Grace A. A. and Bunney B. S. (1984a) The control of firing pattern in nigral dopamine neurons: burst firing. *J. Neurosci.* **4**, 2877–2890.
- Grace A. A. and Bunney B. S. (1984b) The control of firing pattern in nigral dopamine neurons: single spike firing. *J. Neurosci.* **4**, 2866–2876.
- Grace A. A., Bunney B. S., Moore H. and Todd C. L. (1997) Dopamine-cell depolarization block as a model for the therapeutic actions of antipsychotic drugs. *Trends Neurosci.* **20**, 31–37.
- Granas C., Ferrer J., Loland C. J., Javitch J. A. and Gether U. (2003) N-Terminal truncation of the dopamine transporter abolishes phorbol ester- and substance P receptor-stimulated phosphorylation without impairing transporter internalization. *J. Biol. Chem.* **278**, 4990–5000.
- Grondin R., Cass W. A., Zhang Z., Stanford J. A., Gash D. M. and Gerhardt G. A. (2003) Glial cell line-derived neurotrophic factor increases stimulus-evoked dopamine release and motor speed in aged rhesus monkeys. *J. Neurosci.* **23**, 1974–1980.

- Gulley J. M., Doolen S. and Zahniser N. R. (2002) Brief, repeated exposure to substrates down-regulates dopamine transporter function in *Xenopus oocytes in vitro* and rat dorsal striatum *in vivo*. *J. Neurochem.* **83**, 400–411.
- Haubrich D. R. and Pflueger A. B. (1982) The autoreceptor control of dopamine synthesis: an *in vitro* and *in vivo* comparison of dopamine agonists. *Mol. Pharmacol.* **21**, 114–120.
- Hebert M. A., Van Horne C. G., Hoffer B. J. and Gerhardt G. A. (1996) Functional effects of GDNF in normal rat striatum: presynaptic studies using *in vivo* electrochemistry and microdialysis. *J. Pharmacol. Exp. Ther.* **279**, 1181–1190.
- Heikkilä R. E., Orlansky H., Mytilineou C. and Cohen G. (1975) Amphetamine: evaluation of D- and L-isomers as releasing agents and uptake inhibitors for ^3H -dopamine and ^3H -norepinephrine in slices of rat neostriatum and cerebral cortex. *J. Pharmacol. Exp. Ther.* **194**, 47–56.
- Henry D. J., Hu X. T. and White F. J. (1998) Adaptations in the mesoaccumbens dopamine system resulting from repeated administration of dopamine D1 and D2 receptor-selective agonists: relevance to cocaine sensitization. *Psychopharmacology (Berl.)* **140**, 233–242.
- Henry D. J., Greene M. A. and White F. J. (1989) Electrophysiological effects of cocaine in the mesoaccumbens dopamine system: repeated administration. *J. Pharmacol. Exp. Ther.* **251**, 833–839.
- Hoffman A. F., Zahniser N. R., Lupica C. R. and Gerhardt G. A. (1999) Voltage-dependency of the dopamine transporter in the rat substantia nigra. *Neurosci. Lett.* **260**, 105–108.
- Horn A. S. (1979) Characteristics of dopamine uptake, in: *The Neurobiology of Dopamine* (Westerink, B. H. C., ed.), pp. 217–235. Academic Press, London.
- Horn A. S. (1990) Dopamine uptake: a review of progress in the last decade. *Prog. Neurobiol.* **34**, 387–400.
- Howard S. G., Fisher R. and Landry C. F. (1997) Alterations in the spontaneous release of dopamine and the density of the DA D2 receptor mRNA after chronic postnatal exposure to cocaine. *Brain Res. Bull.* **43**, 101–106.
- Huff R. A., Vaughan R. A., Kuhar M. J. and Uhl G. R. (1997) Phorbol esters increase dopamine transporter phosphorylation and decrease transport V_{max} . *J. Neurochem.* **68**, 225–232.
- Huff R. M., Chio C. L., Lajiness M. E. and Goodman L. V. (1998) Signal transduction pathways modulated by D2-like dopamine receptors. *Adv. Pharmacol.* **42**, 454–457.
- Iannazzo L., Sathananthan S. and Majewski H. (1997) Modulation of dopamine release from rat striatum by protein kinase C: interaction with presynaptic D2-dopamine-autoreceptors. *Br. J. Pharmacol.* **122**, 1561–1566.
- Ingram S. L., Prasad B. M. and Amara S. G. (2002) Dopamine transporter-mediated conductances increase excitability of midbrain dopamine neurons. *Nat. Neurosci.* **5**, 971–978.
- Iravani M. M. and Kruk Z. L. (1995) Effects of amphetamine on carrier-mediated and electrically stimulated dopamine release in slices of rat caudate putamen and nucleus accumbens. *J. Neurochem.* **64**, 1161–1168.
- Jaffé E. H., Marty A., Schulte A. and Chow R. H. (1998) Extrasynaptic vesicular transmitter release from the somata of substantia nigra neurons in rat midbrain slices. *J. Neurosci.* **18**, 3548–3553.
- Jahr C. E. (2003) Drooling and stuttering, or do synapses whisper? *Trends Neurosci.* **26**, 7–9.
- Jones S. R., Garris P. A. and Wightman R. M. (1995a) Different effects of cocaine and nomifensine on dopamine uptake in the caudate-putamen and nucleus accumbens. *J. Pharmacol. Exp. Ther.* **274**, 396–403.
- Jones S. R., Garris P. A., Kilts C. D. and Wightman R. M. (1995b) Comparison of dopamine uptake in the basolateral amygdaloid nucleus, caudate-putamen, and nucleus accumbens of the rat. *J. Neurochem.* **64**, 2581–2589.
- Jones S. R., Lee T. H., Wightman R. M. and Ellinwood E. H. (1996a) Effects of intermittent and continuous cocaine administration on dopamine release and uptake regulation in the striatum: *in vitro* voltammetric assessment. *Psychopharmacology (Berl.)* **126**, 331–338.
- Jones S. R., O'Dell S. J., Marshall J. F. and Wightman R. M. (1996b) Functional and anatomical evidence for different dopamine dynamics in the core and shell of the nucleus accumbens in slices of rat brain. *Synapse* **23**, 224–231.
- Jones S. R., Gainetdinov R. R., Wightman R. M. and Caron M. G. (1998a) Mechanisms of amphetamine action revealed in mice lacking the dopamine transporter. *J. Neurosci.* **18**, 1979–1986.
- Jones S. R., Gainetdinov R. R., Jaber M., Giros B., Wightman R. M. and Caron M. G. (1998b) Profound neuronal plasticity in response to inactivation of the dopamine transporter. *Proc. Natl Acad. Sci. USA* **95**, 4029–4034.
- Jones S. R., Joseph J. D., Barak L. S., Caron M. G. and Wightman R. M. (1999a) Dopamine neuronal transport kinetics and effects of amphetamine. *J. Neurochem.* **73**, 2406–2414.
- Jones S. R., Gainetdinov R. R., Hu X. T., Cooper D. C., Wightman R. M., White F. J. and Caron M. G. (1999b) Loss of autoreceptor functions in mice lacking the dopamine transporter. *Nat. Neurosci.* **2**, 649–655.
- Joseph J. D., Wang Y. M., Miles P. R., Budygin E. A., Picetti R., Gainetdinov R. R., Caron M. G. and Wightman R. M. (2002) Dopamine autoreceptor regulation of release and uptake in mouse brain slices in the absence of D(3) receptors. *Neuroscience* **112**, 39–49.
- Jung M. Y., Skryabin B. V., Arai M., Abbondanzo S., Fu D., Brosius J., Robakis N. K., Polites H. G., Pintar J. E. and Schmauss C. (1999) Potentiation of the D2 mutant motor phenotype in mice lacking dopamine D2 and D3 receptors. *Neuroscience* **91**, 911–924.
- Kalivas P. W. and Duffy P. (1991) A comparison of axonal and somatodendritic dopamine release using *in vivo* dialysis. *J. Neurochem.* **56**, 961–967.
- Kalsner S. (2001) Autoreceptors do not regulate routinely neurotransmitter release: focus on adrenergic systems. *J. Neurochem.* **78**, 676–684.
- Kapatos G. and Zigmond M. J. (1979) Effect of haloperidol on dopamine synthesis and tyrosine hydroxylase in striatal synaptosomes. *J. Pharmacol. Exp. Ther.* **208**, 468–475.
- Kawagoe K. T., Garris P. A., Wiedemann D. J. and Wightman R. M. (1992) Regulation of transient dopamine concentration gradients in the microenvironment surrounding nerve terminals in the rat striatum. *Neuroscience* **51**, 55–64.
- Kawagoe K. T., Zimmerman J. B. and Wightman R. M. (1993) Principles of voltammetry and microelectrode surface states. *J. Neurosci. Methods* **48**, 225–240.
- Kehr W., Carlsson A., Lindqvist M., Magnusson T. and Atack C. (1972) Evidence for a receptor-mediated feedback control of striatal tyrosine hydroxylase activity. *J. Pharm. Pharmacol.* **24**, 744–747.
- Kennedy R. T., Jones S. R. and Wightman R. M. (1992) Dynamic observation of dopamine autoreceptor effects in rat striatal slices. *J. Neurochem.* **59**, 449–455.
- Khan Z. U., Mrzljak L., Gutierrez A., de la Calle A. and Goldman-Rakic P. S. (1998) Prominence of the dopamine D2 short isoform in dopaminergic pathways. *Proc. Natl Acad. Sci. USA* **95**, 7731–7736.
- Khoshbouei H., Wang H., Lechleiter J. D., Javitch J. A. and Galli A. (2003) Amphetamine-induced DA efflux: a voltage sensitive and intracellular Na^+ -dependent mechanism. *J. Biol. Chem.* **29**, 29.

- Kim K. M., Nakajima Y. and Nakajima S. (1995) G protein-coupled inward rectifier modulated by dopamine agonists in cultured substantia nigra neurons. *Neuroscience* **69**, 1145–1158.
- Kimmel H. L., Carroll F. I. and Kuhar M. J. (2003) Withdrawal from repeated cocaine alters dopamine transporter protein turnover in the rat striatum. *J. Pharmacol. Exp. Ther.* **304**, 15–21.
- Kimmel H. L., Joyce A. R., Carroll F. I. and Kuhar M. J. (2001) Dopamine D1 and D2 receptors influence dopamine transporter synthesis and degradation in the rat. *J. Pharmacol. Exp. Ther.* **298**, 129–140.
- King G. R., Xiong Z., Douglas S., Lee T. H. and Ellinwood E. H. (1999) The effects of continuous cocaine dose on the induction of behavioral tolerance and dopamine autoreceptor function. *Eur. J. Pharmacol.* **376**, 207–215.
- Kissinger P. T., Hart J. B. and Adams R. N. (1973) Voltammetry in brain tissue – a new neurophysiological measurement. *Brain Res.* **55**, 209–213.
- Kitai S. T., Shepard P. D., Callaway J. C. and Scroggs R. (1999) Afferent modulation of dopamine neuron firing patterns. *Curr. Opin. Neurobiol.* **9**, 690–697.
- Koeltzow T. E., Xu M., Cooper D. C., Hu X. T., Tonegawa S., Wolf M. E. and White F. J. (1998) Alterations in dopamine release but not dopamine autoreceptor function in dopamine D3 receptor mutant mice. *J. Neurosci.* **18**, 2231–2238.
- Kozminski K. D., Gutman D. A., Davila V., Sulzer D. and Ewing A. G. (1998) Voltammetric and pharmacological characterization of dopamine released from single quantal events in PC12 cells. *Anal. Chem.* **70**, 3123–3130.
- Kreiss D. S., Bergstrom D. A., Gonzalez A. M., Huang K. X., Sibley D. R. and Walters J. R. (1995) Dopamine receptor agonist potencies for inhibition of cell firing correlate with dopamine D3 receptor binding affinities. *Eur. J. Pharmacol.* **277**, 209–214.
- Krueger B. K. (1990) Kinetics and block of dopamine uptake in synaptosomes from rat caudate nucleus. *J. Neurochem.* **55**, 260–267.
- Kudernatsch M. and Sutor B. (1994) Cholinergic modulation of dopamine overflow in the rat neostriatum: a fast cyclic voltammetric study *in vitro*. *Neurosci. Lett.* **181**, 107–112.
- Kuhar M. J. and Pilote N. S. (1996) Neurochemical changes in cocaine withdrawal. *Trends Pharmacol. Sci.* **17**, 260–264.
- Kula N. S. and Baldessarini R. J. (1991) Lack of increase in dopamine transporter binding or function in rat brain tissue after treatment with blockers of neuronal uptake of dopamine. *Neuropharmacology* **30**, 89–92.
- Kulagina N. V., Zigmund M. J. and Michael A. C. (2001) Glutamate regulates the spontaneous and evoked release of dopamine in the rat striatum. *Neuroscience* **102**, 121–128.
- Kullmann D. M. and Asztely F. (1998) Extrasynaptic glutamate spillover in the hippocampus: evidence and implications. *Trends Neurosci.* **21**, 8–14.
- Kuzhikandathil E. V. and Oxford G. S. (1999) Activation of human D3 dopamine receptor inhibits P/Q-type calcium channels and secretory activity in AtT-20 cells. *J. Neurosci.* **19**, 1698–1707.
- Kuzhikandathil E. V. and Oxford G. S. (2000) Dominant-negative mutants identify a role for GIRK channels in D3 dopamine receptor-mediated regulation of spontaneous secretory activity. *J. Gen. Physiol.* **115**, 697–706.
- Kuzhikandathil E. V., Yu W. and Oxford G. S. (1998) Human dopamine D3 and D2L receptors couple to inward rectifier potassium channels in mammalian cell lines. *Mol. Cell Neurosci.* **12**, 390–402.
- L'hirondel M., Chery A., Godeheu G., Artaud F., Saiardi A., Borrelli E. and Glowinski J. (1998) Lack of autoreceptor-mediated inhibitory control of dopamine release in striatal synaptosomes of D2 receptor-deficient mice. *Brain Res.* **792**, 253–262.
- Laakso A., Bergman J., Haaparanta M., Vilkmann H., Solin O., Syvalahti E. and Hietala J. (2001) Decreased striatal dopamine transporter binding *in vivo* in chronic schizophrenia. *Schizophr. Res.* **52**, 115–120.
- Lacey M. G., Mercuri N. B. and North R. A. (1987) Dopamine acts on D2 receptors to increase potassium conductance in neurones of the rat substantia nigra zona compacta. *J. Physiol.* **392**, 397–416.
- Lee T. H., Gao W. Y. and Ellinwood E. H. (1997) Differential effects of SCH 23390 on the apomorphine subsensitivity in the substantia nigra and ventral tegmental area 1 day following withdrawal from continuous or intermittent cocaine pretreatment. *Brain Res.* **744**, 293–301.
- Lejeune F. and Millan M. J. (1995) Activation of dopamine D3 autoreceptors inhibits firing of ventral tegmental dopaminergic neurones *in vivo*. *Eur. J. Pharmacol.* **275**, R7–R9.
- Limberger N., Trout S. J., Kruk Z. L. and Starke K. (1991) 'Real time' measurement of endogenous dopamine release during short trains of pulses in slices of rat neostriatum and nucleus accumbens: role of autoinhibition. *Naunyn Schmiedeberg's Arch. Pharmacol.* **344**, 623–629.
- Lindgren N., Xu Z. Q., Herrera-Marschitz M., Haycock J., Hokfelt T. and Fisone G. (2001) Dopamine D2 receptors regulate tyrosine hydroxylase activity and phosphorylation at Ser40 in rat striatum. *Eur. J. Neurosci.* **13**, 773–780.
- Little K. Y., Elmer L. W., Zhong H., Scheys J. O. and Zhang L. (2002) Cocaine induction of dopamine transporter trafficking to the plasma membrane. *Mol. Pharmacol.* **61**, 436–445.
- Lu W. and Wolf M. E. (1997) Expression of dopamine transporter and vesicular monoamine transporter 2 mRNAs in rat midbrain after repeated amphetamine administration. *Brain Res. Mol. Brain Res.* **49**, 137–148.
- Marsden C. A., Joseph M. H., Kruk Z. L., Maidment N. T., O'Neill R. D., Schenk J. O. and Stamford J. A. (1988) *In vivo* voltammetry – present electrodes and methods. *Neuroscience* **25**, 389–400.
- Matsumoto M., Weickert C. S., Akil M., Lipska B. K., Hyde T. M., Herman M. M., Kleinman J. E. and Weinberger D. R. (2003) Catechol O-methyltransferase mRNA expression in human and rat brain: evidence for a role in cortical neuronal function. *Neuroscience* **116**, 127–137.
- May L. J. and Wightman R. M. (1989) Effects of D-2 antagonists on frequency-dependent stimulated dopamine overflow in nucleus accumbens and caudate-putamen. *J. Neurochem.* **53**, 898–906.
- Mayer A., Limberger N. and Starke K. (1988) Transmitter release patterns of noradrenergic, dopaminergic and cholinergic axons in rabbit brain slices during short pulse trains, and the operation of presynaptic autoreceptors. *Naunyn Schmiedeberg's Arch. Pharmacol.* **338**, 632–643.
- Mayfield R. D. and Zahniser N. R. (2001) Dopamine D2 receptor regulation of the dopamine transporter expressed in *Xenopus laevis* oocytes is voltage-independent. *Mol. Pharmacol.* **59**, 113–121.
- McElvain J. S. and Schenk J. O. (1992) A multisubstrate mechanism of striatal dopamine uptake and its inhibition by cocaine. *Biochem. Pharmacol.* **43**, 2189–2199.
- McGehee D. S., Heath M. J., Gelber S., Devay P. and Role L. W. (1995) Nicotine enhancement of fast excitatory synaptic transmission in CNS by presynaptic receptors. *Science* **269**, 1692–1696.
- Meiergerd S. M., Patterson T. A. and Schenk J. O. (1993) D2 receptors may modulate the function of the striatal transporter for dopamine: kinetic evidence from studies *in vitro* and *in vivo*. *J. Neurochem.* **61**, 764–767.
- Melikian H. E. and Buckley K. M. (1999) Membrane trafficking regulates the activity of the human dopamine transporter. *J. Neurosci.* **19**, 7699–7710.

- Melis M., Mereu G., Lilliu V., Quartu M., Diana M. and Gessa G. L. (1998) Haloperidol does not produce dopamine cell depolarization-block in paralyzed, unanesthetized rats. *Brain Res.* **783**, 127–132.
- Mercuri N. B., Saiardi A., Bonci A., Picetti R., Calabresi P., Bernardi G. and Borrelli E. (1997) Loss of autoreceptor function in dopaminergic neurons from dopamine D2 receptor deficient mice. *Neuroscience* **79**, 323–327.
- el Mestikawy S. and Hamon M. (1986) Is dopamine-induced inhibition of adenylate cyclase involved in the autoreceptor-mediated negative control of tyrosine hydroxylase in striatal dopaminergic terminals? *J. Neurochem.* **47**, 1425–1433.
- Michael D. J. and Wightman R. M. (1999) Electrochemical monitoring of biogenic amine neurotransmission in real time. *J. Pharm. Biomed. Anal.* **19**, 33–46.
- Millar J., Stamford J. A., Kruk Z. L. and Wightman R. M. (1985) Electrochemical, pharmacological and electrophysiological evidence of rapid dopamine release and removal in the rat caudate nucleus following electrical stimulation of the median forebrain bundle. *Eur. J. Pharmacol.* **109**, 341–348.
- Miner L. H., Schroeter S., Blakely R. D. and Sesack S. R. (2000) Ultrastructural localization of the serotonin transporter in superficial and deep layers of the rat prefrontal cortex and its spatial relationship to dopamine terminals. *J. Comp. Neurol.* **427**, 220–234.
- Mintz M., Gordon I., Roz N. and Rehavi M. (1994) The effect of repeated amphetamine treatment on striatal DA transporter and rotation in rats. *Brain Res.* **668**, 239–242.
- Moron J. A., Brockington A., Wise R. A., Rocha B. A. and Hope B. T. (2002) Dopamine uptake through the norepinephrine transporter in brain regions with low levels of the dopamine transporter: evidence from knock-out mouse lines. *J. Neurosci.* **22**, 389–395.
- Mosharov E., Gong L., Khanna B., Sulzer D. and Lindau M. (2003) Intracellular patch electrochemistry: cytosolic catecholamines in chromaffin cells. *J. Neurosci.* **23**, 5835–5845.
- Mundorf M. L., Joseph J. D., Austin C. M., Caron M. G. and Wightman R. M. (2001) Catecholamine release and uptake in the mouse prefrontal cortex. *J. Neurochem.* **79**, 130–142.
- Murphy D. D., Rueter S. M., Trojanowski J. Q. and Lee V. M. (2000) Synucleins are developmentally expressed, and alpha-synuclein regulates the size of the presynaptic vesicular pool in primary hippocampal neurons. *J. Neurosci.* **20**, 3214–3220.
- Murthy V. N., Schikorski T., Stevens C. F. and Zhu Y. (2001) Inactivity produces increases in neurotransmitter release and synapse size. *Neuron* **32**, 673–682.
- Near J. A., Bigelow J. C. and Wightman R. M. (1988) Comparison of uptake of dopamine in rat striatal chopped tissue and synaptosomes. *J. Pharmacol. Exp. Ther.* **245**, 921–927.
- Nicholson C. (1995) Interaction between diffusion and Michaelis–Menten uptake of dopamine after iontophoresis in striatum. *Biophys. J.* **68**, 1699–1715.
- Nicholson C. (2000) Volume transmission in the year 2000. *Prog. Brain Res.* **125**, 437–446.
- Nirenberg M. J., Vaughan R. A., Uhl G. R., Kuhar M. J. and Pickel V. M. (1996) The dopamine transporter is localized to dendritic and axonal plasma membranes of nigrostriatal dopaminergic neurons. *J. Neurosci.* **16**, 436–447.
- Nirenberg M. J., Chan J., Pohorille A., Vaughan R. A., Uhl G. R., Kuhar M. J. and Pickel V. M. (1997) The dopamine transporter: comparative ultrastructure of dopaminergic axons in limbic and motor compartments of the nucleus accumbens. *J. Neurosci.* **17**, 6899–6907.
- O'Hara C. M., Uhland-Smith A., O'Malley K. L. and Todd R. D. (1996) Inhibition of dopamine synthesis by dopamine D2 and D3 but not D4 receptors. *J. Pharmacol. Exp. Ther.* **277**, 186–192.
- Onali P. and Olanas M. C. (1989) Involvement of adenylate cyclase inhibition in dopamine autoreceptor regulation of tyrosine hydroxylase in rat nucleus accumbens. *Neurosci. Lett.* **102**, 91–96.
- Paladini C. A., Robinson S., Morikawa H., Williams J. T. and Palmiter R. D. (2003) Dopamine controls the firing pattern of dopamine neurons via a network feedback mechanism. *Proc. Natl Acad. Sci. USA* **100**, 2866–2871.
- Palij P., Bull. D. R., Sheehan M. J., Millar J., Stamford J., Kruk Z. L. and Humphrey P. P. (1990) Presynaptic regulation of dopamine release in corpus striatum monitored *in vitro* in real time by fast cyclic voltammetry. *Brain Res.* **509**, 172–174.
- Parish C. L., Finkelstein D. I., Drago J., Borrelli E. and Horne M. K. (2001) The role of dopamine receptors in regulating the size of axonal arbors. *J. Neurosci.* **21**, 5147–5157.
- Parker E. M. and Cubeddu L. X. (1986) Effects of D-amphetamine and dopamine synthesis inhibitors on dopamine and acetylcholine neurotransmission in the striatum. I. Release in the absence of vesicular transmitter stores. *J. Pharmacol. Exp. Ther.* **237**, 179–192.
- Parsons L. H., Schad C. A. and Justice J. B. Jr (1993) Co-administration of the D2 antagonist pimozide inhibits up-regulation of dopamine release and uptake induced by repeated cocaine. *J. Neurochem.* **60**, 376–379.
- Persico A. M., Schindler C. W., Brannock M. T., Gonzalez A. M., Surratt C. K. and Uhl G. R. (1993) Dopaminergic gene expression during amphetamine withdrawal. *Neuroreport* **4**, 41–44.
- Phillips P. E. and Stamford J. A. (2000) Differential recruitment of N-, P- and Q-type voltage-operated calcium channels in striatal dopamine release evoked by 'regular' and 'burst' firing. *Brain Res.* **884**, 139–146.
- Phillips P. E., Hancock P. J. and Stamford J. A. (2002) Time window of autoreceptor-mediated inhibition of limbic and striatal dopamine release. *Synapse* **44**, 15–22.
- Pickel V. M., Chan J. and Nirenberg M. J. (2002) Region-specific targeting of dopamine D2-receptors and somatodendritic vesicular monoamine transporter 2 (VMAT2) within ventral tegmental area subdivisions. *Synapse* **45**, 113–124.
- Pothos E., Desmond M. and Sulzer D. (1996) L-3,4-Dihydroxyphenylalanine increases the quantal size of exocytic dopamine release *in vitro*. *J. Neurochem.* **66**, 629–636.
- Pothos E., Davila V. and Sulzer D. (1998a) Presynaptic recording of quanta from midbrain dopamine neurons and modulation of the quantal size. *J. Neurosci.* **18**, 4106–4118.
- Pothos E. N., Przedborski S., Davila V., Schmitz Y. and Sulzer D. (1998b) D2-Like dopamine autoreceptor activation reduces quantal size in PC12 cells. *J. Neurosci.* **18**, 5575–5585.
- Pothos E. N., Larsen K. E., Krantz D. E., Liu Y.-J., Edwards R. H. and Sulzer D. (2000) Synaptic vesicle transporter expression regulates vesicle phenotype and quantal size. *J. Neurosci.* **20**, 7297–7306.
- Povlock S. L. and Schenk J. O. (1997) A multisubstrate kinetic mechanism of dopamine transport in the nucleus accumbens and its inhibition by cocaine. *J. Neurochem.* **69**, 1093–1105.
- Prasad B. M. and Amara S. G. (2001) The dopamine transporter in mesencephalic cultures is refractory to physiological changes in membrane voltage. *J. Neurosci.* **21**, 7561–7567.
- Pristupa Z. B., McConkey F., Liu F., Man H. Y., Lee F. J., Wang Y. T. and Niznik H. B. (1998) Protein kinase-mediated bidirectional trafficking and functional regulation of the human dopamine transporter. *Synapse* **30**, 79–87.
- Puopolo M., Hochstetler S. E., Gustincich S., Wightman R. M. and Raviola E. (2001) Extrasynaptic release of dopamine in a retinal neuron: activity dependence and transmitter modulation. *Neuron* **30**, 211–225.

- Raiteri M., Cerrito F., Cervoni A. M. and Levi G. (1979) Dopamine can be released by two mechanisms differentially affected by the dopamine transport inhibitor nomifensine. *J. Pharmacol. Exp. Ther.* **208**, 195–202.
- Rayport S., Sulzer D., Shi W. X., Sawasdikosol S., Monaco J., Batson D. and Rajendran G. (1992) Identified postnatal mesolimbic dopamine neurons in culture: morphology and electrophysiology. *J. Neurosci.* **12**, 4264–4280.
- Reith M. E., Sershen H. and Lajtha A. (1980) Saturable (^3H)cocaine binding in central nervous system of mouse. *Life Sci.* **27**, 1055–1062.
- Rice M. E. (2000) Distinct regional differences in dopamine-mediated volume transmission. *Prog. Brain Res.* **125**, 277–290.
- Rice M. E., Gerhardt G. A., Hierl P. M., Nagy G. and Adams R. N. (1985) Diffusion coefficients of neurotransmitters and their metabolites in brain extracellular fluid space. *Neuroscience* **15**, 891–902.
- Rice M. E., Cragg S. J. and Greenfield S. A. (1997) Characteristics of electrically evoked somatodendritic dopamine release in substantia nigra and ventral tegmental area *in vitro*. *J. Neurophysiol.* **77**, 853–862.
- Ritz M. C., Lamb R. J., Goldberg S. R. and Kuhar M. J. (1987) Cocaine receptors on dopamine transporters are related to self-administration of cocaine. *Science* **237**, 1219–1223.
- Rivet J. M., Audinot V., Gobert A., Peglion J. L. and Millan M. J. (1994) Modulation of mesolimbic dopamine release by the selective dopamine D3 receptor antagonist, (+)-S 14297. *Eur. J. Pharmacol.* **265**, 175–177.
- Rocha B. A., Fumagalli F., Gainetdinov R. R., Jones S. R., Ator R., Giros B., Miller G. W. and Caron M. G. (1998) Cocaine self-administration in dopamine-transporter knockout mice. *Nat. Neurosci.* **1**, 132–137.
- Rosenblad C., Martinez-Serrano A. and Bjorklund A. (1998) Intrastratial glial cell line-derived neurotrophic factor promotes sprouting of spared nigrostriatal dopaminergic afferents and induces recovery of function in a rat model of Parkinson's disease. *Neuroscience* **82**, 129–137.
- Ross S. B. (1991) Synaptic concentration of dopamine in the mouse striatum in relationship to the kinetic properties of the dopamine receptors and uptake mechanism. *J. Neurochem.* **56**, 22–29.
- Roth R. H., Walters J. R., Murrin L. C., Morgenroth V. H. and 3rd (1975) Dopamine neurons: role of impulse flow and presynaptic receptors in the regulation of tyrosine hydroxylase. *Psychopharmacol. Bull.* **11**, 8.
- Rothblat D. S. and Schneider J. S. (1997) Regionally specific effects of haloperidol and clozapine on dopamine reuptake in the striatum. *Neurosci. Lett.* **228**, 119–122.
- Rouge-Pont F., Usiello A., Benoit-Marand M., Gonon F., Piazza P. V. and Borrelli E. (2002) Changes in extracellular dopamine induced by morphine and cocaine: crucial control by D2 receptors. *J. Neurosci.* **22**, 3293–3301.
- Rubinstein M., Phillips T. J., Bunzow J. R., Falzone T. L., Dziewczapolski G., Zhang G., Fang Y., Larson J. L., McDougall J. A., Chester J. A. *et al.* (1997) Mice lacking dopamine D4 receptors are supersensitive to ethanol, cocaine, and methamphetamine. *Cell* **90**, 991–1001.
- Sabeti J., Adams C. E., Burmeister J., Gerhardt G. A. and Zahniser N. R. (2002) Kinetic analysis of striatal clearance of exogenous dopamine recorded by chronoamperometry in freely-moving rats. *J. Neurosci. Methods* **121**, 41–52.
- Salah R. S., Kuhn D. M. and Galloway M. P. (1989) Dopamine autoreceptors modulate the phosphorylation of tyrosine hydroxylase in rat striatal slices. *J. Neurochem.* **52**, 1517–1522.
- Sandoval V., Riddle E. L., Ugarte Y. V., Hanson G. R. and Fleckenstein A. E. (2001) Methamphetamine-induced rapid and reversible changes in dopamine transporter function: an *in vitro* model. *J. Neurosci.* **21**, 1413–1419.
- Saunders C., Ferrer J. V., Shi L., Chen J., Merrill G., Lamb M. E., Leeb-Lundberg L. M., Carvelli L., Javitch J. A. and Galli A. (2000) Amphetamine-induced loss of human dopamine transporter activity: an internalization-dependent and cocaine-sensitive mechanism. *Proc. Natl Acad. Sci. USA* **97**, 6850–6855.
- Schmitz Y., Schmauss C. and Sulzer D. (2002) Altered dopamine release and uptake kinetics in mice lacking D2 receptors. *J. Neurosci.* **22**, 8002–8009.
- Schmitz Y., Lee C. J., Schmauss C., Gonon F. and Sulzer D. (2001) Amphetamine distorts stimulation-dependent dopamine overflow: effects on D2 autoreceptors, transporters, and synaptic vesicle stores. *J. Neurosci.* **21**, 5916–5924.
- Schonfuss D., Reum T., Olshausen P., Fischer T. and Morgenstern R. (2001) Modelling constant potential amperometry for investigations of dopaminergic neurotransmission kinetics *in vivo*. *J. Neurosci. Methods* **112**, 163–172.
- Schultz W., Dayan P. and Montague P. R. (1997) A neural substrate of prediction and reward. *Science* **275**, 1593–1599.
- Seeman P. and Lee T. (1975) Antipsychotic drugs: direct correlation between clinical potency and presynaptic action on dopamine neurons. *Science* **188**, 1217–1219.
- Sesack S. R., Aoki C. and Pickel V. M. (1994) Ultrastructural localization of D2 receptor-like immunoreactivity in midbrain dopamine neurons and their striatal targets. *J. Neurosci.* **14**, 88–106.
- Sesack S. R., Hawrylak V. A., Matus C., Guido M. A. and Levey A. I. (1998) Dopamine axon varicosities in the prefrontal division of the rat prefrontal cortex exhibit sparse immunoreactivity for the dopamine transporter. *J. Neurosci.* **18**, 2697–2708.
- Shilling P. D., Kelsoe J. R. and Segal D. S. (1997) Dopamine transporter mRNA is up-regulated in the substantia nigra and the ventral tegmental area of amphetamine-sensitized rats. *Neurosci. Lett.* **236**, 131–134.
- Silva N. L. and Bunney B. S. (1988) Intracellular studies of dopamine neurons *in vitro*: pacemakers modulated by dopamine. *Eur. J. Pharmacol.* **149**, 307–315.
- Sonders M. S., Zhu S. J., Zahniser N. R., Kavanaugh M. P. and Amara S. G. (1997) Multiple ionic conductances of the human dopamine transporter: the actions of dopamine and psychostimulants. *J. Neurosci.* **17**, 960–974.
- Sora I., Wichems C., Takahashi N., Li X. F., Zeng Z., Revay R., Lesch K. P., Murphy D. L. and Uhl G. R. (1998) Cocaine reward models: conditioned place preference can be established in dopamine- and in serotonin-transporter knockout mice. *Proc. Natl Acad. Sci. USA* **95**, 7699–7704.
- Sora I., Hall F. S., Andrews A. M., Itokawa M., Li X. F., Wei H. B., Wichems C., Lesch K. P., Murphy D. L. and Uhl G. R. (2001) Molecular mechanisms of cocaine reward: combined dopamine and serotonin transporter knockouts eliminate cocaine place preference. *Proc. Natl Acad. Sci. USA* **98**, 5300–5305.
- Stamford J. A., Kruk Z. L. and Millar J. (1988a) Actions of dopamine antagonists on stimulated striatal and limbic dopamine release: an *in vivo* voltammetric study. *Br. J. Pharmacol.* **94**, 924–932.
- Stamford J. A., Kruk Z. L., Palij P. and Millar J. (1988b) Diffusion and uptake of dopamine in rat caudate and nucleus accumbens compared using fast cyclic voltammetry. *Brain Res.* **448**, 381–385.
- Starke K. (2001) Presynaptic autoreceptors in the third decade: focus on alpha2-adrenoceptors. *J. Neurochem.* **78**, 685–693.
- Starke K., Reimann W., Zumstein A. and Hertting G. (1978) Effect of dopamine receptor agonists and antagonists on release of dopamine in the rabbit caudate nucleus *in vitro*. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **305**, 27–36.

- Strait K. A. and Kuczenski R. (1986) Dopamine autoreceptor regulation of the kinetic state of striatal tyrosine hydroxylase. *Mol. Pharmacol.* **29**, 561–569.
- Suaud-Chagny M. F., Ponec J. and Gonon F. (1991) Presynaptic auto-inhibition of the electrically evoked dopamine release studied in the rat olfactory tubercle by *in vivo* electrochemistry. *Neuroscience* **45**, 641–652.
- Suaud-Chagny M. F., Dugast C., Chergui K., Msghina M. and Gonon F. (1995) Uptake of dopamine released by impulse flow in the rat mesolimbic and striatal systems *in vivo*. *J. Neurochem.* **65**, 2603–2611.
- Sulzer D. and Pothos E. N. (2000) Presynaptic mechanisms that regulate quantal size. *Rev. Neurosci.* **11**, 159–212.
- Sulzer D. and Rayport S. (1990) Amphetamine and other psychostimulants reduce pH gradients in midbrain dopaminergic neurons and chromaffin granules: a mechanism of action. *Neuron* **5**, 797–808.
- Sulzer D., Maidment N. T. and Rayport S. (1993) Amphetamine and other weak bases act to promote reverse transport of dopamine in ventral midbrain neurons. *J. Neurochem.* **60**, 527–535.
- Sulzer D., Chen T. K., Lau Y. Y., Kristensen H., Rayport S. and Ewing A. (1995) Amphetamine redistributes dopamine from synaptic vesicles to the cytosol and promotes reverse transport. *J. Neurosci.* **15**, 4102–4108.
- Sulzer D., Joyce M. P., Lin L., Geldwert D., Haber S. N., Hattori T. and Rayport S. (1998) Dopamine neurons make glutamatergic synapses *in vitro*. *J. Neurosci.* **18**, 4588–4602.
- Svingos A. L., Clarke C. L. and Pickel V. M. (1999) Localization of the delta-opioid receptor and dopamine transporter in the nucleus accumbens shell: implications for opiate and psychostimulant cross-sensitization. *Synapse* **34**, 1–10.
- Svingos A. L., Periasamy S. and Pickel V. M. (2000) Presynaptic dopamine D(4) receptor localization in the rat nucleus accumbens shell. *Synapse* **36**, 222–232.
- Svingos A. L., Chavkin C., Colago E. E. and Pickel V. M. (2001) Major coexpression of kappa-opioid receptors and the dopamine transporter in nucleus accumbens axonal profiles. *Synapse* **42**, 185–192.
- Tang L., Todd R. D. and O'Malley K. L. (1994) Dopamine D2 and D3 receptors inhibit dopamine release. *J. Pharmacol. Exp. Ther.* **270**, 475–479.
- Tepper J. M., Sun B. C., Martin L. P. and Creese I. (1997) Functional roles of dopamine D2 and D3 autoreceptors on nigrostriatal neurons analyzed by antisense knockdown *in vivo*. *J. Neurosci.* **17**, 2519–2530.
- Torres G. E., Gainetdinov R. R. and Caron M. G. (2003) Plasma membrane monoamine transporters: structure, regulation and function. *Nat. Rev. Neurosci.* **4**, 13–25.
- Uhl G. R., Hall F. S. and Sora I. (2002) Cocaine, reward, movement and monoamine transporters. *Mol. Psychiatry* **7**, 21–26.
- Uziel A., Baik J. H., Rouge-Pont F., Picetti R., Dierich A., LeMeur M., Piazza P. V. and Borrelli E. (2000) Distinct functions of the two isoforms of dopamine D2 receptors. *Nature* **408**, 199–203.
- Vander Borght T., Kilbourn M., Desmond T., Kuhl D. and Frey K. (1995) The vesicular monoamine transporter is not regulated by dopaminergic drug treatments. *Eur. J. Pharmacol.* **294**, 577–583.
- Vaughan R. A., Huff R. A., Uhl G. R. and Kuhar M. J. (1997) Protein kinase C-mediated phosphorylation and functional regulation of dopamine transporters in striatal synaptosomes. *J. Biol. Chem.* **272**, 15541–15546.
- Vizi E. S. (1982) Non-synaptic intercellular communication: presynaptic inhibition. *Acta Biol.* **33**, 331–351.
- Wang Y., Xu R., Sasaoka T., Tonegawa S., Kung M. P. and Sankoorikal E. B. (2000) Dopamine D2 long receptor-deficient mice display alterations in striatum-dependent functions. *J. Neurosci.* **20**, 8305–8314.
- Waymunt H. K., Schenk J. O. and Sorg B. A. (2001) Characterization of extracellular dopamine clearance in the medial prefrontal cortex: role of monoamine uptake and monoamine oxidase inhibition. *J. Neurosci.* **21**, 35–44.
- Wheeler D. D., Edwards A. M., Chapman B. M. and Ondo J. G. (1994) Effects of cocaine on sodium dependent dopamine uptake in rat striatal synaptosomes. *Neurochem. Res.* **19**, 49–56.
- White F. J. and Kalivas P. W. (1998) Neuroadaptations involved in amphetamine and cocaine addiction. *Drug Alcohol Depend.* **51**, 141–153.
- Wieczorek W. J. and Kruk Z. L. (1994a) A quantitative comparison on the effects of bupropion, cocaine and nomifensine on electrically evoked dopamine overflow and rate of re-uptake in the caudate putamen and nucleus accumbens in the rat brain slice. *Brain Res.* **657**, 42–50.
- Wieczorek W. J. and Kruk Z. L. (1994b) Differential action of (+)-amphetamine on electrically evoked dopamine overflow in rat brain slices containing corpus striatum and nucleus accumbens. *Br. J. Pharmacol.* **111**, 829–836.
- Wightman R. M. and Zimmerman J. B. (1990) Control of dopamine extracellular concentration in rat striatum by impulse flow and uptake. *Brain Res. Brain Res. Rev.* **15**, 135–144.
- Wightman R. M., Amatore C., Engstrom R. C., Hale P. D., Kristensen E. W., Kuhr W. G. and May L. J. (1988) Real-time characterization of dopamine overflow and uptake in the rat striatum. *Neuroscience* **25**, 513–523.
- Wolf M. E. and Roth R. H. (1990) Autoreceptor regulation of dopamine synthesis. *Ann. N Y Acad. Sci.* **604**, 323–343.
- Wolf M. E., Galloway M. P. and Roth R. H. (1986) Regulation of dopamine synthesis in the medial prefrontal cortex: studies in brain slices. *J. Pharmacol. Exp. Ther.* **236**, 699–707.
- Wonnacott S., Kaiser S., Mogg A., Soliakov L. and Jones I. W. (2000) Presynaptic nicotinic receptors modulating dopamine release in the rat striatum. *Eur. J. Pharmacol.* **393**, 51–58.
- Wu X. and Gu H. H. (1999) Molecular cloning of the mouse dopamine transporter and pharmacological comparison with the human homologue. *Gene* **233**, 163–170.
- Wu Y., Pearl S. M., Zigmund M. J. and Michael A. C. (2000) Inhibitory glutamatergic regulation of evoked dopamine release in striatum. *Neuroscience* **96**, 65–72.
- Wu Q., Reith M. E., Kuhar M. J., Carroll F. I. and Garris P. A. (2001a) Preferential increases in nucleus accumbens dopamine after systemic cocaine administration are caused by unique characteristics of dopamine neurotransmission. *J. Neurosci.* **21**, 6338–6347.
- Wu Q., Reith M. E., Wightman R. M., Kawagoe K. T. and Garris P. A. (2001b) Determination of release and uptake parameters from electrically evoked dopamine dynamics measured by real-time voltammetry. *J. Neurosci. Methods* **112**, 119–133.
- Wu Q., Reith M. E., Walker Q. D., Kuhn C. M., Carroll F. I. and Garris P. A. (2002) Concurrent autoreceptor-mediated control of dopamine release and uptake during neurotransmission: an *in vivo* voltammetric study. *J. Neurosci.* **22**, 6272–6281.
- Yamamoto B. K. and Novotny S. (1998) Regulation of extracellular dopamine by the norepinephrine transporter. *J. Neurochem.* **71**, 274–280.
- Yi S. J. and Johnson K. M. (1990) Chronic cocaine treatment impairs the regulation of synaptosomal ³H-DA release by D2 autoreceptors. *Pharmacol. Biochem. Behav.* **36**, 457–461.
- Yung K. K., Bolam J. P., Smith A. D., Hersch S. M., Ciliax B. J. and Levey A. I. (1995) Immunocytochemical localization of D1 and D2 dopamine receptors in the basal ganglia of the rat: light and electron microscopy. *Neuroscience* **65**, 709–730.
- Zachariou V., Benoit-Marand M., Allen P. B., Ingrassia P., Fienberg A. A., Gonon F., Greengard P. and Picciotto M. R. (2002)

- Reduction of cocaine place preference in mice lacking the protein phosphatase 1 inhibitors DARPP 32 or Inhibitor 1. *Biol. Psychiatry* **51**, 612–620.
- Zahniser N. R. and Doolen S. (2001) Chronic and acute regulation of Na(+)/Cl(-)-dependent neurotransmitter transporters: drugs, substrates, presynaptic receptors, and signaling systems. *Pharmacol. Ther.* **92**, 21–55.
- Zhang L., Coffey L. L. and Reith M. E. (1997) Regulation of the functional activity of the human dopamine transporter by protein kinase C. *Biochem. Pharmacol.* **53**, 677–688.
- Zhang H. and Sulzer D. (2003) Glutamate spillover in the striatum depresses dopaminergic transmission by activating group I metabotropic glutamate receptors. *J. Neurosci.* (in press).
- Zhou F. M., Liang Y. and Dani J. A. (2001) Endogenous nicotinic cholinergic activity regulates dopamine release in the striatum. *Nat. Neurosci.* **4**, 1224–1229.
- Zhu S. J., Kavanaugh M. P., Sonders M. S., Amara S. G. and Zahniser N. R. (1997) Activation of protein kinase C inhibits uptake, currents and binding associated with the human dopamine transporter expressed in *Xenopus* oocytes. *J. Pharmacol. Exp. Ther.* **282**, 1358–1365.
- Zoli M., Jansson A., Sykova E., Agnati L. F. and Fuxe K. (1999) Volume transmission in the CNS and its relevance for neuropsychopharmacology. *Trends Pharmacol. Sci.* **20**, 142–150.