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Regulation of dopamine transporter function and plasma membrane expression by dopamine, amphetamine, and cocaine

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Abstract

Pharmacological alterations in dopamine transporter (DAT) function not only modulate dopamine reuptake, but they can induce rapid changes in the plasmalemmal expression of the transporter. By modifying transporter membrane expression, drugs may alter the maximum rate of neurotransmitter clearance, shifting cellular transport capacity and disrupting normal receptor stimulation. DAT-interacting drugs include the illicit and highly abused psychostimulants amphetamine and cocaine. Regulation of transporter activity and plasma membrane expression by these drugs has been implicated in the long-term processes of reward and addiction. This review summarizes the regulation of DAT by transporter substrates and blockers with particular emphasis on the modulation of DAT cell surface expression by acute exposure to amphetamine and cocaine.

Keywords: Dopamine transporter; Trafficking; Amphetamine; Cocaine

1. Introduction

Proper dopaminergic neurotransmission mediates many physiologic processes including reward, addiction, movement, and lactation (Giros and Caron, 1993; Iversen, 1971). Conversely, improper dopaminergic tone is thought to play a role in disease states such as schizophrenia, Parkinson's disease, and drug addiction (Koob and Bloom, 1988; Kugaya et al., 2000; Seeman and Niznik, 1990). Dopaminergic tone is defined by the properties of synaptic events, which include the amount of released dopamine, the sensitivity of dopamine receptors, and the length of time dopamine spends in the synaptic space. A key mechanism for regulating the level of extracellular dopamine involves a presynaptic, plasmalemmal protein which utilizes the energy stored in the Na^+/Cl^- ionic gradients to reuptake released dopamine into the cytosol (Giros, 1996). The movement of dopamine by the dopamine transporter (DAT) not only reduces receptor stimulation, but also decreases the amount of synthesis required to replenish vesicular dopamine stores (Giros, 1996).

DAT was once thought of as a static component of the presynaptic environment, continuously moving substrate in a non-regulated manner. Irreversible inhibitor studies enabled this belief because they predicted an extremely long physiologic half-life for DAT (approximately 6 days) (Do Rego et al., 1999; Fleckenstein et al., 1996). However, new experiments have now indicated a much shorter half-life (approximately 2–3 days), which is more consistent with dynamic DAT regulation (Kimmel et al., 2000, 2003).

In recent years, new physiologic functions have been assigned to the DAT (in addition to dopamine reuptake). These include the regulation of cell excitability through leak current conductances (Ingram et al., 2002) as well as serving as a pathway for substrate-induced dopamine release at both axonal and dendritic sites (Falkenburger et al., 2001; Sulzer et al., 1993). However, each cellular role currently associated with the DAT depends on plasma membrane expression. Indeed, for the monoamine transporters in general and the DAT in particular, recent reports examining the concomitant changes in transporter function and membrane expression suggest that these events may be temporally correlated (Carneiro et al., 2002; Carvelli et al., 2002; Daws et al., 2002; Doolen and Zahniser, 2001; Little et al., 2002; Loder and Melikian, 2003; Mayfield and Zahniser, 2001; Melikian and Buckley, 1999; Sorkina et al., 2003; Torres et

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al., 2001, 2003). Therefore, transporter trafficking could represent a new mechanism by which cells control the level of extracellular dopamine.

2. Regulation of DAT function by amphetamine and cocaine

2.1. Transporter interacting drugs

Pharmacological agents that interact with DAT function can be divided into two classes: those that compete for dopamine uptake, and those that prevent dopamine uptake. Amphetamine-like drugs, belonging to the first class, not only compete with dopamine for uptake, but also induce DAT-mediated dopamine efflux (Fischer and Cho, 1979; Pierce and Kalivas, 1997). Cocaine-like drugs, belonging to the second class, are able to prevent the reuptake of released dopamine (Ritz et al., 1987). Both classes rapidly increase dopaminergic neurotransmission by interfering with proper DAT function. The subsequent increase in dopaminergic signaling in limbic areas of the brain is believed to mediate the rewarding and addictive properties of these psychostimulants (Koob and Bloom, 1988).

2.2. The hetero-exchanger: amphetamine-induced dopamine efflux

The most widely studied mechanism by which amphetamine increases extracellular dopamine is to promote the *reverse transport* of dopamine through DAT. This carrier-mediated release is independent of action potential depolarization and appears to be only slightly calcium dependent (Pierce and Kalivas, 1997). One of the models used to explain this effect of amphetamine is the *facilitated exchange diffusion model* (Burnette, 1996; Fischer and Cho, 1979), which predicts that dopamine efflux results from the translocation of amphetamine into the cell followed by a counter movement of dopamine out to the extracellular compartment. In this model, amphetamine's movement through the transporter would increase the rate of reverse transport by increasing the availability of intracellular-facing DAT to bind intracellular dopamine. In contrast, the *weak base* or *vesicle depletion model* (Sulzer and Rayport, 1990; Sulzer et al., 1992) suggests that amphetamine induces the reverse transport of dopamine simply by elevating the cytoplasmic dopamine concentration, thus altering the dopamine gradient across the plasma membrane. In this model, dopamine release is independent of any interaction between amphetamine and DAT (Sulzer et al., 1995).

In Jones et al. (1998), published new and notable findings were published which support the facilitated exchange diffusion hypothesis. They reported that Ro4-1284 and reserpine-like compounds, which displace dopamine from vesicles into the cytosol, did not cause dopamine efflux. Thus, the interaction of amphetamine with DAT is essential and purely increasing the intracellular dopamine concentration was not enough to cause reverse transport (Jones et al., 1998).

However, other intriguing experiments have challenged the simple model of facilitated exchange diffusion (Chen and Justice, 2000; Cowell et al., 2000; Kantor et al., 2001; Pifl and Singer, 1999). It has been shown that protein kinase C (PKC) activation results in an increase in the outward transport of dopamine through the norepinephrine transporter (Kantor et al., 2001) and that PKC inhibitors block the ability of amphetamine to induce DAT-mediated dopamine release (Kantor and Gnegy, 1998). In addition to signal transduction pathways, changes in the intracellular availability of ions such as Ca^{2+} (Kantor et al., 2001), Na^{+} (Chen et al., 1998; Khoshbouei et al., 2003; Pifl et al., 1999; Sitte et al., 1998) and Cl^{-} (Nelson and Rudnick, 1982; Pifl and Singer, 1999; Rudnick and Wall, 1992; Sitte et al., 1998) have been indicated as important for amphetamine to induce dopamine efflux. In particular, an increase in the intracellular Na^{+} concentration has been proposed to be an important step for driving the monoamine transporter cycle in reverse (Chen et al., 1998; Khoshbouei et al., 2003; Pifl et al., 1999; Sitte et al., 1998). The ability of amphetamine to stimulate dopamine efflux was further proposed to result from its ability to stimulate inward ion fluxes through DAT (Khoshbouei et al., 2003; Pifl and Singer, 1999; Sitte et al., 1998).

In such a model, the amphetamine-induced, DAT-mediated inward current (most likely generated in part by the flow of Na^{+} into the cell) is sufficient to stimulate the efflux of intracellular substrate because of the increase in intracellular Na^{+}. Indeed, results from Sitte et al. (1998) demonstrated that the releasing properties of DAT substrates are directly proportional to their ability to stimulate DAT-mediated inward currents. Interesting new experiments by Khoshbouei et al. (2003) directly tested the role of intracellular Na^{+} on amphetamine-induced dopamine efflux. Their findings demonstrated that amphetamine increases intracellular Na^{+} availability, and that the intracellular Na^{+} concentration and transmembrane potential modulate the amphetamine-induced, DAT-mediated dopamine efflux. Based on these data, they proposed a model for amphetamine-induced dopamine efflux in which the ability of amphetamine to increase intracellular Na^{+} concentration is essential for its stimulation of dopamine efflux (Khoshbouei et al., 2003).

3. Regulation of DAT cell surface expression

3.1. Amphetamine-induced DAT trafficking

In addition to stimulating DAT activity, DAT substrates also regulate transporter cell surface expression. For example, in *Xenopus laevis* oocytes expressing the human DAT, application of 10 μM dopamine for 40 min reduced DAT

cell surface expression as measured by WIN 35,428 binding (Gulley et al., 2002; Harris, 1973). In addition, intermittent perfusion of voltage-clamped oocytes with dopamine (10 μM for 1 h) reduced transporter-associated currents by 34% (Gulley et al., 2002). In human embryonic kidney cells (HEK 293) expressing the human DAT, pretreatment with dopamine (10 μM for 1 h) also decreased [^{3}H]dopamine uptake by 27% (Saunders et al., 2000). In this cell line, dopamine produced a cell surface redistribution of the transporter, measured by confocal imaging (Saunders et al., 2000). Similar results were obtained in mouse neuroblastoma neurons (N2A neurons) transfected with human DAT (Little et al., 2002). However, dopamine did not induce trafficking of human DAT expressed in Madin–Darby canine kidney cells (Daniels and Amara, 1999). These reports suggest that DAT membrane expression can be regulated by its endogenous substrate and underscore the importance of expression background.

Saunders et al. (2000) demonstrated that acute application of amphetamine also reduces cell surface expression of human DAT with a concomitant loss of DAT activity. Amphetamine (2 μM for 1 h) reduced [^{3}H]dopamine uptake by 22% (a reduction in V_{max} with no change in K_m compared to control cells) and significantly redistributed the transporter from the plasma membrane to the cytosol (Saunders et al., 2000). In addition, the amphetamine-induced transporter-associated currents, measured under whole-cell patch clamp, decreased over-time following amphetamine bath application (Saunders et al., 2000). The physiological relevance of these results is emphasized by the findings of Fleckenstein et al. (1999) in which the administration of a single, high dose of amphetamine acutely (1 h) decreased DAT function in vivo as assessed with striatal synaptosomes prepared from drug-treated rats.

While these results suggest that the substrate-induced trafficking of the transporter may shape dopamine transport capacity, many questions remain unanswered. Particularly, does DAT undergo functional modification in response to amphetamine prior to its cell surface redistribution? Or alternatively does DAT, in response to amphetamine, simply leave the plasma membrane as an active carrier. New types of experiments monitoring both DAT activity and trafficking at a high time resolution are required to answer these questions.

These studies do illustrate that, in general, DAT substrates acutely reduce transporter membrane expression with functional consequences. Fig. 1 shows the regulation of transporter membrane expression by amphetamine, an extensively investigated DAT substrate. Upon application, amphetamine rapidly increases extracellular dopamine and reduces DAT cell surface expression (Fig. 1B). After amphetamine removal, the reduced transporter capacity of the system may allow the extracellular dopamine concentration to remain elevated (Fig. 1C).

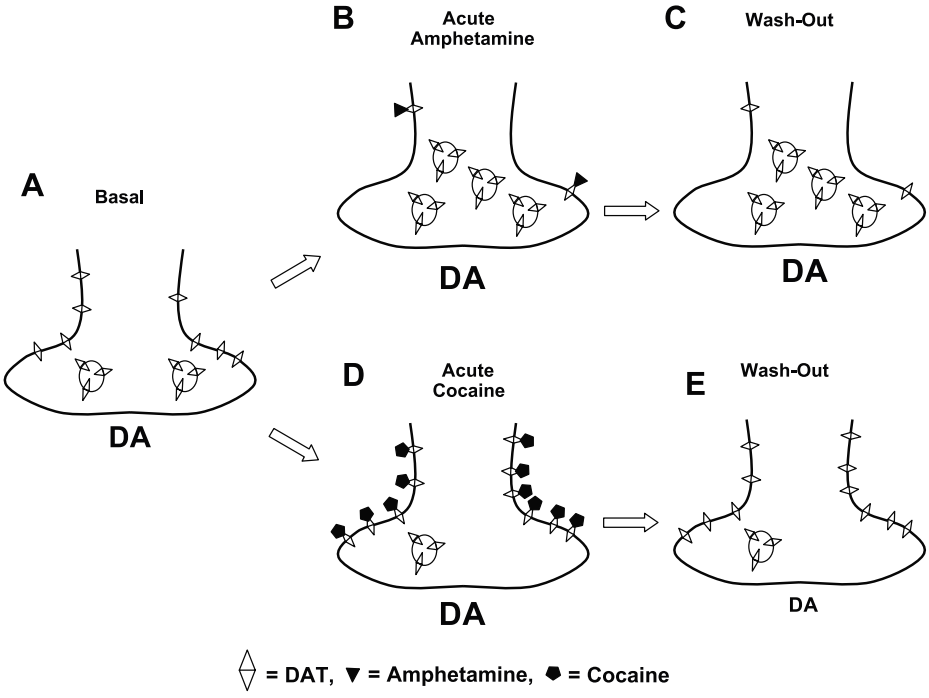

Fig. 1. A model for the regulation of dopamine transport capacity by acute drug exposure. (A) Under basal conditions, DAT is expressed on both cell surface and intracellular membranes. (B) The DAT substrate amphetamine competes with dopamine for uptake and reduces transporter cell surface expression. (C) Following amphetamine wash-out, the extracellular dopamine concentration could remain elevated due the reduction in transport capacity. (D) The DAT blocker cocaine inhibits dopamine uptake and increases transporter cell surface expression. (E) Following cocaine wash-out, the extracellular dopamine concentration could decrease due to the increase in dopamine transport capacity.

3.2. Cocaine-induced DAT trafficking

The regulation of DAT expression by chronic exposure to DAT inhibitors has primarily been studied using models such as postmortem human tissue, rodent, and nonhuman primate. These systems permit long-term drug administration, which is not feasible with cell line models. In particular, cocaine regulation of DAT expression has been studied in vitro using the brains of cocaine addicts obtained post-mortem and in vivo using modern imaging techniques. Most reports demonstrate that chronic exposure to cocaine increases DAT binding sites (Little et al., 1993, 1999; Staley et al., 1994). However, some conflicting reports demonstrate either a decrease (Hurd and Herkenham, 1993) or no change (Wilson et al., 1996). Recently, Mash et al. (2002) reported that DAT binding and activity were upregulated in human striatal synaptosomes obtained post-mortem from cocaine addicts versus age-matched controls. The B_{max} of [^{3}H]WIN 34,428 binding was increased in parallel with an increase in V_{max} for [^{3}H]dopamine uptake, indicating functional upregulation of DAT following chronic cocaine abuse.

Only recently, experiments in cell culture have determined that the increase in DAT transport activity upon cocaine exposure could be accounted for by a parallel increase in DAT cell surface expression (Daws et al., 2002). In HEK 293 cells expressing the human DAT, acute exposure to cocaine (10 μM for 10 min) increased [^{3}H]dopamine uptake 30% compare to control (Daws et al., 2002). Furthermore, exposure to cocaine (10 μM for 1 h) increased the cell surface expression of the transporter (31% versus control) as measured using cell surface biotinylation experiments.

In a second study using N2A neurons stably expressing DAT, cocaine treatment (1 μM for 24 h) also increased DAT membrane expression (Little et al., 2002). [^{3}H]WIN35428 binding B_{max} was increased 34% versus control cells following cocaine treatment (Little et al., 2002). This effect was not specific for cocaine because the DAT blockers methylphenidate (100 nM for 24 h) and WIN 35,428 (10 nM, 24 h) produced similar increases in [^{3}H]WIN 35,428 binding (21% and 26% compared to control, respectively). A similar increase in DAT cell surface expression was obtained in cell surface biotinylation experiments (Little et al., 2002).

These studies indicate that acute exposure to DAT blockers increases DAT membrane expression. Therefore, it is possible that upon administration, cocaine increases extracellular dopamine levels by blocking uptake, while rapidly increasing DAT cell surface expression (Fig. 1D). It would seem likely that following removal of cocaine, the elevated DAT cell surface expression could then cause the extracellular concentration of dopamine to fall below that of basal (Fig. 1E). Consequently, transporter trafficking may represent part of the cascade of changes that triggers relapse of cocaine abuse following withdrawal.

4. Conclusion

Altering DAT membrane expression is a mechanism that cells may use to fine tune transport capacity to their constantly changing environment. Acute exposure to transporter substrates reduces DAT membrane expression, while brief treatment with transporter blockers increases DAT cell surface expression. In addition, the regulation of DAT trafficking has been shown to tightly correlate with the functional regulation of dopamine transport capacity.

Determining the mechanism by which transporter substrates and blockers affect DAT cell surface expression is certain to be important for the development of new therapies for the treatment of drug abuse as well as other disease states such as Attention Deficit Hyperactivity Disorder and Parkinson's disease.

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