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Spontaneous release of acetylcholine in striatum is preferentially regulated by inhibitory dopamine D_2 receptors

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Abstract

The dose-related effects of the direct dopamine D_2 receptor agonist quinpirole [*trans*-(−)-4aR-4,4a,5,6,7,8,8a,9-octahydro-5-propyl-1*H*-pyrazolo[3,4-*g*]quinoline] on the extracellular concentrations of dopamine and acetylcholine in rat striatum were measured using in vivo microdialysis. Quinpirole was administered intraperitoneally at doses of 3, 30, 300, and 3000 μg/kg. Acetylcholine measurements were conducted in the presence of 10 nmol/l of the acetylcholinesterase inhibitor neostigmine in the microdialysis perfusate. The 3 μg/kg dose of quinpirole elicited a significant 26% *decrease* in extracellular dopamine level in striatum whereas the extracellular level of acetylcholine was significantly *increased* by 15%. At the higher doses tested, quinpirole administration produced significant decreases in the extracellular concentrations of both dopamine and acetylcholine. The maximum inhibition of striatal dopamine efflux by quinpirole was 74% and this effect was observed at the 300 μg/kg dose. Inhibition of striatal acetylcholine output reached a maximum of 78% after administration of 3000 μg/kg quinpirole. ED_{50} values (μg/kg) for quinpirole-induced inhibition of release were 12.4 and 240 for striatal dopamine and acetylcholine, respectively. We conclude from these data that dopamine exerts a tonic inhibitory control over spontaneous acetylcholine efflux in striatum that is directly mediated by dopamine D_2 receptors.

Keywords: Acetylcholine; Dopamine; Dopamine D_1 receptor; Dopamine D_2 receptor; Microdialysis; Neostigmine; Striatum

1. Introduction

Dopaminergic regulation of striatal acetylcholine output via inhibitory dopamine D_2 receptors and stimulatory dopamine D_1 receptors can be demonstrated pharmacologically. Thus, dopamine D_2 receptor-selective agonists and antagonists decrease and increase, respectively, indices of striatal acetylcholine release (Bertorelli and Consolo, 1990; Damsma et al., 1990; Scatton, 1982; Stoof et al., 1979). Dopamine D_1 receptor-selective agonists and antagonists exert effects on measures of striatal acetylcholine release that are the opposite of the actions of the dopamine D_2 receptor-selective drugs (Consolo et al., 1987; Fage and Scatton, 1986).

Questions remain as to the relative predominance of dopamine D_2 receptor-mediated inhibition versus dopamine D_1 receptor-mediated excitation of striatal acetylcholine output under physiological conditions and regarding whether the dual dopaminergic regulation of striatal acetylcholine release occurs via offsetting and independent influences versus through coupled mechanisms. A large database, derived primarily from studies of acetylcholine release in vitro or of tissue acetylcholine content, suggests that the predominant influence of endogenous dopamine upon striatal acetylcholine efflux is dopamine D_2 receptor-mediated and inhibitory (Lehmann and Langer, 1983; Stoof et al., 1992). Using in vivo microdialysis, we recently have observed a prevailing dopamine D_2 receptor-mediated inhibition of spontaneous acetylcholine output in striatum (DeBoer and Abercrombie, 1996). The majority of recent studies employing in vivo microdialysis, however, have concluded that the net effect of dopamine upon striatal acetylcholine release is stimulatory and mediated by dopamine D_1 receptor mechanisms (Consolo et al., 1992; Damsma et al., 1991; Di Chiara et al., 1994). Furthermore, some studies suggest that responses classically thought to be dopamine D_2 receptor-mediated, such as increases in the output of acetylcholine after administration of neuroleptic drugs and decreases in acetylcholine output in response to direct dopamine D_2 receptor ago-

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nists, are in fact mediated indirectly by mechanisms that depend on dopamine D_1 receptors (Damsma et al., 1991; Imperato et al., 1993, 1994; Russi et al., 1993). Thus, it has been proposed that increases in extracellular dopamine produced by neuroleptic drugs lead to an increased stimulation of dopamine D_1 receptors which, in turn, stimulates the output of striatal acetylcholine. Conversely, a decrease in dopamine release in response to direct dopamine D_2 receptor agonist administration is suggested to result in a diminished dopamine D_1 receptor stimulation and therefore a decrease in striatal acetylcholine output.

The present experiment was designed to assess: (1) the extent to which inhibitory dopamine D_2 receptor mechanisms versus stimulatory dopamine D_1 receptor mechanisms predominate in modulating the spontaneous level of acetylcholine efflux in striatum in vivo and, (2) whether the antagonistic dopamine D_2 receptor-mediated and dopamine D_1 receptor-mediated actions of dopamine can be shown to independently regulate striatal acetylcholine output under these conditions. In our paradigm, we measured the dose-related effects of systemic quinpirole, a direct dopamine D_2 receptor agonist, on extracellular levels of both dopamine and acetylcholine in striatum. At very low doses, dopamine D_2 receptor agonists such as quinpirole have been shown to have a greater potency for inhibition of striatal dopamine release than for inhibition of the release of striatal acetylcholine in vitro (Claustre et al., 1985; Cubeddu and Hoffman, 1983). If inhibitory dopamine D_2 receptors are predominantly and directly involved in the tonic regulation of spontaneous acetylcholine release, then acetylcholine output should be disinhibited at low, 'autoreceptor-selective' doses of quinpirole whereas decreases in acetylcholine output should be observed after higher doses of the agonist. On the other hand, if dopaminergic activity at stimulatory dopamine D_1 receptors is the primary determinant of the ability of dopamine to modulate striatal acetylcholine release, then a low, 'autoreceptor-selective' dose of quinpirole should elicit a maximal decrease in striatal acetylcholine output.

2. Materials and methods

2.1. Animals

Adult male Sprague-Dawley rats (Zivic-Miller Laboratories, Pittsburgh, PA, USA) were used. Prior to implantation of the dialysis probe, the rats were housed individually in plastic shoebox cages under conditions of constant temperature (21°C) and humidity (40%) on a 12:12 h dark/light cycle (07:00 on and 19:00 off) with food and water available ad libitum. The rats weighed between 350–450 g at the time of the microdialysis probe implantation. Animal procedures were conducted in accordance with guidelines published in the NIH Guide for Care and Use of Laboratory Animals and all protocols were approved by the Rutgers University Institutional Animal Care and Use Committee.

2.2. Drug treatments

Quinpirole was chosen as the test drug because it is a full dopamine D_2 receptor agonist with high efficacy that has been shown to exhibit a significant difference in ED_{50} for dopaminergic activity in behavioral tests of pre-synaptic function (motility inhibition) versus post-synaptic function (circling in hemitransected rat; Arnt and Hyttel, 1990). Quinpirole was administered intraperitoneally in a volume of 1 ml saline/kg (0.9% NaCl in distilled water). A solution containing 3 mg quinpirole/ml was prepared immediately before the experiment and diluted to the desired concentration. Each animal received only a single dose of quinpirole.

For microdialysis experiments in which striatal acetylcholine efflux was measured, the acetylcholinesterase inhibitor neostigmine was dissolved in the microdialysis perfusion solution at an initial concentration of 10 mmol/l and then diluted to a final concentration of 10 nmol/l. The neostigmine solution was applied through the dialysis probe directly into striatum and was present for the entire duration of the experiment. Acetylcholine levels in striatal dialysates are increased 2–3-fold by the presence of 10 nmol/l neostigmine and we previously have shown that this neostigmine concentration does not affect the pharmacological responsiveness of the striatal cholinergic system to administration of quinpirole (DeBoer and Abercrombie, 1996).

2.3. Microdialysis probes

The microdialysis probes used in the present investigation were of a vertical, concentric design and incorporated dialysis membrane with an active length of 2 mm (O.D. 250 μm; Spectra/Por, Spectrum, Houston, TX, USA). A piece of PE-20 tubing (Clay Adams, Parsippany, NJ, USA) served as the probe inlet, whereas a piece of fused silica capillary tubing (I.D. 75 μm and O.D. 150 μm; Polymicro Technologies, Phoenix, AZ, USA) served as the outlet (DeBoer and Abercrombie, 1996).

2.4. Microdialysis probe implantation

Dialysis probes were continuously perfused with artificial cerebrospinal fluid (NaCl 147 mmol/l, KCl 2.5 mmol/l, $CaCl_2$ 1.3 mmol/l, and $MgCl_2$ 0.9 mmol/l, pH 7.4) at a rate of 1.5 μl/min by means of a microliter syringe pump (Harvard Apparatus, South Natick, MA, USA). The animals were anesthetized with chloral hydrate (400 mg/kg) and the microdialysis probe was implanted into the striatum at the following coordinates (flat skull): AP +1.0 mm, ML +2.7 mm relative to bregma, and −6.0 mm below the dura according to Paxinos and Wat-

son (1986). The probe was lowered using a microdrive (Narishige, Japan) or an electrode carrier (Model 1760, David Kopf, Tujunga, CA, USA) at a speed of approximately 400 μm/min and then secured to the skull with fast-curing dental cement and three set-screws. The inlet and outlet lines of the microdialysis probe were guided along a metal tether that was secured to the skull with fast-curing dental cement at one end and connected to a single-channel fluid swivel (Instech Laboratories, Plymouth Meeting, PA, USA) at the other. Microdialysis experiments were conducted 16–20 h after probe implantation.

2.5. Analysis of dialysate

Dialysate samples were collected every 15 min and injected into a 20 μl sample-loop of a HPLC apparatus. Before administration of quinpirole, baseline samples were collected and analyzed until there was less than 10% variation in dopamine content or less than 30% variation in acetylcholine content between the samples. Dopamine and acetylcholine determinations were made in separate groups of animals.

Dopamine was analyzed by reverse-phase high pressure liquid chromatography with electrochemical detection. A Velosep RP-18 column (100 × 3.2 mm; Brownlee Laboratories, Foster City, CA, USA) was used with a mobile phase composed of 0.1 mol/l sodium acetate buffer (pH 4.1), 0.1 mol/l EDTA, 1.2 mmol/l sodium octyl sulfate, and 9% (v/v) methanol. The mobile phase was delivered at a flow rate of 700 μl/min. The system used either a Waters Model 460 detector or an ANTEC Model CU-04-AZ detector. In either case, the potential of the glassy carbon electrode was set at +0.60 V versus a Ag/AgCl reference electrode. The system was calibrated daily with 20 μl of a standard solution containing 10 nmol/l dopamine, dihydroxyphenylacetic acid, and 5-hydroxyindoleacetic acid. The detection limit of the assay was approximately 3 fmol dopamine.

Acetylcholine was separated on a cation-exchange column prepared by loading a reverse-phase column (100 × 2.0 mm), filled with Chromspher 5C18 packing material (Chrompack, Middelburg, Netherlands), with a sodium lauryl sulfate ion-pairing solution (Damsma and Westerink, 1991). An enzymatic post-column reactor was employed for the conversion of acetylcholine to hydrogen peroxide and was prepared by loading a guard column (10 × 1.0 mm or 10 × 2.0 mm) with Lichrosorb-NH_2 (Merck, Darmstadt, Germany). After loading, 1 ml of 25% glutaraldehyde solution was pumped through the guard column at a flow rate of 100 μl/min in order to activate the Lichrosorb-NH_2. Immediately after activation, enzymes were covalently immobilized on the activated matrix by passing 500 μl of a solution containing 40 Units choline oxidase and 80 Units acetylcholinesterase in 0.1 mol/l potassium phosphate buffer (pH 8.0) through the guard column at a flow rate of 50 μl/min. The enzyme reactor thus prepared was rinsed with buffer for an additional 30 min at a flow rate of 400 μl/min before use. The amount of hydrogen peroxide generated by the enzyme reactor was quantified using a platinum wall-jet electrode (ANTEC Model CU-04-AZ, Leiden, Netherlands) set at +0.55 V versus Ag/AgCl. The mobile phase was a 0.1 mol/l potassium phosphate buffer (pH 8.0) containing 1.5 mmol/l tetramethylammonium chloride, 1.5 mmol/l sodium octyl sulfate, and 0.1 mmol/l EDTA and was delivered at a flow rate of 350–450 μl/min by either a Waters model 510 HPLC pump (Waters Chromatography Division, Milford, MA, USA) or an ESA model 580 HPLC pump (ESA, Bedford, MA, USA). The detection limit of the assay was approximately 10 fmol acetylcholine.

2.6. Data analysis

The amount of dopamine or acetylcholine obtained in the dialysate fractions is expressed as fmol/sample. Group values are means ± S.E.M. For the analysis of within-group drug effects, the fmol value for the mean of the 3 final baseline samples and the values for 4 samples collected immediately after quinpirole administration were compared using one-way ANOVA with repeated measures over time ($P \leq 0.05$). Possible between-group differences were analyzed using one-way ANOVA with independent measures ($P \leq 0.05$). When appropriate, ANOVA determinations were followed by Duncan's multiple range post-hoc test. The level of significance for all post-hoc analyses was $P \leq 0.01$. ED_{50} values are expressed as μg/kg and 95% confidence limits and were calculated from the linear portions of the dose-response curves analyzed by simple regression (Lark et al., 1986).

2.7. Materials

Acetylcholinesterase type VI-S, choline oxidase, and neostigmine bromide were purchased from Sigma (St. Louis, MO, USA). Quinpirole hydrochloride (LY171555) was obtained from Eli Lilly (Indianapolis, IN, USA). All other reagents and chemicals were of analytical grade and were obtained from Fisher Scientific (Springfield, NJ, USA).

3. Results

The baseline levels of dopamine and acetylcholine in striatal dialysate samples were 42.8 ± 6.0 fmol ($n = 17$) and 75.8 ± 4.7 fmol ($n = 25$), respectively. There were no significant differences in basal output values for dopamine ($F(3,13) = 0.60$, $P = 0.63$; $n = 4–5$ per group) or acetylcholine ($F(4,24) = 0.34$, $P = 0.85$; $n = 5$ per group) between the groups of animals treated with different doses of quinpirole (Fig. 1).

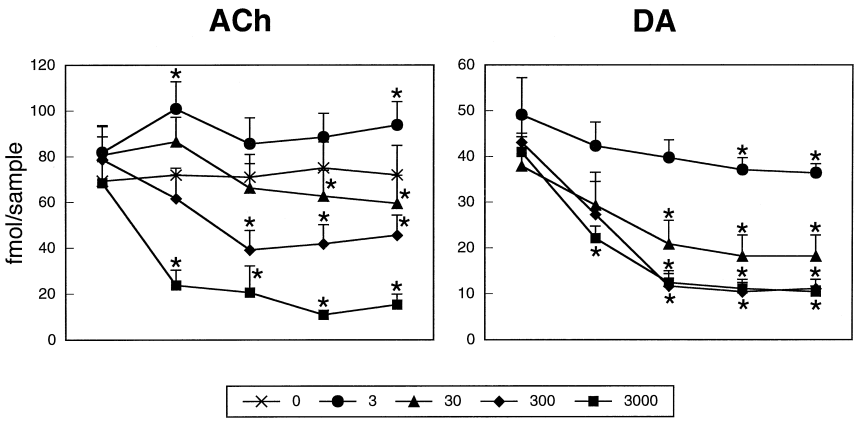

Fig. 1. The effect of quinpirole (QUIN) on the output of acetylcholine and dopamine from striatum. Baseline (BL) values (first sample) and corresponding levels up to 1 h after drug administration are shown. Data are means ± S.E.M. in fmol/sample. * Significantly different from BL value ($P < 0.01$)

Administration of 1 ml/kg saline did not affect the output of striatal acetylcholine ($F(4,16) = 0.29$, $P = 0.88$; $n = 5$). Administration of 3 μg/kg quinpirole differentially altered the output of dopamine and acetylcholine in striatum (Fig. 1). This dose of quinpirole decreased striatal dopamine levels from 49.1 ± 8.1 to 36.4 ± 2.0 fmol/sample ($F(4,12) = 3.41$, $P = 0.04$). In contrast, the output of acetylcholine from striatum was increased from 81.8 ± 11.8 to 100.9 ± 11.9 fmol/sample by 3 μg/kg quinpirole ($F(4,16) = 7.32$, $P = 0.002$).

At doses of 30, 300 and 3000 μg/kg, quinpirole administration significantly inhibited the output of both dopamine and acetylcholine in striatum (Fig. 1). Striatal dopamine levels decreased from 37.9 ± 6.4 to 18.6 ± 4.5 fmol/sample after administration of 30 μg/kg quinpirole ($F(4,16) = 17.34$, $P < 0.001$). The 300 μg/kg dose of quinpirole decreased extracellular dopamine from 43.1 ± 5.2 to 11.3 ± 2.1 fmol/sample ($F(4,12) = 11.07$, $P < 0.001$). Similarly, dopamine efflux was decreased from 41.0 ± 4.1 to 10.6 ± 1.6 fmol/sample after 3000 μg/kg quinpirole ($F(4,12) = 23.53$, $P < 0.001$). Acetylcholine output decreased from 80.7 ± 12.5 to 59.5 ± 12.3 fmol/sample after the 30 μg/kg dose of quinpirole ($F(4,16) = 9.08$, $P < 0.001$). In response to administration of 300 μg/kg quinpirole, acetylcholine efflux decreased from 78.7 ± 10.0 to 39.2 ± 8.4 fmol/sample ($F(4,16) = 11.91$, $P < 0.001$) and a greater decrease, from 68.5 ± 13.1 to 10.8 ± 2.0 fmol/sample, was observed after 3000 μg/kg quinpirole ($F(4,16) = 15.71$, $P < 0.001$).

Significant dose-related effects of quinpirole were observed between groups for both dopamine efflux ($F(3,13) = 14.28$, $P < 0.001$) and acetylcholine output ($F(3,16) = 12.01$, $P < 0.001$). Dopamine output was maximally inhibited after 300 μg/kg quinpirole whereas the greatest inhibition of acetylcholine efflux occurred in response to the 3000 μg/kg dose of the drug. ED_{50} values were calculated from the linear portion of the dose-response curves for dopamine ($r^2 = 0.85$; $F(1,11) = 27.522$, $P < 0.001$) and for acetylcholine ($r^2 = 0.74$; $F(1,13) = 15.418$, $P = 0.002$). These values were 12.4 μg/kg (1–147) and 240 μg/kg (6–979) for dopamine and acetylcholine, respectively (ED_{50} value and 95% confidence limits).

4. Discussion

The present data show that striatal dopamine output *decreases* after a low dose of quinpirole and that this decrease coincides with an *increase* in the output of striatal acetylcholine. Higher doses of quinpirole produce dose-related decreases in the striatal output of both dopamine and acetylcholine. These effects of quinpirole are assumed to reflect a preferential pre-synaptic action on dopamine efflux at the low dose and an increasing post-synaptic activity on acetylcholine output at the higher doses. We conclude from these results: (1) that dopamine predominantly exerts a tonic inhibitory control over spontaneous acetylcholine efflux in striatum in vivo and, (2) that under these conditions inhibition of striatal acetylcholine efflux by dopamine D_2 receptors occurs independent of dopaminergic tone at dopamine D_1 dopamine receptors.

While it is clear that both inhibitory dopamine D_2 receptor-mediated and excitatory dopamine D_1 receptor-mediated influences are involved in the dopaminergic regulation of striatal acetylcholine output (Bertorelli and Consolo, 1990; Damsma et al., 1991; DeBoer and Abercrombie, 1996; Fage and Scatton, 1986), the present data suggest that tonic inhibition of acetylcholine output is the prevalent action of endogenous dopamine under physiological conditions. Striatal acetylcholine output was disinhibited when dopamine release was decreased by an 'autoreceptor-selective' dose of quinpirole. The stimulatory effect of 3 μg/kg quinpirole on acetylcholine output might be considered small (15% above baseline). In an identical experimental paradigm, however, administration of 1 mg/kg haloperidol increased the output of acetylcholine to 40% above baseline (DeBoer and Abercrombie, 1996) and

this change may be considered a maximal effect. Thus, the 15% increase in acetylcholine efflux produced by the low dose of quinpirole in the present study is consistent in magnitude with a partial decrease in dopamine D_2 receptor-mediated inhibition. Moreover, in preliminary studies we have observed a similar 20% increase in striatal acetylcholine output in response to administration of 3 μg/kg of the agonist *R*-(+)-7-OH-DPAT (unpublished data).

The disinhibition of striatal acetylcholine efflux by an 'autoreceptor-selective' dose of quinpirole is consistent with a wealth of neurochemical data showing a preferential dopamine D_2 receptor-mediated inhibition of striatal acetylcholine output (Lehmann and Langer, 1983; Stoof et al., 1992) but is inconsistent with a number of relatively recent microdialysis studies that demonstrate a prevailing dopamine D_1 receptor-mediated stimulation of striatal acetylcholine output in vivo (Consolo et al., 1992; Damsma et al., 1991; Di Chiara et al., 1994). Hitherto, all in vivo microdialysis experiments investigating the interactions between dopamine and acetylcholine have been performed in the presence of high concentrations of acetylcholinesterase inhibitors in the microdialysis perfusate. Recently, we have shown that the inhibitory effects of dopamine D_2 receptor stimulation on striatal acetylcholine efflux are progressively attenuated as extracellular acetylcholine levels are increased by local application of acetylcholinesterase inhibitor (DeBoer and Abercrombie, 1996). In the latter study, administration of 3000 μg/kg quinpirole produced a significant decrease in extracellular acetylcholine levels in striatum only when the applied concentration of the acetylcholinesterase inhibitor neostigmine was less than 100 nmol/l. These in vivo data corroborate an earlier in vitro study by Drukarch et al. (1990) that essentially showed the same effect. Thus, previous microdialysis studies of dopamine-acetylcholine interactions in striatum appear to have underestimated the magnitude of the dopamine D_2 receptor-mediated inhibition of acetylcholine output due to methodological confounds.

The present results also are inconsistent with the proposal that the actions of dopamine D_2 receptor agonists and antagonists in regulating striatal acetylcholine output in vivo are in fact mediated indirectly via alterations in dopamine release and subsequent changes in dopamine D_1 receptor stimulation. The increase in the output of acetylcholine observed after administration of dopamine D_2 receptor antagonists can be reversed or prevented by treatment with the dopamine D_1 receptor antagonist SCH 23390 (Damsma et al., 1991; Imperato et al., 1993, 1994; Russi et al., 1993). We observed, however, that decreasing dopamine release with a low dose of quinpirole led to an increase in striatal acetylcholine output instead of the decrease that would be predicted by the proposed model. Moreover, we observed that the maximum inhibition of striatal dopamine release already had occurred in response to 300 μg/kg quinpirole whereas the maximum inhibition of striatal acetylcholine output occurred after administration of 3000 μg/kg quinpirole. Together, these data demonstrate multiple dissociations between changes in striatal dopamine release and alterations in striatal acetylcholine output, thus arguing strongly in favor of a directly mediated inhibition of striatal acetylcholine efflux by dopamine D_2 receptor agonist drugs. It is suggested that, under physiological conditions, dopamine D_2 receptor-mediated inhibition and dopamine D_1 receptor-mediated stimulation are independent and antagonistic modulatory actions of dopamine upon striatal cholinergic cells (Bertorelli and Consolo, 1990; DeBoer and Abercrombie, 1996; Fage and Scatton, 1986).

The disinhibition of striatal acetylcholine efflux that we observed after the low dose of quinpirole is attributed to the concomitant decrease in dopamine output also observed i.e., to a preferential pre-synaptic action of quinpirole upon dopamine release. This assumption is supported by our finding of a large difference in the ED_{50} of quinpirole for inhibition of striatal dopamine efflux versus acetylcholine output. Quinpirole was approximately 20-fold more potent towards pre-synaptic dopamine D_2 receptors modulating the output of dopamine than towards post-synaptic dopamine D_2 receptors modulating the output of acetylcholine. Similar biochemical observations have been made in studies utilizing a variety of dopamine D_2 receptor-selective dopamine agonists (Arnt and Hyttel, 1990; Claustre et al., 1985; Cubeddu and Hoffman, 1983; Drukarch and Stoof, 1990; Imperato et al., 1988; Robertson et al., 1993). These results have been interpreted as indicating the existence of a large dopamine D_2 autoreceptor reserve on nigrostriatal dopamine neurons and an absence of such a receptor reserve for post-synaptic dopamine D_2 receptors regulating striatal cholinergic activity (Meller et al., 1988; Yokoo et al., 1988).

In conclusion, our results are consistent with the view that endogenous dopamine, acting directly upon dopamine D_2 receptors, exerts a tonic inhibitory modulation of striatal acetylcholine output under physiological conditions. The present data challenge recent models in which striatal acetylcholine efflux in vivo is proposed to be under a tonic facilitatory control by dopamine acting on dopamine D_1 receptors.

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