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Short communication

Effect of dopamine D2/D3 receptor antagonist sulpiride on amphetamine-induced changes in striatal extracellular dopamine

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Abstract

Amphetamine increases extracellular dopamine and induces locomotor and stereotypical behaviors in rats. This study examined the effect of the dopamine D2/D3 receptor antagonist sulpiride (50 mg/kg s.c.) on the dopaminergic response to amphetamine (0.5, 2.0, or 8.0 mg/kg i.p.) in male Sprague-Dawley rats. Extracellular dopamine in the striatum was monitored using in vivo microdialysis and high performance liquid chromatography with electrochemical detection. Dopamine concentration curves were analyzed using non-linear regression and residual *F*-testing. Amphetamine enhanced extracellular dopamine in a dose-dependent manner. Sulpiride augmented the increase in dopamine induced by 0.5 and 2 mg/kg amphetamine by decreasing the rate of dopamine concentration fall off in the extracellular space ($P < 0.05$). Sulpiride also potentiated the amount of dopamine increased by 8 mg/kg amphetamine, but did so by affecting the maximum concentration achieved ($P < 0.05$), not the onset or offset rates. We conclude that the primary effect of a dopamine D2/D3 receptor antagonist is a potentiation of the effect of amphetamine on extracellular striatal dopamine levels, which may contribute to the enhanced stereotypic effects observed when paired with amphetamine. © 2001 Published by Elsevier Science B.V.

Keywords: Amphetamine; Dopamine D2 receptor; Sulpiride; Dopamine receptor antagonist; Microdialysis; Striatum

1. Introduction

Amphetamine, a central nervous system stimulant, increases extracellular dopamine levels from cells in a non-impulse dependent manner by "reversing" the dopamine uptake transporter on catecholamine terminals, causing dopamine release instead of reuptake (Fischer and Cho, 1979). At higher concentrations, amphetamine may also displace vesicular dopamine into the cytoplasm (Sulzer and Rayport, 1990) after which dopamine can be released into the extracellular space via reverse transport.

Amphetamine also causes a complex, dose-dependent, behavioral syndrome. In rats, low doses of amphetamine increase locomotor activity, while higher doses produce intense repetitive movements called stereotypic behavior (Segal and Kuczenski, 1994). A large body of evidence suggests it is mainly the effect on dopamine, which mediates the observed changes in behavior (Kuczenski and Segal, 1994). Amphetamine-induced stereotypic behavior has been linked with changes in dopamine in the striatum (Feldman et al., 1997).

Most antipsychotics which block dopamine D2 receptors (e.g., haloperidol) also potently block amphetamine-induced behaviors. However, some dopamine D2 receptor antagonists only weakly block certain portions of this behavior, or actually enhance the stereotypy response to amphetamine although effectively blocking dopamine receptors (Ljungberg and Ungerstedt, 1985; Tshanz and Rebec, 1989). For example, sulpiride, a selective dopamine D2 and D3 receptor antagonist, increases stereotypy and concurrently increases extracellular dopamine in the striatum after 2 mg/kg amphetamine in rats (Sharp et al., 1986). However, only one dose of amphetamine was used in this study, and it is unclear whether sulpiride would potentiate extracellular dopamine levels across a range of amphetamine doses. Sulpiride may increase dopamine levels above those caused by low to intermediate doses of amphetamine, but not after high doses of amphetamine. For example, the increased synaptic dopamine concentrations caused by high doses of amphetamine may be able to displace the dopamine receptor blockade by sulpiride. In the present study, we used microdialysis to further explore the mechanism by which sulpiride affects amphetamine-

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stimulated dopamine concentrations in rats. We have extended the work of previous authors (Sharp et al., 1986) by studying dopamine concentrations across a range of amphetamine doses.

2. Materials and methods

2.1. Animals

Sprague-Dawley rats (Harlan Sprague-Dawley, Indianapolis) weighing between 260–340 g at the time of the experiments were used. They were group housed prior to surgery, then individually housed thereafter. The rats had free access to food and water, and were maintained on a 12-h light, 12-h dark cycle.

2.2. Surgery

One week after arrival, rats were anesthetized with equithesin (25 mg/kg sodium pentobarbital and 150 mg/kg chloral hydrate). A small hole was drilled in the skull, and a stainless steel guide cannula (22 gauge, Plastics One) was implanted above the left striatum using a stereotaxic frame [A/P +0.8, L/M +3.0, D/V −4.0 from bregma (Paxinos and Watson, 1986)]. Guide cannulae were anchored using dental acrylic and three small screws into the skull. Each rat was given 7–10 days to recover before the experiment.

2.3. Microdialysis probes

Probes were constructed similar to a design previously cited (Pettit and Justice, 1991). Fused silica tubing (40 μm ID, 105 μm OD) served as inlet and outline lines and were arranged so that the outlet line ended at the top of the dialysis membrane (Spectra Por, 13,000 molecular weight cut off) with the inlet line extending 3 mm further to the bottom of the membrane. The probes had an effective membrane of 3 mm (length) and 270 μm (outer diameter).

2.4. Experimental procedure

Between 14 and 18 h before the start of the experiment, a probe was inserted into each rat and perfused with artificial cerebral spinal fluid (ACSF; 145 mM NaCl, 2.7 mM KCl, 1.2 mM $CaCl_2$, and 1.0 mM $MgCl_2$ in 2 mM phosphate buffer, pH = 6.8) at 0.2 μl/min. Each rat was placed into a Plexiglas box (40 × 40 × 30 cm) with the perfusion lines attached to a liquid swivel on an arm at the top of the cage. Two hours before the experiment, the ACSF perfusion through the probe was increased to 2 μl/min and each rat was transferred into 12 × 12 × 12 in. cages of 1/2 in. wire mesh. During the experiment microdialysis samples were collected every 15 min for the first 6 h then every 30 min for the final 2 h. After 1 h of sample collection, each rat was given vehicle or 50 mg/kg sulpiride (s.c.), followed 1 h later by 0, 0.5, 2, or 8 mg/kg amphetamine (i.p.). All samples were stored at −70°C until analyzed. After each experiment, rats were perfused with 10% formalin following euthanasia by chloral hydrate overdose. Brains were removed, sectioned, and stained with Cresyl violet to verify correct probe placement. One rat was excluded from the study due to probe placement outside the striatum.

2.5. Dopamine analysis

Samples were analyzed for dopamine using high performance liquid chromatography with electrochemical detection. A Keystone 100 × 3 mm reverse phase Hypersil C-18 BDS column was used. Peaks were measured with a Hewlett-Packard 3390A or a Shimadzu C-R3A integrator. Detection parameters were: guard potential, +400 mV; pre-detection potential, −100 mV; and detection potential, +200 mV. Mobile phase (75 mM NaH_2PO_4, with 408 mg octane sulfonic acid, 750 mg EDTA, and 70 ml acetonitrile/l, at a pH of 5.6) was pumped through the column at 0.5 ml/min.

2.6. Drugs

D-amphetamine (RBI, Natick MA) was dissolved in 0.9% NaCl, and sulpiride (RBI) was dissolved in a quarter final volume 2.5% lactic acid and brought up to volume with 0.9% NaCl. Amphetamine was given i.p. in a volume of 1 ml/kg, and sulpiride was given s.c. in a volume of 2 ml/kg.

2.7. Data analysis

All of the data are represented as means ± S.E.M. Analysis of variance was used (SPSS), followed by Bonferroni-corrected Dunn's test on log-transformed data for the multiple-individual comparisons. Onset rate, offset rate, maximum response and half-life were calculated using iteratively reweighted, constrained non-linear regression (SPSS). Because the standard deviation of the data was proportional to the value of the means, mean data were weighted by the inverse of the expected variance (weighted inversely to the square of the mean) and were fit using the formula $C(t) = A(e^{-k_{off}t} - e^{-k_{on}t})$ where C is the concentration of dialysate dopamine, A is the maximal response, k_{off} is the offset rate constant, and k_{on} is the onset rate constant. Standard errors for parameter estimates represent asymptotic standard errors obtained from the dispersion matrix. Comparisons of model parameters between groups were done using a residual F-test. Statistical significance for all analyses was determined when $P < 0.05$.

3. Results

Basal values of dopamine in this study were 0.49 ± 0.04 pg/μl and did not differ between groups ($P > 0.05$).

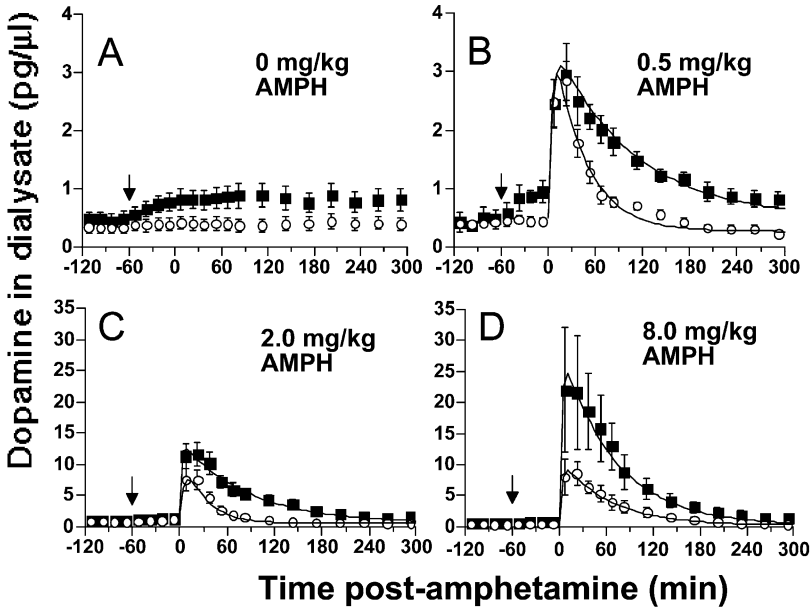

Fig. 1. Effect of 50 mg/kg s.c. sulpiride (■) or vehicle (○) pretreatment on i.p. amphetamine (AMPH)-induced changes in extracellular dopamine concentrations in the striatum. Concentrations of dopamine in dialysate are plotted as a function of time post-amphetamine. Data points are mean ± S.E.M., and the lines represent the best fit of the data using the formula described in the methods. Sulpiride or vehicle was administered 1 h before amphetamine, as indicated by the arrows. Amphetamine was given at time zero. A: 0 mg/kg amphetamine with sulpiride ($n = 4$) or vehicle ($n = 5$) pretreatment. B: 0.5 mg/kg amphetamine with sulpiride ($n = 5$) or vehicle ($n = 5$) pretreatment. C: 2 mg/kg amphetamine with sulpiride ($n = 4$) or vehicle ($n = 5$) pretreatment. D: 8 mg/kg amphetamine with sulpiride ($n = 4$) or vehicle ($n = 6$) pretreatment.

Sulpiride pretreatment caused dopamine concentrations in the dialysates to roughly double ($P < 0.05$) (Fig. 1A). The vehicle pretreatment had no effect. Administration of amphetamine caused an immediate and dose-dependent increase in dopamine levels, which peaked between 15 and 30 min post-amphetamine (Fig. 1B,C,D). This amphetamine-induced increase in dopamine was significant at all doses ($P < 0.05$). Sulpiride pretreatment enhanced the stimulation of dopamine levels after all doses of amphetamine ($P < 0.05$).

Non-linear regression was used to further analyze the effect of sulpiride on the time course of amphetamine-stimulated dopamine levels (Table 1). Sulpiride slowed the offset rate of dopamine while not affecting the maximum concentration achieved after 0.5 and 2 mg/kg amphetamine. This resulted in greatly enhancing the half-life of dopamine for both doses of amphetamine. Sulpiride also affected the dopamine time course after 8 mg/kg amphetamine, but did so by increasing the maximum response achieved, not by changing the offset rate.

4. Discussion

Sulpiride has previously been shown to increase extracellular dopamine and increase amphetamine-induced stereotyped movements in rats after 2 mg/kg am-

Table 1
Effect of sulpiride (50 mg/kg, s.c.) pretreatment on maximum response, onset rate (k_{on}), offset rate (k_{off}), and half-life ($T_{1/2}$) of striatal dialysate dopamine concentrations after (i.p.) amphetamine administration

Parameter	Amphetamine dose					
	0.5 mg/kg		2.0 mg/kg		8.0 mg/kg	
	Control	Sulpiride	Control	Sulpiride	Control	Sulpiride
Maximum response (pg/µl)	3.9 ± 0.5	84.2 ± 0.6	12.9 ± 1.5	13.4 ± 1.2	11.1 ± 0.9	29.3 ± 4.8[a]
k_{off} (min^{-1})	0.025 ± 0.003	0.009 ± 0.001[a]	0.036 ± 0.005	0.012 ± 0.001[a]	0.016 ± 0.002	0.015 ± 0.003
k_{on} (min^{-1})	0.25 ± 0.01	0.31 ± 0.11	0.19 ± 0.05	0.52 ± 0.19[a]	0.30 ± 0.13	0.35 ± 0.07
$T_{1/2}$ (min)[b]	28.2	78.4	19.2	59.2	42.5	47.7

Values represent means ± S.E.M.
[a] Indicates $P < 0.05$ for control vs. sulpiride.
[b] The half-life $T_{1/2}$ is directly calculated as $\ln(2)/k_{off}$.

phetamine administration (Sharp et al., 1986). In the same study, sulpiride blocked the increased locomotion caused by amphetamine. However, this is generally viewed as a potentiation of the amphetamine effect. Escalating doses of amphetamine will first increase and then decrease locomotion as stereotyped movements begin to occur. In rats, stereotypies such as focussed sniffing and repetitive head movements preclude locomotion (Segal and Kuczenski, 1994). In the current study, sulpiride pretreatment potentiated the increase in extracellular dopamine caused by a range of amphetamine doses (0.5–8.0 mg/kg). Unpublished cage-crossing and rearing data from our lab demonstrate a potentiation of the behavioral effect of amphetamine across this dose range by sulpiride. Thus, the increased dopamine released by the combination of sulpiride and amphetamine may be responsible for the increased behavioral effects observed. Although extracellular dopamine modulation appears to be mainly the result of a presynaptic effect, stereotypic behaviors are probably also mediated by postsynaptic dopamine receptors in the striatum. Differences in the functionality of presynaptic vs. postsynaptic dopamine receptors have been observed (Drukarch and Stoof, 1990; McElvain and Schenk, 1992; Andersen and Gazzara, 1994). Hence, the synaptic concentrations of dopamine achieved in this study may be overcoming the postsynaptic but not the presynaptic functional antagonism by sulpiride. Sulpiride has previously been shown to only weakly antagonize postsynaptic striatal dopamine receptors (Kohler et al., 1981).

Amphetamine blocks dopamine uptake and releases dopamine from the cytoplasm of cells in a non-exocytotic manner. In support of this, dopamine release by amphetamine has been shown to be insensitive to sodium channel blockade by tetrodotoxin (Nomikos et al., 1990; Westerink et al., 1987) depletion of Ca^{2+} (Arnold et al., 1977), and autoreceptor blockade (Kamal et al., 1981). However, amphetamine-induced increases in extracellular dopamine appear to inhibit subsequent impulse-dependent activity of the cell via an effect on dopamine D2-like receptors (Bunney et al., 1973; Bunney and Aghajanian, 1978; Innis et al., 1992). Iravani and Kruk (1995) demonstrated that amphetamine-induced dopamine release from striatal slices was not increased by preincubation with sulpiride, but amphetamine decreased the dopaminergic response to a subsequent electrical pulse, and this effect was prevented by sulpiride. Similar to our results, pretreatment with dopamine D2 receptor antagonist haloperidol resulted in increased dialysate dopamine levels in the striatum after amphetamine treatment (Pehek, 1999).

Interestingly, the effect of sulpiride on amphetamine-induced increases in dopamine in our study appeared to be dose-dependent. Sulpiride decreased the offset rate of dopamine after 0.5 and 2 mg/kg amphetamine; however, sulpiride increased the maximum release of dopamine caused by 8 mg/kg amphetamine. This suggests that amphetamine may display a dose-related difference in its mechanism of action. Interpretation of these effects is difficult. However, a hypothesis can be offered.

The effect of sulpiride on the offset rate of dopamine may involve dopamine transporters. Dopamine D2 receptor activation in several areas of the brain including the striatum and nucleus accumbens appears to increase dopamine uptake via an effect on dopamine transporters (Cass and Gerhardt, 1994; Meiergerd et al., 1993; Parsons et al., 1993). For example, Meiergerd et al. (1993) demonstrated an increase in dopamine uptake into striatal synaptosomes by quinpirole, a dopamine D2 receptor agonist, and blockade of this effect by the addition of sulpiride, the dopamine D2 receptor antagonist. Dopamine released by 0.5 and 2.0 mg/kg of amphetamine may increase uptake by activating dopamine D2 receptors. This effect is blocked by sulpiride, leading to the decreased fall-off rate of dialysate dopamine. This effect was not observed after 8 mg/kg amphetamine; however, the high concentrations of dopamine released by this dose may have desensitized the dopamine D2 receptors, preventing an effect of sulpiride. Note that the offset rate after 8 mg/kg amphetamine in the control group is already low (Table 1). Supporting this, dopamine autoreceptors from the ventral tegmental area have been shown to acutely desensitize to amphetamine in vitro (Seutin et al., 1991).

The maximum response of dopamine released by amphetamine may be more dependent on the velocity of reverse transport elicited by amphetamine and thus may be limited by the availability of cytosolic dopamine. The supply of cytosolic dopamine may in turn be limited by the synthesis of dopamine. Dopamine autoreceptor activation regulates dopamine synthesis by inhibiting the rate limiting enzyme tyrosine hydroxylase, creating a feedback inhibition of synaptic dopamine (for review see Jackson and Westlind-Danielsson, 1994). In rat striatal synaptosomes, tyrosine hydroxylase is dose-dependently inhibited by dopamine, and this inhibition is antagonized by sulpiride (Johnson et al., 1992; Tissari and Lillgäls, 1993). The increase in extracellular dopamine after amphetamine administration may normally be self-limiting, as increased extracellular dopamine activates autoreceptors and decreases impulse-dependent dopamine release. Sulpiride may prevent dopaminergic feedback inhibition of tyrosine hydroxylase via dopamine D2 receptors, resulting in greater dopamine synthesis and a higher maximum response after 8 mg/kg amphetamine. The reason for the lack of an effect on the maximum response by sulpiride after 0.5 and 2.0 mg/kg amphetamine is unclear but may be due to insufficient feedback inhibition of tyrosine hydroxylase activity. On the other hand, the increased maximum response of dopamine after 8 mg/kg amphetamine may be related to the ability of higher concentrations of amphetamine to displace vesicular dopamine into the cytosol (Sulzer and Rayport, 1990). Pothos et al. (1998) demonstrated that dopamine autoreceptor activation in PC12 cells resulted in reduced quantal size. This effect was blocked

by sulpiride. In our study, sulpiride pretreatment may result in increased vesicular dopamine concentrations. Treatment with 8 mg/kg amphetamine may then displace this vesicular dopamine into the cytosol and ultimately into the extracellular space.

Clearly more work remains to be done before the mechanism of the potentiation of amphetamine-induced increases in dialysate dopamine by a dopamine D2/D3 receptor antagonist is understood. In fact, a recent study by Shi et al. (2000) using in vivo single-unit recording in rats reported that blocking the amphetamine-induced inhibition of cell firing mediated by dopamine D2/D3 receptors with the dopamine D2/D3 receptor antagonist raclopride uncovered an excitatory effect of amphetamine on both firing rate and burst activity, which appeared to be caused in part by an interaction with adrenergic α_1 receptors. Thus, non-dopaminergic receptors also may be involved in the effects seen here.

In summary, this experiment has confirmed and extended previous findings (Sharp et al., 1986) demonstrating that pretreatment with sulpiride potentiates the effect of amphetamine on extracellular striatal dopamine levels across a wide range of amphetamine doses. The varied manner in which sulpiride increased dopamine concentrations after different doses of amphetamine suggests that amphetamine displays a dose-related difference in its mechanism of action. Additionally, the increase in dopamine caused by sulpiride may contribute to the observed potentiation of stereotypy caused by sulpiride in amphetamine-treated rats.

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