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Idazoxan preferentially increases dopamine output in the rat medial prefrontal cortex at the nerve terminal level

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Abstract

The effects of the α_2-adrenoceptor antagonist idazoxan on extracellular concentrations of dopamine in major dopaminergic terminal regions in the brain were investigated by means of microdialysis in freely moving rats. Systemic administration of idazoxan markedly increased dopamine output in the medial prefrontal cortex, whereas it failed to affect dopamine efflux in the striatum or in the nucleus accumbens. Local perfusion of idazoxan via reversed dialysis markedly enhanced dopamine efflux in cortical but not subcortical areas, in which dopamine output was but little affected. Infusion of idazoxan into the ventral tegmental area did not alter the dopamine efflux in the medial prefrontal cortex. Moreover, the increase in cortical dopamine efflux induced by systemic administration of idazoxan was unaffected by tetrodotoxin perfusion of the ventral tegmental area. These data show that the α_2-adrenoceptor antagonist idazoxan preferentially increases basal dopamine output in the medial prefrontal cortex through a local mechanism, an effect which appears largely independent of dopaminergic neuronal activity. An enhanced output of cortical dopamine may contribute to the purported augmentation by α_2-adrenoceptor antagonists of the therapeutic effects of both antidepressant and antipsychotic drugs.

Keywords: α_2-Adrenoceptor; Dopamine extracellular; Microdialysis dual-probe; Idazoxan

1. Introduction

Clinical studies have indicated that α_2-adrenoceptor antagonists may be beneficial not only in the pharmacological treatment of depression but also in schizophrenia (Van Dorth, 1983; Davis and Wilde, 1996; Litman et al., 1996), and the relatively high α_2-adrenoceptor affinity of some antipsychotic drugs such as clozapine and risperidone support a role for α_2 adrenoceptor blockade in the generation of antipsychotic drug activity (Nutt, 1994; Schotte et al., 1996; Hertel et al., 1997).

Preclinical studies demonstrate that α_2-adrenoceptor antagonists may facilitate the output of dopamine in the medial prefrontal cortex (Gresch et al., 1995; Tanda et al., 1996; Gobert et al., 1998; Yamamoto and Novotney, 1998). Although the precise mechanism involved presently remains to be elucidated, it has been suggested to involve a local mechanism at the dopaminergic nerve terminal level (Gresch et al., 1995; Yamamoto and Novotney, 1998). However, some α_2-adrenoceptor antagonists may also stimulate neuronal activity of midbrain dopamine neurons, an effect which, consequently, may contribute to increase the release of dopamine in the medial prefrontal cortex (see Grenhoff and Svensson, 1989). Furthermore, although an interaction between the noradrenergic and the mesocortical dopaminergic systems via α_2-adrenoceptors seems rather well established, the effect of α_2 adrenoceptor blockade on dopamine efflux in other major dopaminergic terminal areas, such as the nucleus accumbens and the striatum, appears less well characterized. Consequently, the present study, using microdialysis in freely moving animals, was undertaken to compare the effects of α_2-adrenoceptor antagonism on extracellular concentration of dopamine in the medial prefrontal cortex, nucleus accumbens and the striatum as well as to investigate further the mechanisms underlying the increase in cortical dopamine output induced by α_2-adrenoceptor blockade.

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2. Materials and methods

2.1. Animals, microdialysis procedure and biochemical assay

All experiments were performed in strict accordance with the guidelines and with the consent of the local ethical committee (Stockholms Norr och Södra Försöksdjursetiska Kommitteér). Implantation and dialysis procedure as well as biochemical analysis were, in principal, identical to those previously described (Hertel et al., 1996). Briefly, anesthetized male BKl:WR rats (BK Universal, Sollentuna, Sweden; sodium pentobarbital, 60 mg/kg, i.p.) weighing 275–350 g were implanted with dialysis probes in the medial prefrontal cortex, nucleus accumbens or striatum. The coordinates (in mm), according to the atlas of Paxinos and Watson (1986), were: AP = +3.0, +1.6, +0.7; ML = 0.6, 1.4, 3.5 and DV = −5.2, −8.2, −6.2, respectively, relative to bregma and dural surface. In some medial prefrontal cortex implanted rats, a second probe was implanted in the ipsilateral ventral tegmental area (AP = +3.8, ML = 0.7 and DV = −8.7 relative to interaural line and dural surface). Dialysis experiments were conducted approximately 48 h after surgery in freely moving rats. On-line quantification of dopamine and dihydroxyphenylacetic acid (DOPAC) in the dialysate was accomplished by high-performance liquid chromotography coupled to electrochemical detection. The detection limit for dopamine and DOPAC was approximately 0.1 and 9.5 fmol/min, respectively.

2.2. Drugs

Idazoxan (Sigma) and tetrodotoxin (Sigma) were dissolved in saline (0.9% NaCl) or perfusion solution (a modified Ringeŕs solution containing 147 mM NaCl, 3.0 mM KCl, 1.3 mM $CaCl_2$, 1.0 mM $MgCl_2$ and 1.0 mM sodium phosphate; pH 7.4). Systemic or local administration (subcutaneous injections in the neck region at a volume of 1.0 ml/kg or via reversed microdialysis) was performed after a stable outflow (< 10% variation) of dopamine and DOPAC.

2.3. Data analysis

Data were calculated as changes of basal dopamine and DOPAC output over time or as average percent change of baseline over the entire sampling period (overall dopamine and DOPAC output). Baseline (= 100%) was defined as the average of the last three preinjection values. Data were statistically evaluated using two-way (area, concentration or treatment × time) analysis of variance (ANOVA) for repeated measures followed by the Newman–Keuls test for multiple comparisons with a criterion of $P < 0.05$ to be considered significant.

3. Results

3.1. Systemic administration of idazoxan preferentially increases dopamine efflux in the medial prefrontal cortex

The mean baseline concentration (fmol/min ± S.E.M.) of dopamine or DOPAC in the medial prefrontal cortex, nucleus accumbens and striatum was 0.59 ± 0.055 or 35 ± 11.2 ($n = 49$), 4.19 ± 0.33 or 659 ± 78.3 ($n = 20$) and 8.36 ± 1.04 or 809 ± 88.2 ($n = 21$) fmol/min, respectively. Data not corrected for in vitro dialysis probe recov-

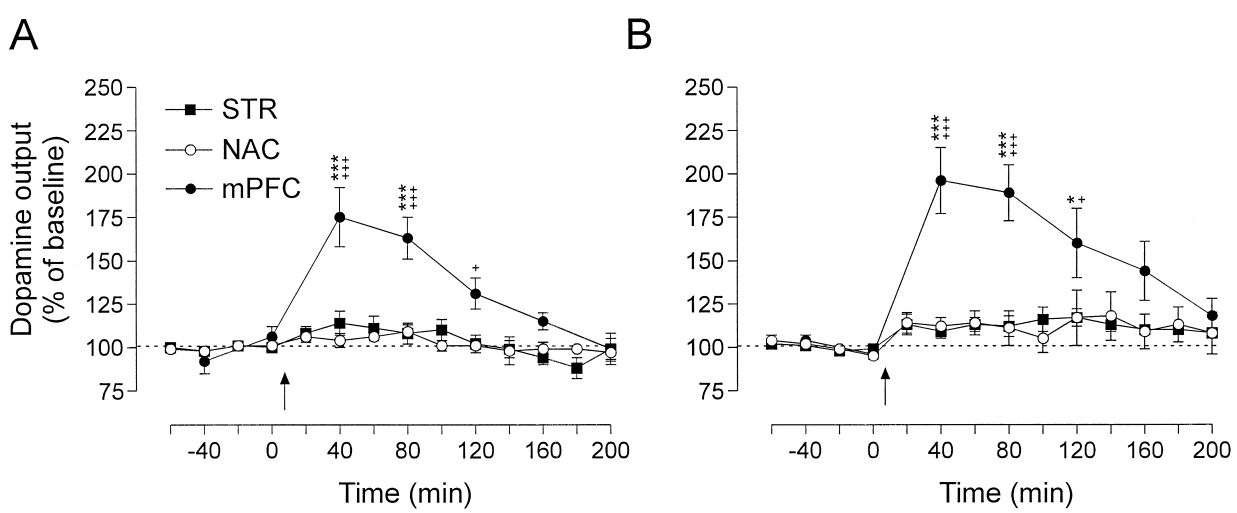

Fig. 1. Effects of idazoxan on dopamine output in the striatum (STR), nucleus accumbens (NAC) and medial prefrontal cortex (mPFC). Arrow indicates injection of (A) 0.5 or (B) 1.5 mg/kg idazoxan (s.c.). Data are presented as the mean ± S.E.M. ($n \geq 5$) percent change of baseline and analyzed by two-way (area × time) ANOVA followed by Newman–Keuls test for multiple comparisons. (A): F(area; 2,14) = 12.8, $P < 0.001$; F(time; 5,70) = 17.4, $P < 0.001$ and F(area × time; 10,70) = 8.1, $P < 0.001$. (B): F(area; 2,14) = 12.8, $P < 0.001$; F(time; 5,70) = 1.4, $P < 0.001$ and F(area × time; 10,70) = 8.1, $P < 0.001$. $^{*}P < 0.05$ and $^{***}P < 0.001$ compared to baseline. $+P < 0.05$ and $+++P < 0.001$ compared between the medial prefrontal cortex and the striatum as well as the nucleus accumbens group.

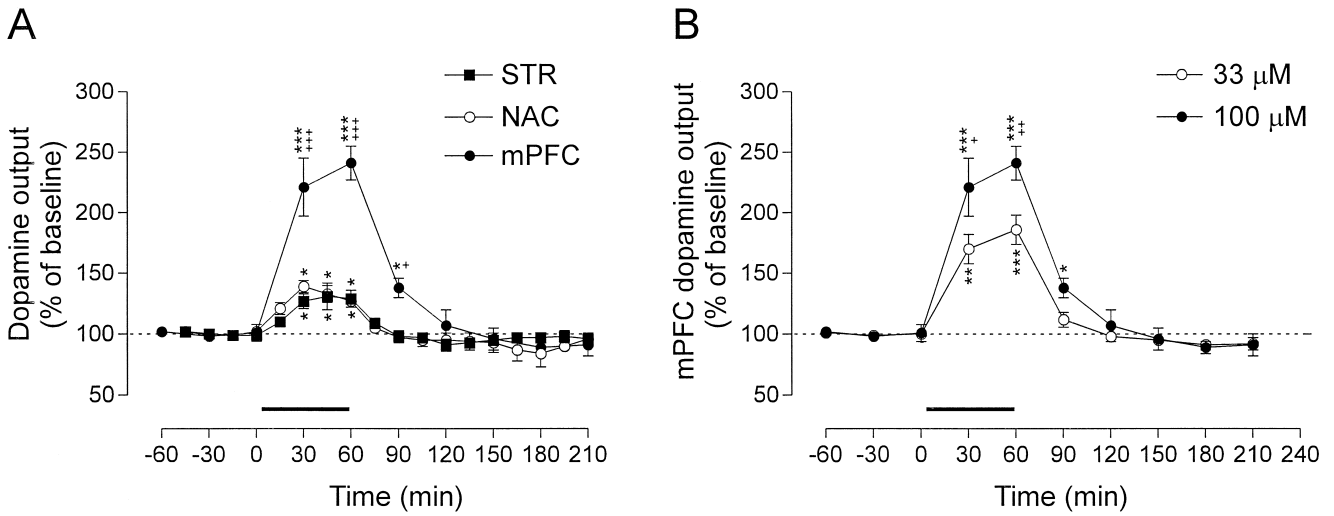

Fig. 2. Effect of (A) local administration of idazoxan (100 μM, 60 min) on dopamine output in the striatum (STR), nucleus accumbens (NAC) and medial prefrontal cortex (mPFC), and (B) effect of cortical administration of idazoxan (33 and 100 μM, 60 min) on dopamine output in the medial prefrontal cortex. Bar indicates time (60 min) of drug infusion. Data are presented as the mean ± S.E.M. ($n \geq 4$) percent change of baseline and analyzed by two-way (area × time or concentration × time) ANOVA followed by Newman–Keuls test for multiple comparisons. (A): F(area; 2,9) = 30.8, $P < 0.001$; F(time; 5,45) = 46.3, $P < 0.001$ and F(area × time; 10,45) = 10.7, $P < 0.001$. (B): F(concentration; 1,6) = 7.9, $P < 0.05$; F(time; 5,30) = 45.9, $P < 0.001$ and F(concentration × time; 5,30) = 3.1, $P < 0.05$. $^{*}P < 0.05$, $^{**}P < 0.01$ and $^{***}P < 0.001$ compared to baseline. $+P < 0.05$, $++P < 0.05$ and $+++P < 0.001$ compared between (A) the medial prefrontal cortex and the striatum as well as the nucleus accumbens group and (B) between concentration groups.

ery. No statistically significant differences in mean baseline concentrations of dopamine or DOPAC were found between different treatment groups within the same dialysis area. Saline injections failed to significantly affect dopamine or DOPAC efflux in all the areas investigated.

Systemic idazoxan injection (0.5 or 1.5 mg/kg) significantly increased dopamine output in the medial prefrontal cortex whereas the same treatment failed to affect dopamine efflux in the nucleus accumbens or the striatum (Fig. 1A–B). Furthermore, statistical analysis indicated that the

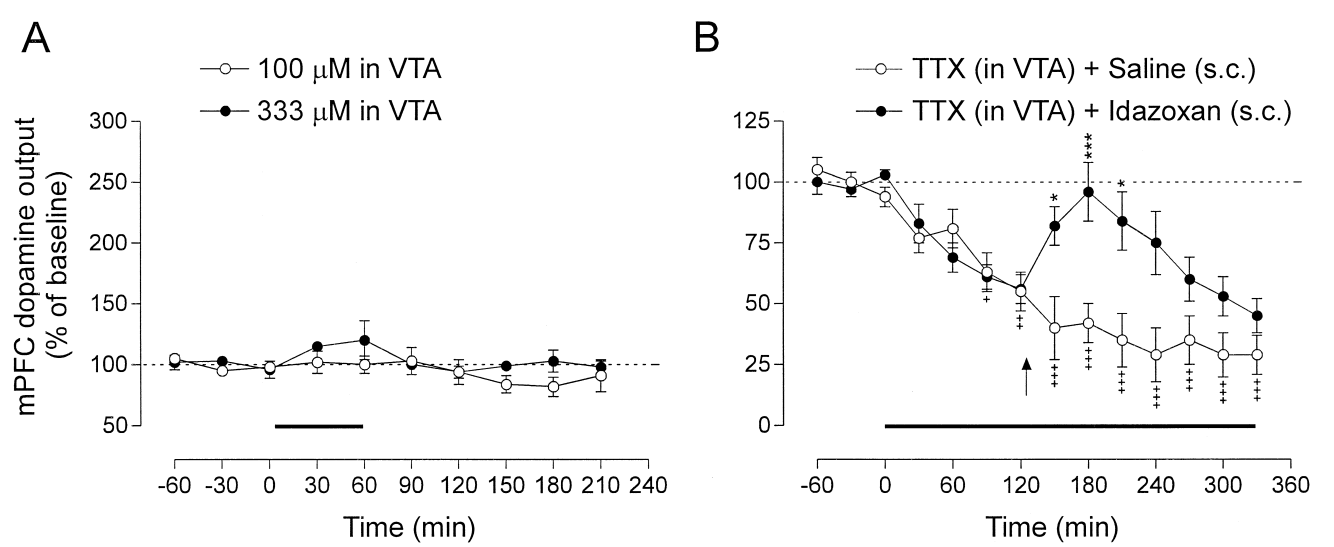

Fig. 3. Effects of local ventral tegmental area (VTA) perfusion with (A) idazoxan (100 and 333 μM, 60 min) and (B) tetrodotoxin (TTX; 1 μM, 330 min) on basal (A, B) as well as on idazoxan (1.5 mg/kg, s.c.) evoked (B) output of dopamine in the medial prefrontal cortex (mPFC). Bar or arrow indicates time (60 or 300 min) of drug infusion or injection of idazoxan or saline, respectively. Data are presented as the mean ± S.E.M. ($n = 5$) percent change of baseline. Data were analyzed by two-way (concentration or treatment × time) ANOVA followed by Newman–Keuls test for multiple comparisons. (A): F(concentration; 1,9) = 0.3, $P > 0.05$; F(time; 7,63) = 1.3, $P > 0.05$ and F(concentration × time; 7,63) = 1.7, $P > 0.05$. (B): F(treatment; 1,9) = 5.3, $P < 0.05$; F(time; 7,63) = 5.4, $P < 0.001$ and F(treatment × time; 7,63) = 4.5, $P < 0.001$. $^{*}P < 0.05$ and $^{***}P < 0.001$ compared to the sample immediately preceding injection of idazoxan or saline. $+P < 0.05$, $++P < 0.01$ and $+++P < 0.001$ compared to baseline within the saline treated group.

high as well as the low dose of idazoxan induced a larger effect on dopamine efflux in the medial prefrontal cortex as compared to both the nucleus accumbens and striatum within the 40–120 min time interval. Although the high dose of idazoxan induced a more pronounced increase in cortical dopamine output as compared to the lower dose (overall dopamine output ± S.E.M: 164 ± 16 and 138 ± 24% of baseline, respectively; data not shown), this difference did not reach statistical significance, i.e., no significant dose effect was indicated.

In similarity with the regional effects on dopamine, systemic administration of idazoxan (1.5 mg/kg) increased extracellular concentrations of DOPAC in the medial prefrontal cortex (overall DOPAC output ± S.E.M: 138 ± 6.6% of baseline, $n = 8$; data not shown) whereas it only moderately affected DOPAC efflux in the nucleus accumbens (overall DOPAC output ± S.E.M: 104 ± 3.8% of baseline, $n = 6$; data not shown) or the striatum (overall DOPAC output ± S.E.M: 106 ± 2.8% of baseline, $n = 6$; data not shown).

3.2. Local administration of idazoxan dose-dependently increases dopamine efflux preferentially in the medial prefrontal cortex

Local administration of idazoxan (100 μM, 60 min) via the dialysis probe significantly increased dopamine efflux in all investigated areas (Fig. 2A). However, statistical analysis indicated that the idazoxan-induced increase in dopamine efflux in the medial prefrontal cortex was more long-lasting as well as more pronounced compared to both nucleus accumbens and striatum. Furthermore, statistical analysis of the data obtained after idazoxan administration (33 and 100 μM, 60 min) revealed a significant concentration-dependent effect of idazoxan on cortical dopamine efflux (Fig. 2B).

3.3. The idazoxan-induced increase of cortical dopamine is mediated via a local mechanism at the nerve terminal level

Intrategmental administration of idazoxan (100 or 300 μM, 60 min) failed to significantly affect dopamine efflux in the medial prefrontal cortex (Fig. 3A). Tetrodotoxin perfusion (1 μM) of the ventral tegmental area, which significantly reduced the cortical output of dopamine, did not prevent the ability of systemic idazoxan (1.5 mg/kg) to enhance dopamine efflux in the medial prefrontal cortex.

4. Discussion

The major conclusions of the present study are that the α_2-adrenoceptor antagonist idazoxan preferentially increases basal dopamine output in the medial prefrontal cortex through a local mechanism at the level of the nerve terminals and that this effect is largely independent of dopamine neuronal activity.

4.1. Influence of α_2-adrenoceptor mediated modulation of cortical dopamine levels

It is by now well established that α_2-adrenoceptors exert a tonic, inhibitory influence on extracellular concentration of dopamine in the medial prefrontal cortex (Gresch et al., 1995; Tanda et al., 1996; Gobert et al., 1998; Yamamoto and Novotney, 1998). In line with these studies, we found that systemic administration of idazoxan markedly increased dopamine efflux in the medial prefrontal cortex. The present data agree with the notion that this facilitatory effect of α_2-adrenoceptor antagonism on dopamine output in the medial prefrontal cortex is essentially mediated via a local mechanism within the cortex (Gresch et al., 1995; Yamamoto and Novotney, 1998): First, cortical infusion of idazoxan dose-dependently enhanced dopamine output in the medial prefrontal cortex. Second, local application of idazoxan in the ventral tegmental area, the major origin of the cortically projecting dopaminergic neurons, failed to affect dopamine efflux in the medial prefrontal cortex. Third, tetrodotoxin perfusion of the ventral tegmental area did not profoundly affect the increase in dopamine efflux in the medial prefrontal cortex induced by systemic administration of idazoxan, a finding which indicates that the facilitatory effect on cortical dopamine output elicited by α_2-adrenoceptor antagonism is, indeed, largely independent of the neuronal activity of ventral tegmental area dopamine cells. Although some α_2-adrenoceptor antagonists seem to stimulate the electrophysiological activity of midbrain dopamine neurons (see Grenhoff and Svensson, 1989), the present findings, collectively, suggest that the nerve terminal region is the major site of action of systemic idazoxan on basal dopamine efflux in the cortex.

Several mechanisms by which α_2-adrenoceptor antagonists may act at the terminal level to enhance cortical dopamine efflux have been suggested. Since the medial prefrontal cortex appears to exhibit a high density of α_2-adrenoceptor binding sites and previous data suggest that presynaptic α_2-heteroreceptors may regulate dopamine release in other brain areas, i.e., the hypothalamus, the effect of idazoxan may be a consequence of a direct heteroreceptor-mediated interaction on the dopaminergic nerve terminals (Ueda et al., 1983; Talley et al., 1996). In addition, idazoxan may affect dopamine levels in the medial prefrontal cortex indirectly through its ability to facilitate cortical noradrenaline efflux (Dennis et al., 1987). Since the noradrenaline transporter significantly contributes to the clearance of both noradrenaline and dopamine from the extracellular compartment within the cortex, an increase in cortical extracellular noradrenaline concentration, e.g., induced by blockade of inhibitory α_2-autoreceptors, would by itself secondarily contribute to

increase extracellular dopamine concentrations in the medial prefrontal cortex, i.e., by means of a competitive interaction between noradrenaline and dopamine for the same transporter (Carboni et al., 1990; Pozzi et al., 1994). It should, however, be mentioned that recent data demonstrate that the stimulatory effect of idazoxan on dopamine efflux in the medial prefrontal cortex can be prevented by lesions of the serotonergic system, a phenomenon which indicates a significant role also of serotonin in the mechanism of action of idazoxan in this regard (Matsumoto et al., 1998). Clearly, further work is necessary to clarify this matter.

4.2. Regional selectivity of α_2-adrenoceptor mediated modulation of dopamine levels

The regional differences in dopamine output observed after idazoxan administration may, at least partly, be related to differences in the distribution of central α_2-adrenoceptors. Thus, the pronounced effect of α_2 adrenoceptor antagonism on dopamine efflux in the medial prefrontal cortex as compared to the striatum is consistent with the dense noradrenergic innervation of the cortex and the high expression of α_2-adrenoceptors this area as opposed to the striatum (Ungerstedt, 1971; Talley et al., 1996). Interestingly, we found in consonance with previous data (Tanda et al., 1996) that idazoxan administration produced only a minor effect on dopamine levels in the nucleus accumbens, an effect which cannot be explained by a sparse noradrenergic input or by a low level of α_2-adrenoceptor expression. One reason for the lack of effect of idazoxan on dopamine output in the nucleus accumbens might be that the purported competition between dopamine and noradrenaline for the noradrenaline transporter seems less pronounced in subcortical regions, as previously indicated (Carboni et al., 1990; Pozzi et al., 1994). Significantly, a recent report indicates that the noradrenergic nerve terminals in the nucleus accumbens, in contrast to the terminals in the medial prefrontal cortex, appear to lack inhibitory α_2-adrenoceptor mediated autoregulation of neurotransmitter release (Schoffelmeer et al., 1998). Thus, if the effect of idazoxan on cortical dopamine output is, indeed, critically related to alterations in noradrenaline output (see above), it seems possible that the only modest effect of idazoxan on dopamine levels in the nucleus accumbens is a consequence of a relative failure to influence noradrenaline release in this area.

4.3. Therapeutic significance

Clinical studies have suggested that treatment with antagonists at α_2-adrenoceptors may improve depressive symptoms as well as augment the clinical action of neuroleptic drugs, particularly as regards negative symptoms in schizophrenia (Van Dorth, 1983; Davis and Wilde, 1996; Litman et al., 1996). Given the purported importance of cortical dopamine for the treatment of such symptoms as well as for cognitive functioning (see Brozoski et al., 1979; Weinberger, 1987; Svensson et al., 1993; Sawaguchi and Goldman-Rakic, 1994), the therapeutic usefulness of α_2-adrenoceptor antagonists in schizophrenia as well as depression might well be related to the ability to facilitate cortical dopamine efflux.

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