

## Nicotine produces antidepressant-like actions: Behavioral and neurochemical evidence

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### Abstract

Converging lines of evidence indicate the involvement of nicotinic acetylcholine receptors in depressive illness and antidepressant drug action. We investigated the effects of sub-chronic and chronic treatment with imipramine, nicotine and their combination on: (a) the ability of a dopamine-mimetic challenge to produce locomotor stimulation and (b) cortical density of  $\beta$ -adrenoceptors. One week of treatment with imipramine (10 mg/kg, twice daily) did not result in an altered response to the apomorphine (0.15 mg/kg) challenge, but after 2 weeks, the imipramine-treated rats demonstrated hyperactivity. Conversely, such increased locomotor response was observed in rats treated with nicotine (0.4 mg/kg, twice daily) for 1 but not for 2 weeks. Groups treated with nicotine + imipramine for 1 and 2 weeks demonstrated equally high hyperactivity in response to the apomorphine challenge. This effect was not different from the effects of 1-week treatment with nicotine or 2-week treatment with imipramine. The density of  $\beta$ -adrenoceptors was equally decreased by 2 (but not 1) weeks of the treatment with imipramine, nicotine and their combination. The present behavioral and neurochemical data suggest the antidepressant-like effect of the chronic treatment with nicotine. It appears that the potentiation of the dopamine-mimetic-induced hyperactivity cannot be explained by  $\beta$ -adrenoceptor down-regulation.

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### 1. Introduction

It is known that nicotinic acetylcholine receptors are involved in major depression and effects of antidepressant drugs. For instance, it has been postulated that nicotine may have antidepressant properties and that smokers self-medicate the underlying depression (Markou et al., 1998). Indeed, epidemiological findings suggest that smokers more often demonstrate depressive symptoms than non-smokers, and that depressed patients are less likely to cease smoking. Depressed smokers are more dependent on cigarettes, and smoking cessation is often followed by a

depressive episode. Smokers with a history of major depressive episode are more likely to relapse than smokers with no history of depression (see Picciotto et al., 2002) for the review). Furthermore, nicotine patches can improve the mood of depressed patients (Salin-Pascual et al., 1996), although it has been argued that in healthy smokers nicotine enhances mood by an alleviation of withdrawal distress (Parrott, 2003).

Preclinical data regarding this issue are ambiguous. For example, in the studies of Ferguson et al. (2000), nicotine appeared not to influence the learned helplessness response, though a subtype-selective nicotinic acetylcholine receptor agonist produced antidepressant-like effect. Perhaps more suggestive are studies on the Flinders Sensitive Line rats, regarded as a “genetic animal model of depression”. In these rats, which demonstrate an exaggerated immobility in

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drug-free state, acute or chronic administration of nicotine (0.4 mg/kg) significantly improved the performance in the forced swimming test (Tizabi et al., 1999). The most convincing results demonstrating antidepressant-like effect of nicotine were reported by Semba et al. (1998) who showed that the chronic treatment with nicotine produced antidepressant-like effects in the learned helplessness model of depression.

We have demonstrated recently that in the tail-suspension test in C57Bl/6J mice, nicotine did not produce antidepressant-like effects per se (0.8–1.2 mg/kg s.c. or i.p. 15–60 min before the test) but it dramatically potentiated the antidepressant-like actions of imipramine and citalopram. Specifically, co-administration of nicotine (0.8 mg/kg) to citalopram (2 mg/kg)-treated mice resulted in a robust decrease in immobility while the same dose of citalopram given with vehicle produced only a slight anti-immobility effect. Imipramine (4 mg/kg) did not affect immobility, but given in combination with 0.8 mg/kg of nicotine, it significantly reduced immobility (Popik et al., 2003). These findings suggested that acute administration of nicotine might enhance the antidepressant-like effects of imipramine and citalopram given acutely in a relatively simple screening procedure.

Although a behavioral test provides (to the greatest possible extent) an ultimate insight as to the overall effect of a treatment in a given model, in the majority of cases, it does not address the mechanism of action of that treatment (Willner, 1991). This is particularly evident in screening procedures, like the tail suspension test (Steru et al., 1985), which is characterized by a decent predictive, but not face and construct validity (Willner, 1991). This is because in the tail suspension test, like in the forced swim test (Porsolt et al., 1977), treatments with purported antidepressive actions are effective after a single administration that contrasts with their clinical efficacy appearing after at least 2 weeks of administration. For these reasons, we decided to investigate if nicotine might affect the behavioral and neurochemical alterations produced by chronic treatment with the antidepressant drug, imipramine.

At present, there is no doubt that a long-term (i.e.,  $\geq 2$  weeks) treatment with antidepressants produces gradually developing adaptations of pre- and post-synaptic neurotransmitter receptors, second messenger systems and changes in gene expression (see Skolnick, 1999; Vetulani and Nalepa, 2000; Duman, 2002 for the reviews). It is still disputable, which of these effects are the most common, characteristic, relevant and indicative of the antidepressant action. In fact, despite years of intense research, the causes of behavioral, neurochemical and molecular alterations induced by the treatment with antidepressants remain enigmatic.

The present experiments were carried out to investigate the effects of chronic treatment with imipramine with and without nicotine on: (a) behavioral response produced by apomorphine challenge (Spyraki and Fibiger, 1981), and (b)

the number of  $\beta$ -adrenoceptors (Banerjee et al., 1977). We decided to use these two assays, as they have long been regarded as indicative, at least in some cases, of the effects of antidepressant drugs given chronically.

## 2. Methods

### 2.1. Subjects

Male Wistar rats (Institute of Pharmacology Breeding Facility) weighing  $\sim 250$  g at the start of the experiments were used. The rats were housed in groups in standard laboratory cages and kept in a humidity- and temperature ( $21 \pm 2$  °C)-controlled colony room with a 12-h light/dark cycle (lights on from 07:00). Commercial food and tap water were available ad libitum. All rats were used only once.

### 2.2. Drugs

Imipramine HCl (ICN Polfa, Krakow, Poland), apomorphine HCl and (–)-nicotine hydrogen bitartrate (Sigma-Aldrich, Poznan, Poland) were dissolved in sterile saline (vehicle). When appropriate, pH was adjusted to 7.0 with 10 N NaOH solution. The drug or vehicle solutions were administered in a volume of 1 ml/kg. Imipramine, nicotine and apomorphine were administered at the doses of 10 (i.p.), 0.4 (s.c.) and 0.15 (s.c.) mg/kg, respectively. The dose of nicotine is expressed in terms of its free base concentration, for all other compounds, the doses were calculated as respective salts. The selection of doses was based on several grounds. Imipramine given repeatedly at the dose of 10 mg/kg produces reliable alterations in the response to apomorphine challenge (Serra et al., 1979) and down-regulates cAMP in response to norepinephrine (Nalepa and Vetulani, 1996). Our preliminary observations indicated that given repeatedly, the dose of 0.4 mg/kg of nicotine is the highest that produced no adverse impact on rat's health (body weight decrease). In naive rats, apomorphine at 0.15 mg/kg produces no significant alterations of locomotor activity (the dose of 0.05 and doses higher than 0.15 mg/kg produce locomotor inhibition and stimulation, respectively, unpublished results).

### 2.3. Design of experiments

First, we tested if 2 weeks of nicotine+imipramine treatment would have greater impact on locomotor activity evoked by the apomorphine challenge than that produced by the treatment with vehicle+imipramine. Control rats were similarly treated, but “challenged” with vehicle. Second, it was of interest to investigate if nicotine+imipramine treatment could facilitate the appearance of apomorphine-induced hyperactivity. To this end, the rats treated with

nicotine, imipramine and their combination for 1 week were challenged with apomorphine (but not vehicle, because we found that the 2-week treatment does not affect locomotor activity in vehicle-“challenged” rats).

The phenomenon of  $\beta$ -adrenoceptor down-regulation appears typically after at least 2 weeks of treatment with a majority of antidepressants (Vetulani and Nalepa, 2000). We tested if it appears in rats treated with nicotine, imipramine and their combination after 1 and 2 weeks of treatment.

#### 2.4. Apomorphine challenge: drug effects on locomotor activity

Four groups of rats were treated for 2 weeks, twice daily (08:30 and 18:00), with either vehicle+vehicle, nicotine+vehicle, vehicle+imipramine or nicotine+imipramine. Another four groups were treated for the first week with vehicle and for the next week with imipramine, nicotine and their combination (to keep the number of injections and thus the intensity of handling similar to the groups treated for 2 weeks). The last drug administration was in the evening preceding the apomorphine challenge. In the morning of the next day (~ 10:00), the rats were transferred for adaptation to the testing room at least 2 h prior to apomorphine administration. For this challenge, the 2-week treatment groups were further divided: a half of the rats received apomorphine (0.15 mg/kg) and the other half received vehicle. Ten minutes after vehicle or apomorphine challenge, the rats were placed individually in the activity cages for observation that lasted for 30 min. There were 9–10 rats per a given treatment condition.

Locomotor activity was measured in custom-made aluminum rectangular 50 × 50 × 25 cm (W × L × H) activity cages under low illumination. Two pairs of photocell beams automatically recorded gross movements; due to the construction of apparatus, the minor repetitive movements (that would reflect stereotypies) were not recorded. Photocells were located 1.5 cm above the floor of the apparatus and the beams crossed each other in its center.

#### 2.5. $\beta$ -Adrenoceptor assay

At the end of 1 and 2 weeks of treatment, 12–16 h after the last dose of imipramine, nicotine and their combination, the rats were killed by decapitation, their brains were removed and cerebral cortices dissected. The membrane preparation (P2 fraction) was obtained by homogenization of the tissue in 20 volumes of 50 mM Tris–HCl buffer, pH 7.5, using a Polytron homogenizer (at 7000 rpm, for 30 s), as described by Nalepa and Vetulani (1991). The supernatant after centrifugation of the homogenate (1000 × g, 10 min) was re-homogenized at 25,000 × g for 30 min, the resulting pellet was re-suspended and re-centrifuged under the same conditions, and the preparation was stored at –20 °C until incubation.

Homogenization and centrifugation were carried out at 0–4 °C. Immediately before the assay, the pellet was reconstituted in 50 mM Tris–HCl buffer, pH 7.6, to obtain the final concentration of protein of approximately 0.42 mg/ml (assayed using the method of Lowry et al., 1951).

The  $\beta$ -adrenoceptors were labeled with 6 concentrations (ranging from 0.09 to 3.12 nM) of [<sup>3</sup>H]CGP 12177 (S.A. 48 Ci/mM, Amersham) and 10  $\mu$ M propranolol (Sigma Co.) was used to define nonspecific binding in the assay. The final incubation mixture contained 450  $\mu$ l of membrane suspension, 50  $\mu$ l of radioligand, and 50  $\mu$ l of Tris–HCl buffer or of solution of displacer. The incubations were carried out at 25 °C for 30 min in a water bath shaker, and were terminated by vacuum-assisted filtration through Whatman GF/C filters. The filters were then rinsed twice with 5-ml portions of ice-cold Tris–HCl buffer, placed in polyethylene minivials in 3 ml of Akwascent solution (BioCare, Poland), and radioactivity was counted in a Beckman LS 6500 liquid scintillation counter ([<sup>3</sup>H] channel).

#### 2.6. Data presentation and statistics

Locomotor activity data (in arbitrary units per 30 min) were used for statistical analyses. The density of  $\beta$ -adrenoceptors was expressed as  $B_{\max}$  [fmol/mg protein] and their affinity as  $K_D$  [nM].  $B_{\max}$  and  $K_D$  values were calculated from saturation isotherm using GraphPad Prism v. 4 software. Statistical analyses involved a three-way analysis of variance (ANOVA) with weeks (1 or 2), imipramine and nicotine presence and interactions as well as subsequent two-way ANOVA for each treatment duration with nicotine, imipramine and interaction factors. Newman–Keul’s test was used as a post-hoc test. A  $P < 0.05$  was considered significant. Statistica 5.0 for Windows was used throughout.

#### 2.7. Ethics

All experiments were carried out according to the National Institutes of Health Guide for the Care and Use of Laboratory Animals (revised 1996) and were approved by the Animal Care and Use Bioethics Commission, Institute of Pharmacology, Polish Academy of Sciences in Krakow.

### 3. Results

#### 3.1. Locomotor response to apomorphine challenge

Neither nicotine nor imipramine given separately or in combination for 2 weeks produced any changes in the basal (saline-induced) locomotor activity. The locomotor activity counts for the treatment with vehicle+vehicle, nicotine+

vehicle, vehicle+imipramine or nicotine+imipramine, were  $198 \pm 24.2$ ,  $182.6 \pm 13.95$ ,  $177.4 \pm 16.26$  and  $136.2 \pm 19.02$  arbitrary units, respectively (ANOVA:  $F(3,35)=1.88$ ,  $P>0.05$ ,  $N=9-10$ ).

Fig. 1 shows that nicotine administration for 1 week produced an increase in the responsiveness to apomorphine, and this effect disappeared after 2 weeks of treatment. On the contrary, twice daily administration of imipramine caused a slowly developing hyper-responsiveness to apomorphine, which became significant only after 2 weeks of treatment. The combined administration of nicotine and imipramine resulted in hyperactivity that was already developed after 1 week, and remained significant after 2 weeks of treatment.

### 3.2. Effect of treatments on $\beta$ -adrenoceptors

Neither nicotine nor imipramine administered separately or in combination for 1 week produced any changes in  $\beta$ -adrenoceptor density and affinity (Table 1). On the contrary, 2 weeks of treatment with nicotine or imipramine, as well as with their combination significantly decreased the density of  $\beta$ -adrenoceptor binding sites in the cerebral cortex, by 21%, 33%, 25%, respectively, compared to the vehicle control. Neither

Table 1

Effects of the treatment with imipramine, nicotine and their combination for 1 and 2 weeks on  $\beta$ -adrenoceptor binding sites in the rat cerebral cortex.

Treatment	1 week		2 weeks	
	$B_{\max}$	$K_D$	$B_{\max}$	$K_D$
VEH+VEH	$102.65 \pm 5.72$	$0.38 \pm 0.05$	$115.48 \pm 6.12$	$0.47 \pm 0.04$
NIC+VEH	$109.27 \pm 9.59$	$0.42 \pm 0.08$	$91.10 \pm 5.38^a$	$0.46 \pm 0.05$
VEH+IMI	$102.31 \pm 10.17$	$0.44 \pm 0.07$	$77.44 \pm 5.93^a$	$0.57 \pm 0.05$
NIC+IMI	$104.20 \pm 8.23$	$0.49 \pm 0.13$	$86.51 \pm 4.56^a$	$0.59 \pm 0.08$

$B_{\max}$  data are expressed as the mean  $\pm$  S.E.M. fmol/mg protein, and  $K_D$  data as the mean  $\pm$  S.E.M. nM from 6 (for 1 week) or 9–10 (for 2 weeks) independent assays. The  $\beta$ -adrenoceptor sites were labeled with six concentration of [ $^3$ H]CGP 12177, ranging from 0.090 to 2.91 nM (for 1 week) or 0.099 to 3.12 nM (for 2-week treatment). Propranolol (10  $\mu$ M) was used to define nonspecific binding in this assay. Three-way ANOVA demonstrated significant effect of the WEEKS  $F(1,54)=7.69$ ,  $P<0.01$ , IMIPRAMINE  $F(1,54)=4.50$ ,  $P<0.05$ ; and WEEKS  $\times$  IMIPRAMINE interaction  $F(1,54)=5.15$ ,  $P<0.05$ . The separate two-way ANOVA carried out on the data from 2-week treatment ( $B_{\max}$  data) demonstrated significant effect of IMIPRAMINE  $F(1,35)=14.29$ ,  $P<0.001$  with significant interaction NICOTINE  $\times$  IMIPRAMINE  $F(1,35)=8.79$ ,  $P<0.01$ . No other factors or interactions yielded significant results. Symbols: VEH—saline control; NIC—nicotine; IMI—imipramine.

<sup>a</sup>  $P<0.01$  versus corresponding VEH.

treatment affected the  $K_D$  coefficient of this radioligand for the  $\beta$ -adrenoceptor.

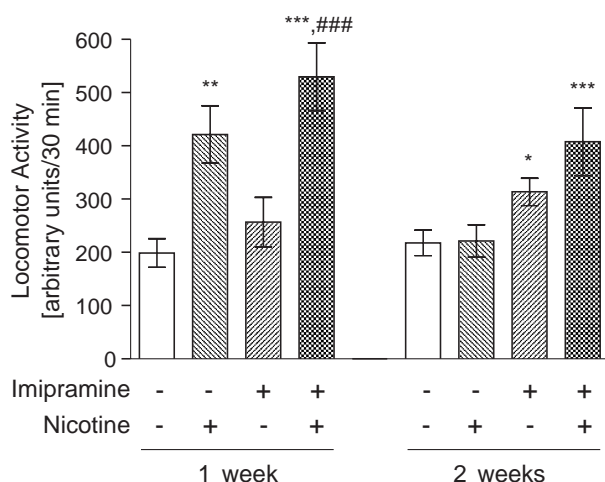


Fig. 1. Effects of the treatment with imipramine, nicotine and their combination for 1 and 2 weeks on locomotor activity evoked by apomorphine. Data are expressed as the mean  $\pm$  S.E.M. arbitrary units per 30 min. Three-way ANOVA demonstrated significant effect of the WEEKS  $F(1,74)=4.07$ ,  $P<0.05$ , IMIPRAMINE  $F(1,74)=13.47$ ,  $P<0.001$ ; NICOTINE  $F(1,74)=23.64$ ,  $P<0.001$  and WEEKS  $\times$  NICOTINE interaction  $F(1,74)=10.62$ ,  $P<0.01$ . Separate two-way ANOVAs demonstrated significant effects of NICOTINE  $F(1,33)=23.89$ ,  $P<0.001$  (1-week data) and IMIPRAMINE  $F(1,41)=14.98$ ,  $P<0.001$ , (2-week data). Other factors or interactions were not significant. Symbols: \* $P<0.05$ , \*\* $P<0.01$ , \*\*\* $P<0.001$  versus the effect of corresponding vehicle; ### $P<0.001$  versus the effect of corresponding dose of imipramine. There was no difference between the effect of 1 and 2 weeks of treatment for groups treated with imipramine+nicotine.  $N=9-10$  per each condition.

### 4. Discussion

Extending our earlier studies, which demonstrated a potentiation of antidepressant-like action of imipramine by nicotine in a screening test in mice (Popik et al., 2003), we now report that 1- and 2-weeks of treatment with nicotine produced, respectively, behavioral and neurochemical manifestations characteristic of antidepressant-like actions in rats.

The potentiation of apomorphine-induced hyperactivity, regarded as a characteristic effect of antidepressants (Spyraki and Fibiger, 1981), was observed after 2 weeks of chronic treatment with imipramine and after 1-week of the treatment with a combination of nicotine and imipramine. Similar though transient increase in the responsiveness to apomorphine was produced by 1-week (sub-chronic) administration of nicotine alone. These behavioral data may indicate that nicotine itself induces transient antidepressant-like effect that disappears due to some presently unknown adaptive process. This first main finding of the present study may suggest that stimulation of nicotinic cholinergic receptors at the beginning of therapy with antidepressants would accelerate the appearance of the antidepressant effects. The second main finding demonstrates a decreased density of cortical  $\beta$ -adrenoceptors due to chronic treatment with nicotine. The phenomenon of  $\beta$ -adrenoceptor “down-regulation” since long has been regarded as characteristic of the action of most



(though not all) clinically active antidepressants (Banerjee et al., 1977). In addition, most of compounds that have no antidepressant properties do not cause  $\beta$ -adrenoceptor down-regulation. However, there are some examples of “false-positives”, e.g., some agonists of  $\beta$ -adrenoceptor, such as clenbuterol (Ordway et al., 1987) may produce this phenomenon. This may, however, result from their direct interaction with  $\beta$ -adrenoceptor, as, conversely,  $\beta$ -adrenoceptor antagonists produce an up-regulation of the system (Takita et al., 1995). The “false-positives”, which are infrequent, may be, therefore, explained by some specific actions of those drugs. While nicotine does not interact with  $\beta$ -adrenoceptors, it may be supposed that its action reflects an adaptation to nicotine-induced increase in norepinephrine availability.

The fact that chronic treatment with nicotine produces  $\beta$ -adrenoceptor “down-regulation” supports the epidemiological observations in humans discussed in the Introduction section, and in our view is the first demonstration of neurochemical antidepressant-like effects of long-term administration of nicotine in Wistar rats.

Prolonged treatment with several antidepressant drugs produces a number of neuroadaptations (Skolnick, 1999; Nalepa and Sulser, 2004). While apomorphine-induced potentiation of locomotor activity apparently reflects an adaptation of dopaminergic neurotransmission, the phenomenon of  $\beta$ -adrenoceptor “down-regulation” has been regarded as an alteration of norepinephrine system.

Although it has been demonstrated long ago that a prolonged treatment with at least some antidepressants produces the hypersensitivity of the mesolimbic dopamine system at the behavioral level (Spyraki and Fibiger, 1981; Maj et al., 1984; Plaznik and Kostowski, 1987), the involvement of dopamine in melancholia and antidepressant drug action remains one of the less understood phenomena in contemporary psychopharmacology. In vivo microdialysis studies demonstrated that several antidepressants increased the extracellular levels of dopamine (Ainsworth et al., 1998), particularly in response to a dopamine-mimetic challenge (Nomikos et al., 1991). It was suggested that this phenomenon was related to an increased expression of pre- and post-synaptic dopamine D2 receptors in the nucleus accumbens (Dziedzicka-Wasylewska, 1997; Ainsworth et al., 1998). Unfortunately, the mechanisms leading to these changes have not been elucidated.

Similarly, the prolonged treatment with nicotine produces adaptations of the dopaminergic system, as, for instance, it is known to increase extracellular concentrations of dopamine in mesolimbic areas (Damsma et al., 1989). This is most likely due to the fact that activation of pre-synaptic nicotinic acetylcholine receptors evokes the vesicular release of dopamine (e.g. Grady et al., 1992, see Wonnacott, 1997 for the review), and, in addition, at least in some brain regions, the nicotinic receptors can regulate the release of dopamine via the dopamine transporter (Drew et al., 2000).

Depending on the schedule of exposure to nicotine and the experimental settings, the effects of nicotine on dopamine transmission do not change, tolerate or sensitize (reviewed by Di Chiara, 2000). In our studies, 1-week treatment with nicotine produced a robust behavioral response to the apomorphine challenge; however, in rats treated with nicotine for 2 weeks, this behavioral manifestation was gone. It is unlikely that this was due to the development of tolerance to nicotine actions (Damsma et al., 1989); one may only speculate that another alteration counteracting the adaptation of dopaminergic system to chronic nicotine has occurred.

The “down-regulation” of  $\beta$ -adrenoceptor system has been frequently observed after chronic treatment with antidepressants, in particular, those with strong norepinephrinergic component of their action (Nalepa and Sulser, 2004). Although the mechanism responsible for the down-regulation of  $\beta$ -adrenoceptors is not fully understood (see Skolnick, 1999; Nalepa and Sulser, 2004 for the reviews), it is usually explained as an adaptation to the increased availability of norepinephrine in synaptic cleft. In the present study, 2-week treatment with nicotine decreased  $\beta$ -adrenoceptor density in the cerebral cortex to the similar extent, as did imipramine. Since no changes were observed after 1 week of the treatment, this effect can be considered to be nicotine-induced slow adaptation of  $\beta$ -adrenoceptors, similar to that produced by imipramine. While imipramine increases the availability of synaptic norepinephrine by inhibiting its reuptake, nicotine enhances norepinephrine release through stimulation of acetylcholine receptors in the brain cortices of rats (Rao et al., 2003) and humans (Amtage et al., 2004). Since the combined treatment lowered the density of  $\beta$ -adrenoceptors to the similar extent as that produced by nicotine and imipramine given separately, it is likely that both drugs affected similar norepinephrinergic mechanism to evoke “down-regulation” of  $\beta$ -adrenoceptors. One also cannot exclude the possibility that combinations of lower doses of imipramine and nicotine may act synergistically, as was reported in the studies with the tail suspension test (Popik et al., 2003).

We report an apparent discrepancy between the effect of nicotine and imipramine in a behavioral test (rapid though transient effect of nicotine, and slowly developing though sustained effect of imipramine) and neurochemical assay (nicotine acting as slowly as imipramine). These findings suggest that the early behavioral response induced by nicotine could be due to its adaptive action on dopaminergic system, while the antidepressant-like effect of imipramine, requiring more time to develop, could be rather due to the adaptation of norepinephrine system. Although the present data do not provide evidence that adaptations of dopaminergic and norepinephrinergic systems depend on each other, this does not exclude the possibility that both those mechanisms may participate in the antidepressant action of each treatment.

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