Reboxetine Modulates the Firing Pattern of Dopamine Cells in the Ventral Tegmental Area and Selectively Increases Dopamine Availability in the Prefrontal Cortex

LOVE LINNÉR, HANNA ENdersZ, DANIEL ÖHMAN, FINN BENGTSSON, MARTIN SCHALLING, and TORGNY H. SVENSSON

Section of Neuropsychopharmacology, Department of Physiology and Pharmacology, Karolinska Institutet, Stockholm, Sweden (L.L., T.H.S.); Division of Clinical Pharmacology, Department of Medicine and Care, University Hospital, Linköping, Sweden (D.O., F.B.); and Neurogenetics Unit, Department of Molecular Medicine, Karolinska Hospital, Stockholm, Sweden (M.S.)

Received October 26, 2000; accepted January 18, 2001 This paper is available online at http://jpet.aspetjournals.org

ABSTRACT

Central dopaminergic neurons have been suggested to be involved in the pathophysiology of several psychiatric disorders, including depression, and appear to be modulated by noradrenergic activity both at the nerve terminal level and at the somatodendritic level. In recent years reboxetine, a selective noradrenaline reuptake inhibitor that differs from tricyclic antidepressants by its low affinity for muscarinic, cholinergic and $\alpha_1$-adrenergic receptors, has been introduced clinically. In the present study the effect of reboxetine on the function of the mesolimbocortical dopamine system was investigated by means of single cell recording and microdialysis in rats following administration of reboxetine in doses that appear to yield clinically relevant plasma concentrations. Reboxetine (0.625–20 mg/kg intravenously) induced an increase in burst firing, but not in average firing frequency of dopamine (DA) cells in the ventral tegmental area (VTA). Moreover, reboxetine (0.15–13.5 mg/kg intraperitoneally) caused a significantly enhanced DA output in the medial prefrontal cortex, whereas no effect was observed in the nucleus accumbens. Local administration of reboxetine (333 $\mu$M, 60 min), by means of reversed microdialysis into these brain regions, caused a significant increase in DA output in both brain regions. However, local administration of reboxetine into the VTA (333 $\mu$M, 60 min) did not affect DA availability in these terminal areas. Our results imply that clinical treatment with reboxetine may result in facilitation of both prefrontal DA output and the excitability of VTA DA neurons, effects that may contribute to its antidepressant action, especially on drive and motivation.

The mesolimbocortical dopamine (DA) system has, based on pharmacological evidence, been suggested to be implicated in the pathophysiology of depression as well as schizophrenia (Carlsson, 1988) and one common effect of acute treatment with several antidepressant drugs with different primary mechanisms of action is an augmentation of extracellular DA availability in the prefrontal cortex of rats (Tanda et al., 1994). This effect is also exerted by many atypical antipsychotic drugs. Central noradrenaline (NA) neurons, which mainly originate in the locus coeruleus, interact with the mesolimbocortical DA system (Andén and Grabowska, 1976) both at the terminal level (Tassin, 1992) and at the cell body level, i.e., the ventral tegmental area (VTA; Hervé et al., 1982; Grenhoff et al., 1993, 1995). Previously, systemic administration of the NA reuptake-inhibiting, tricyclic antidepressant drug desipramine has been found to increase extracellular DA output preferentially in the prefrontal cortex (Carboni et al., 1990), although upon local application an effect was seen also in the nucleus accumbens (NAC; Li et al., 1996; Yamamoto and Novotney, 1998). Both physiological and pharmacological evidence shows that the noradrenergic control of the mesolimbocortical DA neurons in the VTA specifically regulates burst firing (Grenhoff and Svensson, 1989; Grenhoff et al., 1993; Shi et al., 2000), a functional mode of these neurons that, in turn, is driven by glutamatergic afferents acting at somatodendritic $N$-methyl-$d$-aspartate receptors associated with the DA neurons (Chergui et al., 1993). Interestingly, when locally applied through microiontophoresis onto VTA neurons NA elicits a nonhomogenous although mainly inhibitory effect on the average firing frequency of individual neurons (Aghajanian and Bunney, 1977), an inhibition that may be attributable to activation of somatodendritic DA-D$_{2}$ autoreceptors (White and Wang, 1984). However, following blockade of these autoreceptors, an $\alpha_1$-adrenoceptor-mediated excitatory effect on the DA neurons in the VTA is observed in a majority of the cells (Grenhoff et al., 1995).

ABBREVIATIONS: DA, dopamine; NA, noradrenaline; VTA, ventral tegmental area; NAC, nucleus accumbens; REB, reboxetine; NRI, noradrenaline reuptake inhibitor; mPFC, medial prefrontal cortex; SSRI, selective serotonin reuptake inhibitor.
The new antidepressant drug reboxetine (REB; Montgomery, 1997) is a selective NA reuptake inhibitor (NRI), which unlike the tricyclic antidepressants has low affinity for the muscarinic, cholinergic, and α₁-adrenergic receptor families (Wong et al., 2000). The present study was designed to characterize the effects of this selective NA reuptake inhibitor on the somatodendritic and terminal regions of the mesolimbocortical DA system in the rat. By means of extracellular single cell recording and in vivo microdialysis the effects of acutely administered REB on the firing characteristics of DA neurons in the VTA, as well as on DA release in the medial prefrontal cortex (mPFC) and NAC were analyzed, following both systemic and local drug administration. The plasma concentrations achieved by systemic administration of REB were also measured.

Materials and Methods

All experiments were performed in strict accordance with the guidelines and consent of the local ethical committee (Stockholms Nurr och Södra Försöksdjursetiska Kommittén).

Electrophysiology

Single cell recording in vivo from identified midbrain DA neurons in the VTA was performed in rats, essentially as previously described (Murase et al., 1993a). Anesthetized (chloral hydrate, 400 mg/kg i.p.) male Sprague-Dawley rats (BK Universal, Sollentuna, Sweden) weighing 230 to 300 g were mounted in a stereotaxic frame. A hole was drilled in the skull above the VTA and a recording electrode, filled with a solution of 2% Pontamine sky blue dissolved in 0.06 M sodium acetate, was lowered into the brain by means of a hydraulic microdrive. Surgical anesthesia was maintained throughout the experiment and body temperature was kept at 36.5–37.5°C by means of an electric heating pad. Before initiation of the experiments a tail vein catheter for i.v. injections was inserted. Putative VTA DA cells, with the typical characteristics of identified DA neurons previously described (Grace and Bunney, 1984), were usually encountered 2.8 to 3.2 mm anterior and 0.8 to 1.0 mm lateral to lambda at a depth of 7.5 to 8.5 mm from brain surface. At the end of an experiment, a cathodal current (5 to 8.5 mA) was passed through the electrode leaving a blue dye spot, which later was used to identify the location of the recording site in slices stained with neutral red. The location of the probe(s) was later verified in slices stained with neutral red.

Plasma Concentrations of Reboxetine

Male BKL:WR (Wistar) rats (BK Universal) weighing 280 to 310 g were administered REB (0.15–13.5 mg/kg i.p.). Thirty minutes later rats were anesthetized (sodium pentobarbital, 90 mg/kg i.p.) and blood was collected (heart puncture) in test tubes containing one drop of heparin (500 IU/ml), which was put on ice. After centrifugation (2500 rpm, 4°C, 25 min), the supernatant was collected and frozen. Concentrations of racemic reboxetine in plasma were subsequently analyzed. One milliliter of plasma was extracted using solid phase extraction columns C2. The final extract was evaporated to dryness and resolved in 100 μl of the mobile phase of the high pressure liquid chromatography analytical system (27% acetonitrile in 10 mM phosphate buffer, pH 4.9). The resolved extract (25 μl) was then injected on to the Zorbax Eclipse XDB-phenyl analytical column and detected with UV detection at 210 nm. The analytical methodology showed a good correlation coefficient (r² > 0.99). The intercept and standard deviation of variance was below 5% and the limit of quantification was 5 nM (Ohman et al., 2001).

Drugs

Reboxetine (Pharmacia Corporation, Kalamazoo, MI) was dissolved in saline or perfusion solution. In electrophysiological experiments REB (0.625–20 mg/kg i.v.) was administered in cumulative doses starting at 0.625 or 5 mg/kg 3 to 4 min after saline injection with subsequent intervals of 3 to 4 min. Systemic or local administration of drug (i.p. injection (1.0 ml/kg) or via reversed microdialysis) during microdialysis experiments was performed after a stable baseline (<15% variation) of dopamine outflow had been established.

Representation and Analysis of Data

Electrophysiology. Firing rate and burst firing values are presented as mean ± S.E.M. The effects of REB on firing characteristics were evaluated by Student’s t test for dependent samples. The effect at each dose was compared with baseline, which was defined as the neuronal activity recorded after saline injection. A two-tailed P value less than 0.05 was considered significant.

Microdialysis. Data were calculated as average percentage of change in extracellular concentration of DA compared with baseline. Baseline (=100%) was defined as the average of the last two pre-injection values. Data obtained from microdialysis in the NAC (15-min samples) were converted to 30-min values to facilitate comparison with data from the mPFC. The effect of acute administration of REB was evaluated both over the whole time course (Figs. 3B and 4) of the experiment and as the mean of two (Table 1) or four (Fig. 3A) consecutive samples following administration. Data were statisti-
TABLE 1
Dopamine levels (percentage of baseline) during local administration of reboxetine

<table>
<thead>
<tr>
<th>Area</th>
<th>Concentration (μM)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>33</td>
<td>100</td>
</tr>
<tr>
<td>NAC</td>
<td>114.6 ± 5.0**</td>
<td>106.3 ± 4.4**</td>
<td>143.8 ± 10.2***</td>
</tr>
<tr>
<td>mPFC</td>
<td>137.6 ± 10.2 (4)</td>
<td>149.7 ± 10.5 (3)</td>
<td>179.5 ± 15.9***</td>
</tr>
</tbody>
</table>

**P < 0.05, ***P < 0.001, F(3,10) = 9.45, P < 0.01; F(NAC; 5,20) = 14.06, P < 0.001.


cally analyzed using one- (treatment) and two-way (treatment × time) ANOVA for repeated measures followed by Newman-Keuls test for multiple comparisons with a criterion of P < 0.05 to be considered significant.

Results

Effects of REB on Firing Characteristics of Dopaminergic Neurons in VTA. The mean firing frequency and burst firing of DA cells in the VTA was 4.82 ± 0.29 Hz and 23.74 ± 5.30%, respectively (n = 22). Intravenous administration of REB in cumulative doses (0.625–20 mg/kg) did not exert any significant effect on firing frequency (Fig. 1A). The response of individual cells to low (0.625–2.5 mg/kg i.v.) and high doses of REB (5–20 mg/kg i.v.) was either an increase (+10%; n = 6 and 7, respectively) but also no effect (±10%; n = 8 and 4, respectively) or a decrease (10%; n = 4 and 3, respectively) in firing frequency. In contrast, reboxetine consistently and significantly increased burst firing in VTA DA cells at all but the two lowest doses tested (Fig. 1B).

Effects of Systemic Administration of REB on Terminal DA Output. The mean baseline concentrations (fmol/min ± S.E.M) of DA in the mPFC and the NAC were 0.41 ± 0.05 (n = 35) and 2.31 ± 0.25 (n = 33) fmol/min, respectively (data not corrected for in vitro dialysis probe recovery). Saline injections failed to significantly affect DA extracellular concentrations in both areas investigated. Acute administration of REB significantly increased DA output in the mPFC. No significant effect was observed in the NAC (Figs. 3 and 4A).

Effects of Local and Intra-VTA Administration of REB on Terminal DA Output. Local administration of REB (333 μM, 60 min) via the dialysis probe significantly increased extracellular concentrations of DA both in the mPFC and the NAC (Fig. 4B). Local administration of lower doses of REB (33 and 100 μM, 60 min) caused an increase in DA availability in the mPFC at both concentrations, but in the NAC only at 100 μM (Table 1). Intra-VTA administration of REB (333 μM, 60 min) failed to significantly affect DA output in both the mPFC and the NAC (Fig. 4C).

Effects of Systemic Administration of REB on Plasma Concentrations of Drug. Thirty minutes after i.p. injection of REB (0.15, 0.67, 3.0, and 13.5 mg/kg) detectable plasma levels of the drug were obtained (Fig. 5).

Discussion

In the present study we demonstrate that systemic administration of the selective NRI reboxetine preferentially increases burst firing of dopaminergic neurons in the VTA, and moreover, that no significant effect on average firing frequency is obtained (Figs. 1 and 2). These findings are consistent with recently published results showing a similar effect of the NRI nisoxetine (Shi et al., 2000) as well as previous data showing a stimulatory effect on dopaminergic burst firing by administration of α2-adrenoceptor antagonists (Grenhoff and Svensson, 1989, 1993), drugs that also increase extracellular concentrations of NA (Dennis et al., 1987). Thus, systemic administration of two different types of drugs that both act to enhance central NA availability in NA terminal areas preferentially increases burst firing in ventral tegmental DA neurons with almost negligible effects on average firing frequency. In contrast, drugs that diminish central NA tone have been found to exert an opposite effect (Grenhoff and Svensson, 1989, 1993). A stimulatory effect of locally released NA in the VTA on postsynaptic α2-adrenoceptors located on DA neurons has been suggested to at least partially explain these observations (Grenhoff et al., 1993), and under concomitant D2 blockade, application of NA in vitro produces indeed an α2-adrenoceptor-mediated stimulatory effect in approximately 60% of DA neurons in the VTA.
The facilitated burst firing mode of VTA DA neurons that can be elicited by $\alpha_1$-adrenoceptor activation may generally fit the typical characteristics of $\alpha_1$-receptors as being modulatory, serving to enhance excitation from other afferents (Aghajanian, 1985). In cases of the DA neurons in the VTA such excitatory input may be provided by glutamatergic afferents, originating from several areas, including the prefrontal cortex (Sesack and Pickel, 1992; Chergui et al., 1993; Murase et al., 1993b). In contrast to the above-mentioned findings, local application of NA onto VTA DA neurons without concomitant D2 blockade may cause inhibition of the firing frequency of the DA neurons via D2 receptor activation (Aghajanian and Bunney, 1977; White and Wang, 1984; Grenhoff et al., 1995). However, in spite of the fact that systemic (Reith et al., 1997) as well as local intra-VTA administration (Chen and Reith, 1994) of the NRI desipramine has been found to increase the extracellular concentration of both NA and DA in the VTA, systemic administration of NRIs, which basically serve to facilitate the physiological effect of endogenous NA, does not cause any inhibitory effect on VTA DA neurons (Figs. 1 and 2; Shi et al., 2000). Thus, the excitatory, $\alpha_1$-adrenoceptor-mediated effect of NRIs on the DA neurons appears to be of predominant importance during systemic drug treatment.

The burst facilitating effect of specific NA reuptake inhibitors such as REB on DA neurons may also be related to an $\alpha_1$-adrenoceptor-mediated increase in the activity of glutamatergic input to the VTA, e.g., originating in the prefrontal cortex (Darracq et al., 1998; Zhang et al., 1999). Such an effect should cause stimulation of burst firing in VTA neurons through activation of N-methyl-D-aspartate receptors on the VTA DA neurons (Chergui et al., 1993). In consonance with this interpretation, both our present (Fig. 3C) and previous data (Hertel et al., 1999) fail to demonstrate any stimulatory (or inhibitory) effect of NRIs or $\alpha_2$-adrenoceptor antagonists on terminal output of DA when administered locally into the VTA. Still, considering the fact that electrophysiological experiments were performed in anesthetized animals, whereas microdialysis was performed in awake, freely moving rats, comparisons between the two experiments should be done with caution. Nevertheless, our results indicate that local augmentation of noradrenergic neurotransmission within the VTA may not cause any major effect on basal dopaminergic activity, at least as indirectly assessed by means of microdialysis. Yet, even if baseline activity of the DA neuron may not be significantly affected, the excitability of the cells may still be enhanced (cf. above) through facilitation of excitatory input. The magnitude of such an effect from other afferents (Aghajanian, 1985). In cases of the DA neurons in the VTA such excitatory input may be provided by glutamatergic afferents, originating from several areas, including the prefrontal cortex (Sesack and Pickel, 1992; Chergui et al., 1993; Murase et al., 1993b). In contrast to the above-mentioned findings, local application of NA onto VTA DA neurons without concomitant D2 blockade may cause inhibition of the firing frequency of the DA neurons via D2 receptor activation (Aghajanian and Bunney, 1977; White and Wang, 1984; Grenhoff et al., 1995). However, in spite of the fact that systemic (Reith et al., 1997) as well as local intra-VTA administration (Chen and Reith, 1994) of the NRI desipramine has been found to increase the extracellular concentration of both NA and DA in the VTA, systemic administration of NRIs, which basically serve to facilitate the physiological effect of endogenous NA, does not cause any inhibitory effect on VTA DA neurons (Figs. 1 and 2; Shi et al., 2000). Thus, the excitatory, $\alpha_1$-adrenoceptor-mediated effect of NRIs on the DA neurons appears to be of predominant importance during systemic drug treatment.

The burst facilitating effect of specific NA reuptake inhibitors such as REB on DA neurons may also be related to an $\alpha_1$-adrenoceptor-mediated increase in the activity of glutamatergic input to the VTA, e.g., originating in the prefrontal cortex (Darracq et al., 1998; Zhang et al., 1999). Such an effect should cause stimulation of burst firing in VTA neurons through activation of N-methyl-D-aspartate receptors on the VTA DA neurons (Chergui et al., 1993). In consonance with this interpretation, both our present (Fig. 3C) and previous data (Hertel et al., 1999) fail to demonstrate any stimulatory (or inhibitory) effect of NRIs or $\alpha_2$-adrenoceptor antagonists on terminal output of DA when administered locally into the VTA. Still, considering the fact that electrophysiological experiments were performed in anesthetized animals, whereas microdialysis was performed in awake, freely moving rats, comparisons between the two experiments should be done with caution. Nevertheless, our results indicate that local augmentation of noradrenergic neurotransmission within the VTA may not cause any major effect on basal dopaminergic activity, at least as indirectly assessed by means of microdialysis. Yet, even if baseline activity of the DA neuron may not be significantly affected, the excitability of the cells may still be enhanced (cf. above) through facilitation of excitatory input. The magnitude of such an effect

Fig. 2. Effects of intravenous administration of reboxetine on the firing pattern of a VTA DA cell as shown by a ratemeter recording (top) and sequential interspike time interval histograms (500 spikes, A–C; bottom). Burst firing is illustrated by black columns. Drug injections indicated at arrows.

Fig. 3. A, effect of systemic i.p. administration of reboxetine (0.15–13.5 mg/kg) on average dopamine availability in the NAC (□) and the mPFC (○) during four consecutive samples after injection (n = 7). B, effect of systemic administration of reboxetine (3 mg/kg i.p., n = 7) on dopamine availability in the NAC (□) and mPFC (○). Arrow indicates injection of reboxetine. Data are presented as the mean ± S.E.M. percentage of baseline and were analyzed by one-way (concentration) (A) and two-way (area × time) ANOVA (B) followed by Newman-Keuls test for multiple comparisons. For A, F(area) = 12.18, P < 0.001; F(time) = 0.87, P = 0.50. For B, F(area) = 40.00, P < 0.001; F(time) = 13.10, P < 0.001; and F(area × time) = 12.6, P < 0.001. ***P < 0.001 compared with saline injection (A) and baseline (B) and **P < 0.001 compared between mPFC and NAC.
might, in turn, depend on the endogenous tone of these inputs. At any rate, since local administration of amphetamine into the VTA has, indeed, been found to cause a stimulatory effect on DA output in terminal areas (Pan et al., 1996) this issue remains, as yet, to be definitely resolved. Tentatively both cortical and subcortical α1-adrenoceptors may contribute to the preferential stimulation of burst-like firing in VTA DA neurons following administration of NRIs. Generally, the facilitatory effect of NRIs on central DA neurons contrasts the effect of selective serotonin reuptake inhibitors (SSRIs), which following acute administration cause inhibition of dopaminergic neuronal activity in the VTA (Prisco and Esposito, 1995).

Systemic administration of REB also increased extracellular DA concentrations in the mPFC, but not in the NAC (Figs. 3 and 4A). These results are supported by several previous studies showing a substantial effect of systemic administration of NRIs on central DA output, particularly in the mPFC (Carboni et al., 1990; Tanda et al., 1994) with small or absent effects in the NAC (Nomikos et al., 1991; Tanda et al., 1994; Reith et al., 1997). The elevated extracellular levels of DA in the mPFC may be due to inhibition of DA reuptake by the NA transporter in areas where NA terminals are in abundance, such as the mPFC (Tanda et al., 1997; Yamamoto and Novotney, 1998). Consequently, regional variations in the density of the NA innervation may largely explain the differential effects of systemically administered NRIs on extracellular DA concentrations in the mPFC and the NAC, respectively. In contrast, local administration of NRIs in the NAC caused an increase in DA extracellular availability (Fig. 4B; Table 1; Li et al., 1996; Yamamoto and Novotney, 1998). The discrepancy between the effects of systemically and locally administered REB on extracellular accumbal DA levels may have several explanations. First, the tissue concentration of the drug during local perfusion may well be higher than during systemic administration. Second, systemic administration of REB affects NA terminals in many parts of the brain that may not be affected by its local administration into one particular area. Such differences may subsequently contribute to a selective increase in DA release in the mPFC and/or inhibition of DA release in the NAC. Support for this

![Fig. 4.](image)

**Fig. 4.** Effect of systemic (0.15 mg/kg) (A) local (333 μM) (B), and intraventricular tegmental area (333 μM) (C) administration of reboxetine on dopamine release in the NAC (C) and the mPFC (○). Bar or arrow indicates time of drug infusion (60 min) or injection of reboxetine, respectively. Data are presented as mean ± S.E.M. (n ≥ 4) percentage of baseline. Data were analyzed by one-way (time; B and C) and two-way (area × time; A and B) ANOVA followed by Newman-Keuls test for multiple comparisons. For A, F(area; 1,12) = 9.42, P < 0.01; F(time; 7,84) = 8.51, P < 0.001; and F(area × time; 7,84) = 7.47, P < 0.001. For B, F(area; 1,8) = 4.67, P = 0.063; F(time; 7,56) = 26.93, P < 0.001; F(area × time; 7,56) = 1.94, P = 0.081; F(mPFC, time; 7,28) = 15.34, P < 0.001; and F(NAC, time; 7,28) = 12.77, P < 0.001. For C, F(mPFC, time; 7,35) = 0.97, P = 0.47; and F(NAC, time; 7,28) = 0.91, P = 0.51. *P < 0.05, **P < 0.01, and ***P < 0.001 compared with baseline. *P < 0.05 and **P < 0.001 compared between mPFC and NAC.

![Fig. 5.](image)

**Fig. 5.** Mean plasma concentrations of reboxetine in rats 30 min after intraperitoneal administration (0.15–13.5 mg/kg). Each dot indicates a single observation. Solid line and gray area represents mean ± 0.5 S.D. serum concentration in humans undergoing chronic reboxetine treatment (8 mg/day; Ohman et al., 2001).
tion has previously been provided by the observation of a decreased DA utilization in the mPFC, but not in the NAC, following selective destruction of NA fibers innervating the VTA (Hervé et al., 1982). The previously demonstrated, inhibitory role of prefrontal DA on stimulated release of DA in the NAC (Deutch et al., 1990) may also influence the net effect of systemically administered NRIs on regional DA release. In view of the quantitatively similar effects of systemically and locally administered REB on extracellular concentrations of DA in the mPFC, and the differential effects of these drug treatments observed in the NAC (Fig. 4, A and B), it appears as if systemic REB may exert its selective augmenting effect on DA availability in the mPFC by several converging mechanisms.

By measuring plasma concentrations of REB in rats we were able to define a range of doses that yield plasma concentrations of similar magnitude as those obtained in patients undergoing chronic REB treatment (Fig. 5; Öhman et al., 2001). By inference, our data thus suggest that clinical treatment with REB (8 mg/day) might well cause an increase in cortical DA availability.

Although REB may exert a similar overall antidepressant efficacy as the SSRI fluoxetine (Montgomery, 1997), it appears as if selective NRIs, i.e., REB, may possess an advantageous effect compared with SSRIs, when the patients' subjective assessment of their motivation related to action, i.e., drive, is included in the analysis (Dubini et al., 1997; Massana et al., 1999). Interestingly, a relative inactivity of the prefrontal cortex has been observed in subjects suffering from depression as well as some other psychiatric disorders (Kennedy et al., 1997). Moreover, the function of prefrontal cortical neurons has been shown to be subjected to an intrinsic regulation by the mesocortical DA system (Arnsten, 1997). In light of these findings the effects of NRIs on the function of the mesolimbocortical DA system may well be of interest with regard to their clinical profile. In fact, chronic treatment with NRIs, such as desipramine, has been shown to cause an enhanced DA output in the mPFC, whereas during chronic fluoxetine administration, prefrontal DA is unaltered (Tanda et al., 1996). Such results gain additional impact given the involvement of DA neuronal activity in reward-related learning (Schultz, 1998). An increased excitability of the VTA DA neurons may generally be important for the function of the mesolimbocortical DA system but not in the nucleus accumbens after selective destruction of noradrenergic fibers innervating the ventral tegmental area in the rat. Brain Res 237:510–516.


Tanda G, Carbone E, Prau R and Di Chiara G (1994) Increase of extracellular...


Send reprint requests to: Prof. Torgny H. Svensson, Section of Neuropsychopharmacology, Department of Physiology and Pharmacology, Nanna Svartz väg 2, Karolinska Institutet, S-171 77, Stockholm, Sweden. E-mail: torgny.svensson@fyfa.ki.se