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Effect of single and repeated administration of fluvoxamine on noradrenaline release in rat brain

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Abstract

In vivo microdialysis in conscious rats was used to evaluate the effect of acute and chronic administration of fluvoxamine on extracellular levels of noradrenaline, dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA), and 5-hydroxyindole acetic acid (5-HIAA) in the frontal cortex. A single administration of fluvoxamine (12 mg/kg i.p.) during dialysate collection caused a significant delayed decrease in 5-HIAA and a mild increase in noradrenaline with no change in HVA and DOPAC levels. Chronic administration of fluvoxamine (12 mg/kg i.p. daily for 3 weeks, last dose 24 h prior to microdialysis) or a single dose 24 h prior to microdialysis had no effect on noradrenaline, DOPAC and HVA levels in the frontal cortex; 5-HIAA levels were significantly decreased 24 h after a single dose, but increased following long term treatment. Tissue concentrations of 5-HT and 5-HIAA in the frontal cortex showed a mild (though not significant) increase in rats chronically treated with fluvoxamine. Release of noradrenaline in the frontal cortex may be enhanced initially by a 5-HT uptake inhibitor, but this effect is not seen following drug washout. © 1997 Elsevier Science B.V.

Keywords: Fluvoxamine; 5-HT (5-hydroxytryptamine, serotonin); Microdialysis; Frontal cortex; Dopamine; Noradrenaline

1. Introduction

The involvement of serotonin (5-HT) in the regulation of a variety of neuronal functions is the basis for the pharmacological effects of selective serotonin reuptake inhibitors, which are important drugs in the treatment of depression and other neuropsychiatric disorders. The blockade of 5-HT reuptake by these drugs increases 5-HT concentrations in the region of cell bodies and terminals of the serotonergic and other types of neurons. Although selective serotonin reuptake inhibitors inhibit the 5-HT transporter within minutes after systemic administration, their full clinical action is seen only after a few weeks of treatment. This fact has been explained by observations in rats that treatment with serotonin reuptake inhibitors initially attenuates firing activity of the serotonergic neurons by activation of somatodendritic 5-HT_{1A} autoreceptors, thus reducing 5-HT release from the terminals. After prolonged exposure to the drug, 5-HT_{1A} autoreceptors become desensitized and the normal firing activity is restored, resulting in a marked increase of 5-HT extracellular concentration at the terminals (Bel and Artigas, 1993).

Most of the preclinical studies on serotonin reuptake inhibitors have been limited to the serotonergic function. However, alterations in 5-HT release may impinge on other neurotransmitters in an intact organism, since 5-HT receptors are situated on a variety of different neuronal types. One neurotransmitter whose release may be modulated by 5-HT, and which is also implicated in antidepressant drug action, is noradrenaline. An interaction between serotonergic and noradrenergic neurons has been described at a number of levels. Tryptophan hydroxylase-positive neurons originating from the dorsal raphe nucleus (Imai et al., 1986) exist in the locus coeruleus (Pickel et al., 1977). Evidence has been produced for an inhibitory action of 5-HT on the excitatory effect of glutamate on noradrenergic neurons in the locus coeruleus of the rat, by both post-synaptic (Aston-Jones et al., 1991) and presynaptic (Bobker and Williams, 1989) actions. The presynaptic effect was attributed to activation of 5-HT_{1A} and 5-HT_{1B} receptors.

At the axon terminal level, a facilitatory action of 5-HT on release of noradrenaline from noradrenergic neurons by activation of presynaptic 5-HT_3 heteroreceptors has been described both in peripheral sympathetic neurons (Fozard, 1984) and in the central nervous system. A close apposi-

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tion of serotonergic and noradrenergic neurons exists in the hippocampus (Storm-Mathisen, 1977), and a facilitation of ^{3}[H]noradrenaline release by 5-HT has been shown in tissue slices obtained from this area of rabbit brain (Feuerstein and Hertting, 1986). Activation of 5-HT_3 receptors by direct agonists or by the serotonin reuptake inhibitor paroxetine also facilitated the release of ^{3}[H]noradrenaline from slices of rat hippocampus and hypothalamus, although only weakly from the frontal cortex (Mongeau et al., 1994). Other noradrenergic neurons, or other receptor types, however, may show an inhibitory response to 5-HT. Activation of 5-HT_2 receptors decreased endogenous noradrenaline release from the rat hippocampus in vivo (Done and Sharp, 1992), and 5-HT_3 receptor activation inhibited K^+-induced release of endogenous noradrenaline from rat hypothalamus slices (Blandina et al., 1991). Enhanced synaptic 5-HT levels may also affect noradrenaline release from terminal fields by modulating the release of an intermediate neurotransmitter such as glutamate, γ-aminobutyric acid (GABA), or opiate peptides, as in the cell body area. Release of dopamine from both nigrostriatal (see Kelland et al., 1990) and mesolimbic (Jiang et al., 1990) pathways can also be stimulated by 5-HT, acting on a variety of receptors, including 5-HT_3 (Blandina et al., 1989) and 5-HT_4 (Steward et al., 1996).

The purpose of this study was to investigate the alterations of the noradrenaline concentration and release in rat brain induced by acute and prolonged treatment with fluvoxamine, since relatively few studies have attacked the question of modification of noradrenaline release in vivo following administration of serotonin reuptake inhibitors. We have investigated noradrenaline release using the in vivo technique of microdialysis, because we were interested in determining the net effect of the drug in the clinically relevant in vivo setting. We studied release of noradrenaline and monoamine metabolites in the frontal cortex, in view of the relevance of this area to affective disorders, and the ease of reproducible placement of microdialysis probes. Fluvoxamine was chosen as serotonin reuptake inhibitor drug because of its high selectivity for the 5-HT transporter, with only low affinity for 5-HT and noradrenaline receptors (Claassen et al., 1977; Hyttel, 1994), and because of the observed increase in extracellular 5-HT levels in the frontal cortex following acute and chronic treatment with this drug (Bel and Artigas, 1993).

2. Materials and methods

2.1. Animal treatment

Sprague–Dawley male rats (250–300 g) were housed under standard conditions. Three different experimental protocols were carried out. In the first study (acute fluvoxamine), microdialysis probes were implanted in previously untreated rats. One day after surgery, 4 control collections were made, and then fluvoxamine (12 mg/kg) was injected i.p. and collections of microdialysate carried on for a further 160 min. The second study comprised 3 groups of animals. One group received fluvoxamine for 21 days (12 mg/kg daily i.p.), a second group received the same dose of fluvoxamine once only, and a third group received saline injections. One day after the last of the 21 injections, or one day after the single injection, the animals were anesthetized for implantation of microdialysis probes. In these animals, following 4 baseline collections, KCl (100 mM) was administered as a 20 min bolus in the microdialysate, and collections continued for a further 160 min. In the third study protocol, two groups of animals were used (21 days fluvoxamine and 21 days saline). One day after the last injection, the animals were sacrificed for determination of tissue levels of amines and metabolites.

2.2. Surgery and microdialysis

Rats were stereotactically implanted with 4 mm (active length) microdialysis probes under anesthesia with a mixture of 15 mg/kg pentobarbital and 60 mg/kg chloralhydrate. The probe was placed in the frontal lobe of the cortex, using the coordinates AP +3.2, ML −1.2, DV −6.0 mm with reference to bregma (Paxinos and Watson, 1982). After surgery, rats were housed individually and had free access to food and water throughout the experimental period. The probe was continuously perfused with artificial cerebrospinal fluid (CSF) (NaCl 189, KCl 3.9, $CaCl_2$ 3.4 mM) at a rate of 2 μl/min. In vitro recovery of the probes for 10^{-7} M noradrenaline was $11.5 \pm 0.8\%$. One day after surgery, dialysates were collected every 20 min and added to perchloric acid (0.1 M). Samples were immediately frozen and stored at −70°C until detection by high pressure liquid chromatography (HPLC) as described previously (Lamensdorf et al., 1996).

2.3. Brain tissue monoamines

Animals were sacrificed by decapitation, their brains quickly removed, put on ice, and the frontal cortex, striatum, hippocampus and mid brain dissected and immediately placed in liquid nitrogen. Tissue sections were then weighed, homogenized in 0.1 M $HClO_4$, centrifuged and the supernatant stored at −70°C until estimation by HPLC with an electrochemical detector.

2.4. Statistical analysis

Statistic analysis was performed by two-way ANOVA followed by Student's *t*-test.

3. Results

Basal concentrations of monoamines and metabolites in the dialysates from the frontal cortex of control rats are

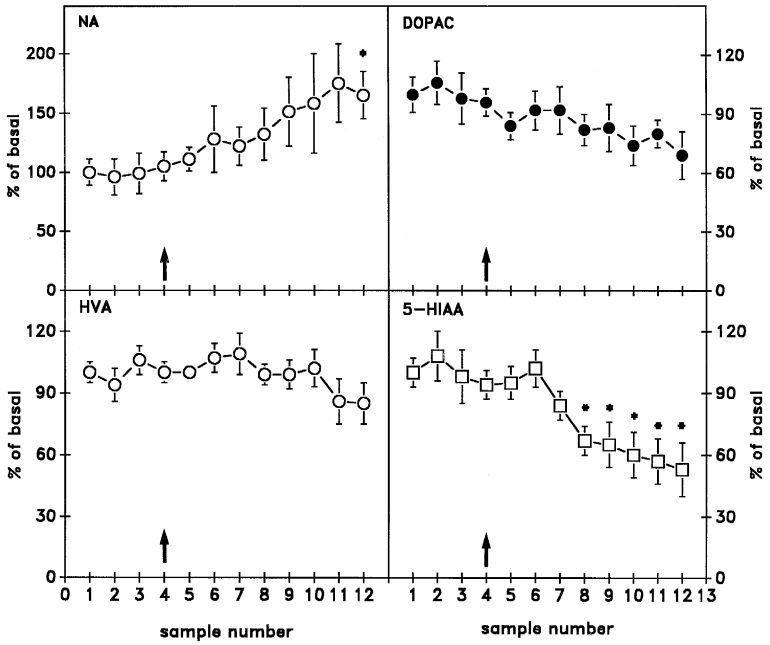

Fig. 1. Effect of acute administration of fluvoxamine (12 mg/kg i.p.) on frontal cortex extracellular concentrations of noradrenaline (NA), DOPAC, HVA and 5-HIAA. Data shown are means ± S.E.M. of amine or metabolite concentration expressed as percentage of basal concentration, for 6 rats in each group (for concentrations in basal microdialysate, see text). The injection time of fluvoxamine is indicated by the arrowhead. * $P < 0.05$ vs. basal level.

given in Table 1. Administration of fluvoxamine (12 mg/kg i.p.) 80 min after the start of dialysate collection caused a significant delayed decrease in 5-HIAA and a mild increase in noradrenaline concentrations in the frontal cortex without any significant effect on HVA or DOPAC levels (Fig. 1).

Administration of fluvoxamine daily for 21 days, or once only 24 h before microdialysis collections, had no

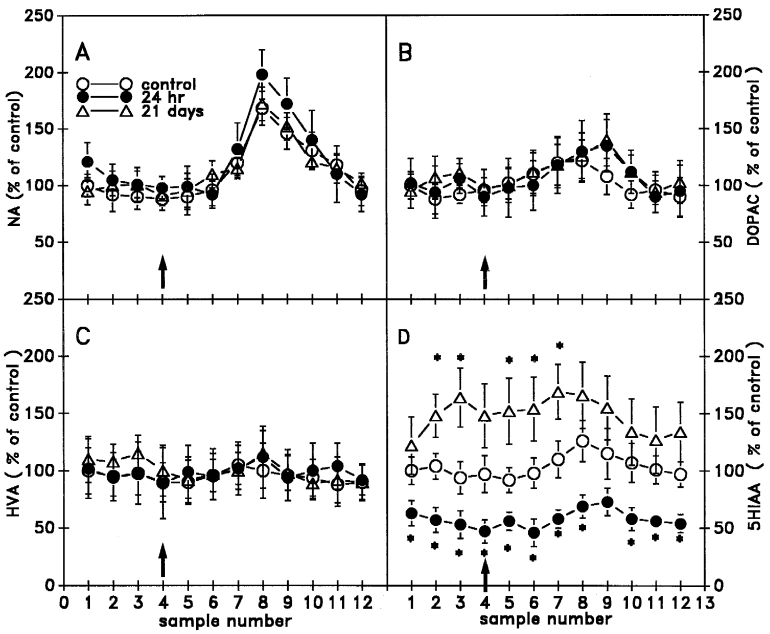

Fig. 2. Effect of chronic (21 days) and single (24 h before microdialysis collection) administration of fluvoxamine (12 mg/kg i.p.) on frontal cortex extracellular concentrations of noradrenaline (NA) (A), DOPAC (B), HVA (C) and 5-HIAA (D). Data shown are means ± S.E.M. of amine or metabolite concentration expressed as percentage of basal concentration in the control group (for concentrations in basal microdialysate, see text). The arrowhead indicates the start of administration of KCl bolus (100 mM) in microdialysate for 20 min. * $P < 0.05$ vs. basal level.

Table 1
Monoamine and metabolites concentrations in frontal cortex dialysate of control rats

	Basal concentrations ($\times 10^{-8}$ M)
NA	0.29 ± 0.04
DOPAC	3.66 ± 0.56
HVA	7.62 ± 1.70
5-HIAA	4.44 ± 0.53

Dialysate samples were collected from the frontal cortex as described in Section 2. Values are means ± S.E.M. of four initial dialysates samples from 10 control rats.

effect on resting basal levels of noradrenaline, DOPAC and HVA in the frontal cortex. The increment in microdialysate noradrenaline following infusion of a depolarizing concentration of KCl was also not significantly altered in fluvoxamine-treated rats (Fig. 2). Basal 5-HIAA levels were significantly decreased after a single treatment but were increased following chronic treatment with fluvoxamine (Fig. 2).

Tissue concentrations of monoamines and their metabolites in four different brain regions from rats treated chronically with fluvoxamine and saline controls are summarized in Table 2. It is interesting that in the frontal cortex, 5-HT and 5-HIAA levels show a mild, though not significant, increase in the fluvoxamine-treated group, which parallels the change seen on microdialysis. In the striatum, chronic fluvoxamine treatment induced a significant increase in 5-HT levels which was accompanied by a significant decrease in 5-HIAA concentrations. The dihydroxyphenylalanine (DOPA) level was significantly increased in the treated group in all brain regions except for the hippocampus in which none of the monoamines or their metabolites were changed by chronic fluvoxamine treatment.

4. Discussion

The conditions of our experimental protocol for examination of the acute effect of fluvoxamine on monoamine release in the frontal cortex of rats were very similar to those of Bel and Artigas (1992). The latter workers studied the effect of fluvoxamine (1 and 10 mg/kg i.p.) on microdialysate 5-HT in the frontal cortex and raphe, and observed a maximal increase in the frontal cortex 5-HT of 255% with a decrease in 5-HIAA of 33% at the 10 mg/kg dose, which is very close to the 12 mg/kg dose used by us. The increased frontal cortex 5-HT level was already nearly maximal 30 min after drug administration and was maintained at a constant level for the next 3.5 h.

Our study of the acute effect of fluvoxamine on frontal cortex extracellular amine and metabolite levels indicates that these actions of acute fluvoxamine administration on 5-HT release are accompanied by an increased extracellular level of noradrenaline, which occurs shortly after systemic administration of the drug. This elevation in extracellular noradrenaline could result from a stimulatory effect of 5-HT at 5-HT_3 receptors on noradrenergic axon terminals, in view of the simultaneous increase in extracellular 5-HT concentration demonstrated by Bel and Artigas (1992). We were unable to determine 5-HT simultaneously with noradrenaline in our HPLC system, and the main point of our investigation was to determine changes in the noradrenergic system following fluvoxamine. However, we detected a reduced level of 5-HIAA of a similar degree to that observed by Bel and Artigas (1992) together with the rise in noradrenaline following acute fluvoxamine, so

Table 2
The effect of chronic treatment with fluvoxamine on the concentrations of brain monoamines

	NA	DOPA	DOPAC	DA	HVA	5-HT	5-HIAA
Frontal cortex							
Control	0.25 ± 0.013	0.025 ± 0.003	0.065 ± 0.016	0.23 ± 0.03	0.093 ± 0.017	1.11 ± 0.10	0.87 ± 0.08
Fluvoxamine	0.26 ± 0.017	0.043 ± 0.002 [b]	0.048 ± 0.007	0.18 ± 0.02	0.087 ± 0.019	1.43 ± 0.12	1.07 ± 0.13
Striatum							
Control	0.25 ± 0.014	0.040 ± 0.004	0.336 ± 0.029	4.97 ± 0.12	1.00 ± 0.07	1.54 ± 0.09	1.28 ± 0.12
Fluvoxamine	0.28 ± 0.009	0.082 ± 0.008 [c]	0.270 ± 0.015	5.25 ± 0.13	1.37 ± 0.08 [b]	2.07 ± 0.21 [a]	0.74 ± 0.02 [c]
Hippocampus							
Control	0.22 ± 0.007	0.030 ± 0.002	0.062 ± 0.018	0.12 ± 0.02	0.063 ± 0.005	0.97 ± 0.06	1.05 ± 0.14
Fluvoxamine	0.24 ± 0.013	0.031 ± 0.003	0.068 ± 0.021	0.13 ± 0.02	0.057 ± 0.010	1.06 ± 0.07	0.91 ± 0.13
Midbrain							
Control	0.27 ± 0.014	0.019 ± 0.003	0.085 ± 0.015	0.26 ± 0.02	0.074 ± 0.013	1.50 ± 0.13	1.25 ± 0.21
Fluvoxamine	0.28 ± 0.012	0.044 ± 0.009 [a]	0.076 ± 0.010	0.29 ± 0.01	0.083 ± 0.014	1.89 ± 0.15	1.66 ± 0.19

Rats were treated with fluvoxamine for 21 days (12 mg/kg daily i.p.). Control group received saline. Concentrations of monoamines and their metabolites are expressed in pmol/mg tissue and are means ± S.E.M. of 10–12 rats in each group.
[a] $P < 0.05$; [b] $P < 0.005$; [c] $P < 0.001$.

that we can presume that 5-HT increased to a similar extent as observed by Bel and Artigas (1992). Reduction in 5-HIAA generation is the expected response with acute administration of a compound which inhibits 5-HT reuptake (Claassen et al., 1977). This effect is normally thought to result from reduced reuptake and neuronal metabolism of synaptic 5-HT released into the synaptic cleft.

An alternative mechanism for the increased extracellular noradrenaline following acute fluvoxamine is increased activity of the frontal cortical noradrenergic neurons following reduction in the inhibitory 5-HT input onto locus coeruleus neurons and consequent increase in neuronal firing. Such a mechanism is consistent with the known inhibition of activity of raphe neurons following acute treatment with selective serotonin reuptake inhibitors (Chaput et al., 1986), but implies a reduction in extracellular 5-HT in the region of the locus coeruleus, which has not so far been demonstrated. The net result of administration of selective serotonin reuptake inhibitors on extracellular 5-HT levels in any brain area will depend on the balance between decreased neuronal firing (action at the raphe) tending to decrease 5-HT release, and inhibition of neuronal reuptake (tending to increase synaptic amine levels). Since following acute fluvoxamine, 5-HT extracellular level increases in most brain areas so far studied, it is difficult to imagine that the 5-HT extracellular level at the locus coeruleus would decrease. More likely, the mild increase in frontal cortex extracellular noradrenaline is the resultant of increased release from terminals.

When determined 24 h after a single administration of the drug, noradrenaline levels in the frontal cortex returned to control values, although the reduction in extracellular 5-HIAA was maintained. However, following chronic treatment with the drug and a 24 h washout period, noradrenaline release was the same as in control animals, although 5-HIAA release in the frontal cortex was enhanced. In comparing this result of elevated 5-HIAA following chronic serotonin reuptake inhibitors with data obtained by other workers, one should consider the effect of the 24 h washout period before microdialysis, as recently discussed by Moret and Briley (1996). When animals are studied without drug washout before microdialysis, increased 5-HT and reduced 5-HIAA in the projection areas is seen following chronic treatment with fluvoxamine (Bel and Artigas, 1993) and citalopram (Moret and Briley, 1996). However, when a 24 h washout period is allowed after chronic serotonin reuptake inhibitor administration, 5-HT levels in the projection areas are unchanged (Hjorth and Auerbach, 1994, with citalopram; Invernizzi et al., 1994, with citalopram; and Bosker et al., 1995, with fluvoxamine). When a 24 h washout period was given following chronic treatment with citalopram (Moret and Briley, 1996), hypothalamic 5-HIAA levels were insignificantly changed (although it is interesting that their data show a slight increase in levels). Our data support their proposal that following 24 h washout, the effect of the serotonin reuptake inhibitor to enhance synaptic 5-HT is lost, whereas the downregulation of the somatodendritic 5-HT_{1A} receptors remains, leading to a rebound increase in firing of raphe neurons. This would lead to enhanced release and turnover of 5-HT, and elevated 5-HIAA levels as a result, although the absence of an inhibitory effect on the membrane 5-HT transporter would result in no change in extracellular 5-HT levels. The fact that we observed an enhancement of 5-HIAA levels with chronic fluvoxamine whereas others reported no change may be the result of the particular experimental conditions (drug dose, animal strain, etc.). The fact that extracellular 5-HT levels are unchanged following 24 h washout of drug explains the lack of change in noradrenaline frontal cortex levels in the present study. Although the neuronal firing rate, and associated release of 5-HT may be enhanced, yet the released 5-HT may not diffuse out of the synapse and therefore may not increase extracellular levels, or interact with receptors on nearby noradrenergic neurons.

Other studies using isolated tissues have shown an enhancement of 5-HT release from cortical slices in vitro following chronic serotonin reuptake inhibitor (Moret and Briley, 1990). The possible explanation for this phenomenon is that terminal presynaptic receptors downregulate, resulting in reduced inhibitory feedback control on 5-HT release, although such a mechanism has so far not been demonstrated in vivo (Moret and Briley, 1996). If 5-HT neuronal release in fact increases following chronic fluvoxamine, then this could exert two opposing effects on noradrenaline release, as discussed above: activation of presynaptic terminal heteroreceptors (inhibitory 5-HT_{1B} or excitatory 5-HT_{3}), and inhibition of firing of locus coeruleus neurons. The net effect of these opposing influences may be no change in noradrenaline release from projection areas.

In order to confirm the finding of elevated frontal cortex extracellular 5-HIAA following chronic fluvoxamine treatment, we determined amine and metabolite levels in brain tissue. These findings corroborated the microdialysis data, in that content of both 5-HIAA and 5-HT in frontal cortical tissue showed a tendency to increase following the chronic treatment. The tissue data therefore provide support for an increased turnover of 5-HT in the frontal cortex. The increase in levels of DOPA in the frontal cortex may imply an enhanced catecholamine synthesis. An additional study is required to prove this point, using determination of noradrenaline metabolites, and tyrosine hydroxylase activity.

Additional information on modification of dopaminergic systems in the brain was obtained from analysis of dopamine metabolite levels in brain tissue. A twofold increase in DOPA and a 37% increase in HVA in the striatum accompanied a 34% increase in 5-HT and 42% decrease in 5-HIAA. This suggests a reduction in 5-HT catabolism or a reduction in 5-HT release in the striatum after chronic fluvoxamine treatment, together with an in-

creased turnover of dopamine. It is well established that the substantia nigra receives a serotonergic inhibitory input from the raphe nucleus (Dray et al., 1978). Moreover, it was found that 5-HT exerts an inhibitory effect on dopamine synthesis in the striatum through 5-HT_{1A} receptors (Johnson et al., 1993). On the other hand, in the substantia nigra, tyrosine hydroxylase activity and mRNA were unchanged following intracerebroventricular injection of the serotonergic neurotoxin 5,6-dihydroxytryptamine (Sturtz et al., 1994), indicating a lack of tonic serotonergic control on dopamine release. Other studies have demonstrated that activation of 5-HT_3, 5-HT_{1B} or 5-HT_4 receptors facilitates striatal dopamine release both in vivo and in vitro (Benloucif and Galloway, 1991; Grant, 1995; Steward et al., 1996). In addition it has been demonstrated in vitro and in vivo that 5-HT is able to enter striatal dopamine terminals via dopamine uptake sites, leading to increased dopamine outflow by the displacement of dopamine from its vesicular pool (Yi et al., 1991; Jacocks and Cox, 1992; De Deurwaerdere et al., 1996). Our results, which are indicative of enhanced striatal dopamine synthesis and release following chronic fluvoxamine, could be explained by a modulating influence of 5-HT on dopamine release, both at cell body and axon terminal receptors.

In conclusion, release of noradrenaline from rat frontal cortex projections may be increased after acute treatment with serotonin reuptake inhibitors, although when a 24 h washout period is allowed after the last of a series of chronic doses, no alteration in frontal cortex noradrenaline release could be detected. Our study supports other findings of enhanced 5-HT turnover following chronic serotonin reuptake inhibitor treatment.

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