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Mirtazapine-induced corelease of dopamine and noradrenaline from noradrenergic neurons in the medial prefrontal and occipital cortex

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Abstract

The novel antidepressant mirtazapine has been shown to increase extracellular noradrenaline and dopamine in the medial prefrontal cortex. Our previous studies indicate that extracellular dopamine in the cerebral cortex originates largely from noradrenergic terminals, such release being controlled by α_2-adrenoceptors. Because mirtazapine inhibits α_2-adrenoceptors, the possibility that it might corelease dopamine and noradrenaline was investigated. By means of microdialysis, the effect of mirtazapine on extracellular dopamine, 3,4-dihydroxyphenylacetic acid (DOPAC) and noradrenaline in the medial prefrontal cortex, densely innervated by dopaminergic and noradrenergic neurons, and in the occipital cortex, receiving equal noradrenergic but scarce dopaminergic projections, was compared. Basal extracellular concentration of noradrenaline was similar in both cortices, while dopamine in the occipital cortex was only about 50% lower than in the medial prefrontal cortex, reflecting noradrenergic rather than dopaminergic projections. The intraperitoneal (i.p.) administration of mirtazapine (5 and 10 mg/kg) increased extracellular dopamine, DOPAC and noradrenaline to approximately the same extent in both cortices, an effect totally suppressed by the α_2-adrenoceptors agonist clonidine (0.15 mg/kg, i.p.). To exclude the possibility that mirtazapine-induced increase in dopamine might result from reduced dopamine removal from extracellular space, noradrenaline and dopamine uptake mechanisms were blocked by perfusing 100 μM desipramine into either cortex. The combined i.p. administration of mirtazapine (5 mg/kg) and the local perfusion of desipramine produced an additional increase in extracellular dopamine, DOPAC and noradrenaline in the medial prefrontal cortex and occipital cortex compared with the increase produced by either drug given alone. The results suggest that mirtazapine by inhibiting α_2-adrenoceptors produces a corelease of noradrenaline and dopamine from noradrenergic terminals in the cerebral cortex.

Keywords: α_2-Adrenoceptor antagonist; Desipramine; DOPAC; HPLC; Microdialysis; (Rat)

1. Introduction

The novel antidepressant mirtazapine has been shown to increase extracellular noradrenaline and dopamine in the medial prefrontal cortex, an effect considered to be a potential substrate for the antidepressant activity of the drug (Millan et al., 2000). Because mirtazapine is an α_2-adrenoceptor antagonist (De Boer, 1996), the increase in noradrenaline might be explained with the inhibition of α_2-adrenoceptors located both on the somatodendritic region and on nerve terminals of locus coeruleus noradrenergic neurons, resulting in activation of the firing rate of noradrenergic neurons and in the increase in noradrenaline release (Millan et al., 2000).

On the other hand, to explain mirtazapine-induced increase in extracellular dopamine in the medial prefrontal cortex that accompanies the increased noradrenaline output, it has been suggested that extracellular dopamine in the medial prefrontal cortex is cleared preferentially by noradrenaline transporter into noradrenergic terminals (Carboni et al., 1990; Pozzi et al., 1994). Accordingly, the rise in extracellular dopamine levels would be, at least partially, secondary to the elevation in noradrenaline levels, competing for the same transporter.

Such mechanism has also been suggested to explain the concomitant increase in extracellular dopamine and noradrenaline produced by α_2-adrenoceptor antagonists (Gresch et

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al., 1995; Millan et al., 2000), noradrenaline and dopamine transporter blockers (Gresch et al., 1995; Mazei et al., 2002), monoamine oxidase inhibitors (Wayment et al., 2001) and antipsychotics (Li et al., 1998; Westerink et al., 1998).

However, several other mechanisms have been suggested to explain mirtazapine effect on dopamine output in the medial prefrontal cortex (see Millan et al., 2000).

At variance with the "heterotransport" hypothesis, recent results from our laboratory suggest that extracellular dopamine in the medial prefrontal cortex as well as in other cortices may originate not only from dopaminergic terminals but also from noradrenergic ones, where dopamine would act both as noradrenaline precursor and a cotransmitter (Devoto et al., 2001, 2003a,b). Accordingly, we have provided evidence that the corelease of the two catecholamines is controlled by α_2-adrenoceptors located somatodendritically and on nerve terminals of noradrenergic neurons (Devoto et al., 2003c).

Because mirtazapine is an α_2-adrenoceptor antagonist (De Boer, 1996; Millan et al., 2000), the possibility that it might corelease dopamine and noradrenaline from noradrenergic nerve terminals was analysed. To this aim we compared mirtazapine effect on extracellular dopamine, its deaminated metabolite 3,4-dihydroxyphenylacetic acid (DOPAC) and noradrenaline both in the medial prefrontal cortex, an area densely innervated by noradrenaline and dopamine, and in the occipital cortex, equally innervated by noradrenergic neurons but receiving scarce dopaminergic projections.

2. Materials and methods

2.1. Microdialysis

Experiments were performed in freely moving male rats (Sprague–Dawley, Harlan Italy, S. Pietro al Natisone, Italy) weighing 250–300 g, housed in groups of four per cage prior to surgery and singly afterwards, under controlled conditions of temperature and humidity, with artificial light from 8 a.m. to 8 p.m.; food and water were available ad libitum. The experiment was approved by the local ethical committee and performed according to the UE guidelines for care and use of experimental animals (EEC Council 86/609; D.L. 27/01/1992, n116). Surgery was performed under Equithesin anesthesia. Animals were implanted with transversal probes, (8 mm dialyzing surface, membrane AN 69-HF, Hospal-Dasco, Bologna, Italy; cut-off 40,000 Da) in the occipital cortex (AP −5.0, V −1.8 from bregma), or with I-shaped vertical microdialysis probes (4 mm dialyzing surface) in the medial prefrontal cortex (AP +3.0, L ±0.6, V −6.5), according to the coordinates of the atlas of Paxinos and Watson (1986). In vitro estimated recovery was the same for the two probes, after correction for the different membrane length. Experiments were performed 24–30 h after surgery, from 10 a.m. to 5.00 p.m. on freely moving rats.

An artificial cerebrospinal fluid (147 mM NaCl, 4 mM KCl, 1.5 mM $CaCl_2$, pH 6–6.5) was pumped through the dialysis probes at a constant rate of 2.2 μl/min via a CMA/100 microinjection pump (Carnegie Medicine, Stockholm, Sweden). Samples were collected every 20 min and directly injected into a high-performance liquid chromatography (HPLC) apparatus, equipped with a 3.0 × 150 mm C18 (3.5 μm) Symmetry column (Waters, Milan, Italy) and an ESA Coulochem II detector (Chelmford, MA, USA). The mobile phase consisted of 80 mM Na_2HPO_4, 0.27 mM EDTA, 0.58 mM sodium octyl sulfate, 12% methanol, pH 2.8 with H_3PO_4, delivered by a model 307 Gilson pump (Gilson Italia, Milano, Italy) at 0.4 ml/min. The Coulochem analytical cell first electrode was set at +200 mV, the second at −300 mV. In these conditions, the detection limits (signal to noise ratio 3:1) were 0.5 pg of noradrenaline and dopamine on column.

In all experiments, dialysate was sampled for at least 60 min prior to any treatment, to establish baseline concentrations of neurotransmitters. On termination of experiments, rats were killed with an overdose of Equithesin, the brain was removed and stored with 10% formalin in 0.2 M phosphate buffer until histologically verified. Coronal sections (40 μm thick) were made with a Vibratome, oriented according to the atlas of Paxinos and Watson (1986), stained with fast cresyl violet stain and the location of probes was verified according to the above atlas. If any portion of the active membrane was found to be outside the target location, data from the animal concerned were excluded.

2.2. Drugs and treatments

Clonidine HCl was purchased from Tocris Cookson (Bristol, UK), desipramine–HCl and tetrodotoxin citrate from Sigma-Aldrich (Sigma-Aldrich Srl, Milano, Italy). Mirtazapine was a gift from N.V. Organon (The Netherlands). Mirtazapine was suspended in a drop of Tween 80 and diluted in saline to be i.p. administered in 3 ml/kg. Clonidine was dissolved in saline, and i.p. administered in 1 ml/kg. Pilot experiments showed that i.p. saline administration did not modify basal extracellular noradrenaline and dopamine levels. For the local administration, desipramine and tetrodotoxin were dissolved in artificial cerebrospinal fluid and perfused via reverse dialysis.

2.3. Expression of the results and statistics

The average concentration of three stable samples (less than 15% variation) before treatment was considered as the basal value and was set as 100%. Thus, values are expressed as percentages of basal value ± S.E.M. Statistical significance was evaluated by analysis of variance (ANOVA) for repeated measures, followed by Dunnett multiple comparison test.

3. Results

Basal extracellular noradrenaline, dopamine and DOPAC concentrations in the rat medial prefrontal and occipital cortex are reported in Table 1.

Mirtazapine, i.p. injected at the dose of 5 mg/kg, increased extracellular noradrenaline, dopamine and DOPAC by roughly the same extent in both the prefrontal and the occipital cortex (Fig. 1); maximal increases were 188%, 229% and 183% of the baseline for noradrenaline, dopamine and DOPAC, respectively, in the prefrontal cortex, and 212%, 252% and 248% in the occipital cortex (ANOVA results, medial prefrontal cortex: noradrenaline $P<0.0001$, $F_{(4,32)}=10.290$; dopamine $P<0.0001$, $F_{(4,32)}=11.708$; DOPAC $P<0.0001$, $F_{(4,32)}=8.137$; occipital cortex: noradrenaline $P<0.0001$, $F_{(5,40)}=11.183$; dopamine $P<0.0001$, $F_{(4,32)}=16.813$; DOPAC $P<0.0001$, $F_{(5,40)}=54.940$). On the other hand, the administration of 10 mg/kg elicited increases comparable to those obtained with the lowest dose in the medial prefrontal cortex (maximal increases were 207%, 261% and 175% of the baseline for noradrenaline, dopamine and DOPAC, respectively). However, in the occipital cortex this dose further increased extracellular noradrenaline, dopamine and DOPAC to a maximum of 333%, 426% and 310% of the baseline, respectively (Fig. 1) (ANOVA results, medial prefrontal cortex: noradrenaline $P<0.0001$, $F_{(6,48)}=17.525$; dopamine $P<0.0001$, $F_{(6,48)}=19.912$; DOPAC $P<0.0001$, $F_{(6,48)}=15.057$; occipital cortex: noradrenaline $P<0.0001$, $F_{(5,40)}=20.563$; dopamine $P<0.0001$, $F_{(5,40)}=11.876$; DOPAC $P<0.0001$, $F_{(5,40)}=69.497$).

Peak effect on noradrenaline and dopamine occurred at 40 min, while that on DOPAC took place at 80 min after treatment in either cortex.

Fig. 2 shows that local perfusion of occipital cortex with the sodium channel blocker tetrodotoxin (10 μM), 40 min after mirtazapine administration, totally reversed mirtazapine-induced increase in extracellular dopamine and noradrenaline and rapidly decreased these catecholamines below basal levels. (ANOVA results: noradrenaline $P<0.0001$, $F_{(3,24)}=46.279$; dopamine $P<0.0001$, $F_{(3,24)}=24.485$; DOPAC $P<0.0001$, $F_{(3,24)}=13.704$).

Table 1
Basal extracellular noradrenaline, dopamine and DOPAC concentrations in the rat medial prefrontal and occipital cortex

Cerebral area	Noradrenaline	Dopamine	DOPAC
Medial prefrontal cortex (17)	0.90 ± 0.14	0.68 ± 0.08	35.08 ± 6.42
Occipital cortex (20)	0.90 ± 0.09	0.39 ± 0.06	4.22 ± 0.22
Medial prefrontal cortex + desipramine (6)	7.56 ± 1.02	2.22 ± 0.43	34.16 ± 11.62
Occipital cortex + desipramine (5)	9.35 ± 0.71	1.15 ± 0.57	3.40 ± 0.20

Values are the means ± S.E.M. of data obtained in the number of animals indicated in parenthesis, and are expressed as pg/dialysate injected on column (40 μl) normalized for unitary membrane length. Desipramine (100 μM) was locally perfused via reverse dialysis, and basal values were obtained at the peak effect, 3–4 h after the start of local perfusion.

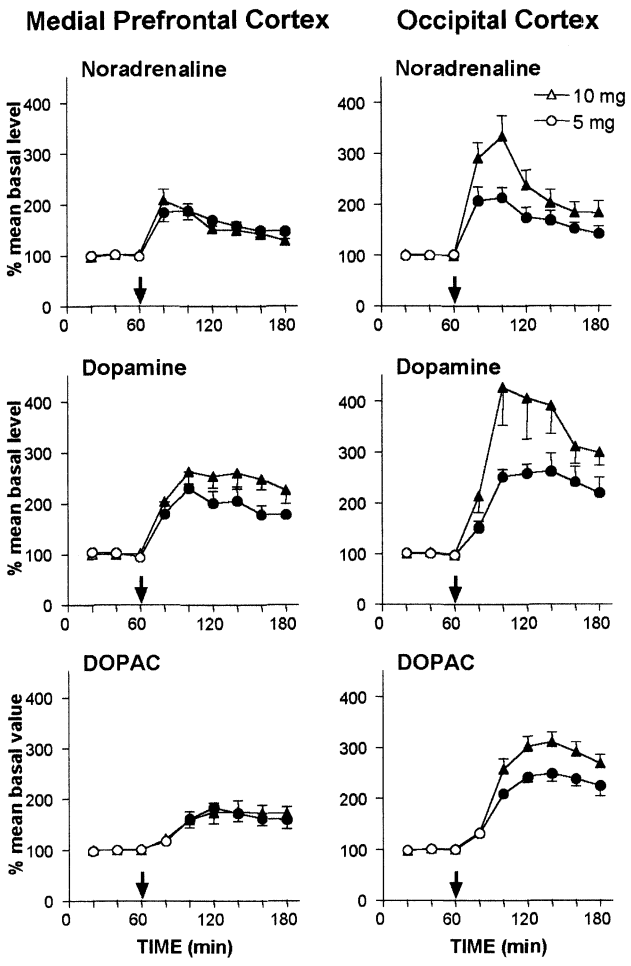

Fig. 1. Effects of mirtazapine (5 and 10 mg/kg, i.p. administered at the time indicated by the arrow) on extracellular noradrenaline, dopamine and DOPAC concentrations in the medial prefrontal cortex or in the occipital cortex. Data are means ± S.E.M. of at least five rats. (●, ▲) indicate $P<0.05$ with respect to basal values (Dunnett test).

The α_2-adrenoceptor agonist clonidine (0.15 mg/kg, i.p., 10 min prior to mirtazapine) suppressed the effect of mirtazapine (5 mg/kg, i.p.) on dopamine, DOPAC and noradrenaline in the medial prefrontal cortex as in the occipital cortex (ANOVA results, medial prefrontal cortex: noradrenaline $P<0.0001$, $F_{(4,32)}=9.554$; dopamine $P<0.0001$, $F_{(4,32)}=13.491$; DOPAC $P=0.0002$, $F_{(4,32)}=5.419$. Occipital cortex: noradrenaline $P<0.0001$, $F_{(4,32)}=15.216$; dopamine $P<0.0001$, $F_{(4,32)}=14.134$; DOPAC $P<0.0001$, $F_{(4,32)}=11.648$). Clonidine per se reduced extracellular noradrenaline and dopamine in both cortices to less than 30% of the baseline, and reduced extracellular DOPAC by about 40% of the baseline in the occipital cortex, but it was ineffective on DOPAC in the medial prefrontal cortex (Fig. 3) (ANOVA results, medial prefrontal cortex: noradrenaline $P<0.0001$, $F_{(7,56)}=73.149$; dopamine $P<0.0001$, $F_{(8,64)}=21.092$;

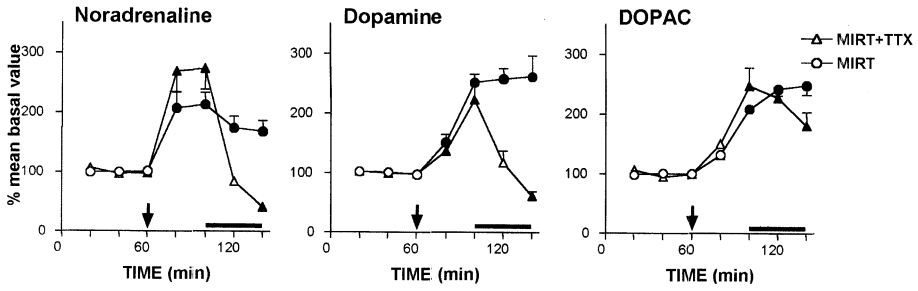

Fig. 2. Effect of tetrodotoxin (TTX, 10 μM) perfusion, indicated by the horizontal bar, on mirtazapine-induced increase on extracellular noradrenaline, dopamine and DOPAC concentrations in the occipital cortex. Mirtazapine (5 mg/kg) was i.p. injected 40 min before tetrodotoxin perfusion, as indicated by the arrow. Data are means ± S.E.M. of at least four rats. (●, ▲) indicate $P<0.05$ with respect to basal values (Dunnett test).

DOPAC $P>0.05$, $F_{(9,72)}=1.821$; occipital cortex: noradrenaline $P<0.0001$, $F_{(5,40)}=53.694$; dopamine $P<0.0001$, $F_{(5,40)}=36.354$; DOPAC $P<0.0001$, $F_{(5,40)}=12.359$).

We analysed the possibility that mirtazapine-induced increase in extracellular dopamine might be secondary to the increase in extracellular noradrenaline, which would compete for the same noradrenaline transporter.

Accordingly, both noradrenaline and dopamine transporter were inhibited by perfusing desipramine via reverse dialysis either into the medial prefrontal cortex or into the occipital cortex at the concentration of 100 μM. Desipramine has been shown to inhibit both noradrenaline and dopamine uptake in synaptosomes with an apparent IC_{50} of 0.37 and 4.0 nM, respectively (Michel

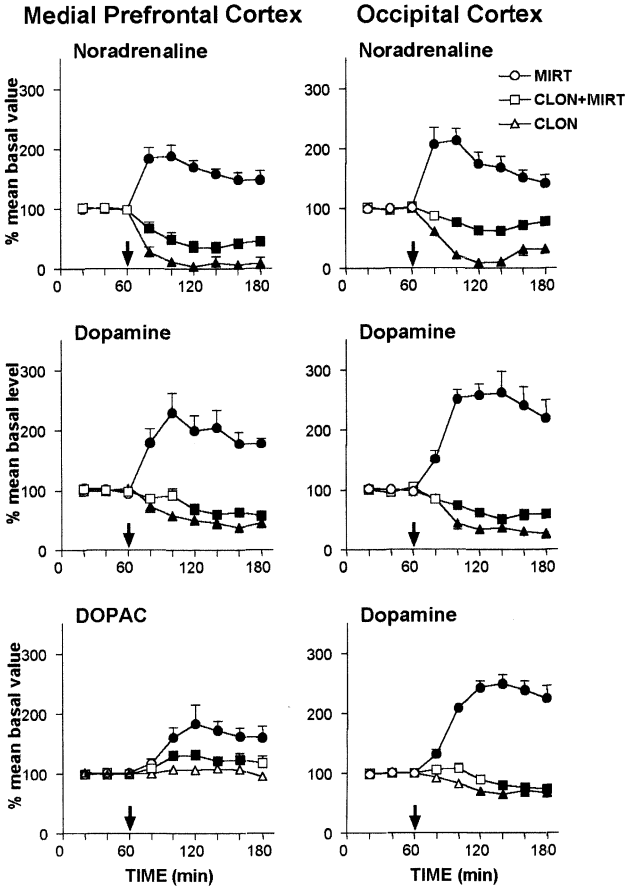

Fig. 3. Effects of mirtazapine (MIRT, 5 mg/kg, i.p. administered at the time indicated by the arrow), alone or in combination with clonidine (CLON, 0.15 mg/kg, i.p. administered 10 min before mirtazapine), on extracellular noradrenaline, dopamine and DOPAC concentrations in the medial prefrontal cortex or in the occipital cortex. Data are means ± S.E.M. of at least five rats. (●, ▲, ■) indicate $P<0.05$ with respect to basal values (Dunnett test).

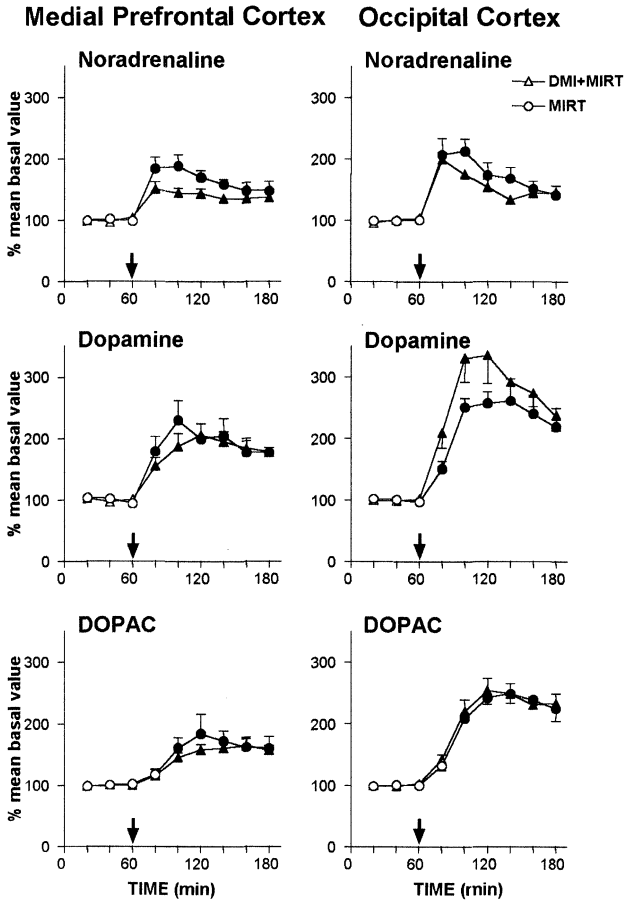

Fig. 4. Effects of mirtazapine (MIRT, 5 mg/kg, i.p. administered at the time indicated by the arrow) on extracellular noradrenaline, dopamine and DOPAC concentrations in the medial prefrontal cortex or in the occipital cortex, alone or during the cortical perfusion with desipramine (DMI, 100 μM). Data are means ± S.E.M. of 4–6 rats per treatment group. (●, ▲) indicate $P<0.05$ with respect to basal values (Dunnett test).

et al., 1984). Therefore, using a 100 μM concentration, both catecholamine transporters were likely to be inhibited. Accordingly, within 3–4 h desipramine perfusion increased both extracellular noradrenaline and dopamine in the medial prefrontal cortex to a stable plateau of respectively 326% and 840% of the baseline (the values obtained without desipramine in the perfusion fluid), while the respective values in the occipital cortex were increased to 295% and 1039%. Desipramine failed to significantly modify extracellular DOPAC in either cortex (Table 1). Mirtazapine (5 mg/kg, i.p.) was administered to desipramine-perfused rats once extracellular catecholamines had reached a stable plateau level, i.e., 3–4 h after the start of the perfusion.

As shown in Fig. 4, during desipramine perfusion mirtazapine still retained its effects on extracellular noradrenaline, dopamine and DOPAC, increasing them by the same percentage observed in control conditions, in the absence of desipramine in the perfusion fluid (ANOVA results, medial prefrontal cortex: noradrenaline $P<0.0001$, $F_{(5,40)}=15.949$; dopamine $P<0.0001$, $F_{(5,40)}=21.709$; DOPAC $P<0.0001$, $F_{(5,40)}=27.213$; occipital cortex: noradrenaline $P<0.0001$, $F_{(4,32)}=29.051$; dopamine $P<0.0001$, $F_{(3,24)}=26.216$; DOPAC $P<0.0001$, $F_{(4,32)}=56.921$). Although the percent increases are similar, due to the higher basal level reached during desipramine perfusion, the absolute amount of extracellular catecholamines elicited by mirtazapine administration was much higher during desipramine perfusion than in control condition.

4. Discussion

The results confirm previous observations that extracellular noradrenaline concentration is similar in the medial prefrontal cortex and in the occipital cortex, consistent with the homogeneous distribution of noradrenergic neurons (Devoto et al., 2003a,b,c), and that extracellular dopamine concentration in the occipital cortex is only 43% lower than in the medial prefrontal cortex, in spite of the scarce dopaminergic projections in the occipital cortex (Descarries et al., 1987). These results support the hypothesis that extracellular dopamine in the cerebral cortex reflects mostly noradrenergic innervation and activity and that dopamine measured by microdialysis in the cerebral cortex originates not only from dopaminergic nerve terminals but also from noradrenergic ones. Consistent with this hypothesis, previous results indicate that extracellular dopamine in the medial prefrontal cortex as well as in the occipital cortex is modified by drugs that act on noradrenergic neurons but not, or very weakly, by selective dopaminergic drugs (Devoto et al., 2003a,b,c).

Several considerations support the idea that mirtazapine acts by inhibiting α_2-adrenoceptor located on noradrenaline neurons. Mirtazapine has considerable affinity for α_2-adrenoceptor (De Boer, 1996; Millan et al., 2000), and increases the firing rate of noradrenaline neurons in the locus coeruleus (Millan et al., 2000). Moreover, mirtazapine effect on extracellular catecholamines in the cerebral cortex is identical to that of other α_2-adrenoceptor antagonists, including idazoxan, RS 79948 and the atypical antipsychotic clozapine, all of which systemically injected or locally perfused into the cortex, have been shown to produce a concomitant increase in noradrenaline and dopamine similar to that observed with mirtazapine (Devoto et al., 2001, 2003b,c). The finding that mirtazapine increased extracellular DOPAC in the occipital cortex confirms previous observations that DOPAC is normally formed in small amounts in noradrenaline neurons, and that DOPAC formation in these neurons may remarkably increase upon their stimulation (Scatton et al., 1984; Curet et al., 1985).

The finding that perfusion of tetrodotoxin in the cerebral cortex profoundly reduced both noradrenaline and dopamine and totally suppressed mirtazapine-induced dopamine and noradrenaline output in the occipital cortex, indicates that both extracellular dopamine and noradrenaline originate from a nerve impulse mediated process.

It is likely that mirtazapine activates noradrenaline neuronal activity and coreleases noradrenaline and dopamine by inhibiting α_2-adrenoceptor. This possibility is supported by the finding that the α_2-adrenoceptor agonist clonidine suppressed not only mirtazapine-induced increase in extracellular noradrenaline, consistent with its ability to suppress noradrenergic neuronal activity, but also mirtazapine-induced increase in extracellular dopamine, both in the medial prefrontal cortex and occipital cortex.

The finding that mirtazapine maintained its ability to increase extracellular dopamine in the medial prefrontal cortex and occipital cortex after inhibition of noradrenaline and dopamine uptake mechanisms, argues against the possibility that mirtazapine might reduce dopamine clearance from extracellular compartments by increasing noradrenaline concentrations at the noradrenaline transporter. In contrast, this finding supports the hypothesis that mirtazapine increases both catecholamines by increasing their corelease from noradrenergic neurons.

Accordingly, previous observations have shown that mirtazapine does not increase dopamine in the striatum, where extracellular dopamine is released from dopaminergic terminals (Millan et al., 2000).

An important question concerns the functional implications of mirtazapine-induced corelease of noradrenaline and dopamine not only in the medial prefrontal cortex but also in the occipital cortex and likely in other cortices.

Cortical noradrenaline plays a key role in depression, arousal, attention, (Rajkowska, 2000; Arnsten, 1997) while dopamine in the prefrontal cortex is implicated in attentional, psychomotor, reinforcing and rewarding behaviours (Steketee, 2003; Jay, 2003; Braver and Barch, 2002).

Thus it is conceivable that the antidepressant effect of mirtazapine is mediated by the activation of noradrenergic

neurons in the cerebral cortex and the resulting corelease of noradrenaline and dopamine.

Moreover, because dopamine and noradrenaline exert an inhibitory effect on cortical glutamatergic neurons projecting to the mesolimbic dopaminergic pathway (Tassin, 1998), mirtazapine, by increasing prefrontal dopaminergic and noradrenergic output might reduce the excitatory input from the frontal cortex to mesolimbic dopaminergic neurons. By this mechanism, mirtazapine might augment the efficacy of antipsychotics in the treatment of schizophrenia and possibly generate an atypical antipsychotic drug profile, as suggested for the noradrenaline uptake inhibitor reboxetine (Linner et al., 2001) and for the α_2-adrenoceptor antagonist idazoxan (Hertel et al., 1999).

Finally, by enhancing catecholamines in the medial prefrontal cortex and in other cortices, mirtazapine might influence attentional process, possibly via dopamine D_1 receptors and α_1-adrenoceptors, known to positively modulate working memory (Arnsten, 2000; Castner et al., 2000). Accordingly, mirtazapine might be of clinical usefulness in attention deficit hyperactivity disorder, a condition in which psycho stimulants and noradrenaline uptake inhibitors are used (Bymaster et al., 2002).

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