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Effect of a selective 5-hydroxytryptamine reuptake inhibitor on brain extracellular noradrenaline: microdialysis studies using paroxetine

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Abstract

The clinical efficacy of selective serotonin (5-hydroxytryptamine, 5-HT) reuptake inhibitors (SSRIs) is normally attributed to their ability to increase brain 5-HT function although recent preclinical findings indicate that their selectivity for 5-HT over noradrenaline may be less evident in vivo. The present study investigated the effects of the SSRI, paroxetine, on extracellular levels of noradrenaline.

Microdialysis was carried out in the hippocampus of the awake rat. In rats treated twice daily for 14 days with paroxetine (5 mg/kg s.c.), dialysate levels of noradrenaline showed a maintained two-fold increase compared to saline-injected controls. Paroxetine (5 mg/kg s.c.) administered once daily for 14 days did not cause a sustained increase in noradrenaline but levels showed a moderate (+58%) increase in response to a paroxetine challenge. Acute injection of paroxetine (5 mg/kg s.c.) did not elevate noradrenaline levels. Paroxetine (5 mg/kg s.c.) elevated dialysate 5-HT after both acute and repeated (twice daily for 14 days) treatment. The paroxetine-induced increase in noradrenaline (and 5-HT) was positively correlated with plasma concentrations of the drug, which were around the therapeutic range. In comparison to paroxetine, desipramine (10 mg/kg s.c.) caused a four-fold increase in dialysate noradrenaline (but did not change 5-HT) following repeated (once daily for 14 days) treatment and a two-fold increase at for acute treatment.

In summary, despite its selectivity as a 5-HT reuptake inhibitor, paroxetine increased extracellular levels of noradrenaline in rat hippocampus following repeated administration. We discuss the possibility that a facilitation of noradrenaline function might be involved in the antidepressant effect of paroxetine, and possibly other SSRIs.

Keywords: Paroxetine; Desipramine; Microdialysis; 5-HT; Noradrenaline

1. Introduction

Current generations of antidepressant drugs include those that are either selective serotonin (5-hydroxytryptamine, 5-HT) reuptake inhibitors (SSRIs) such as paroxetine, fluoxetine, citalopram, fluvoxamine and sertraline, and those that are selective for noradrenaline such as desipramine and reboxetine. When administered over several weeks, both classes of drug have demonstrated efficacy in the treatment of major depression, and SSRIs are finding increasing use in other psychiatric conditions including panic disorder, obsessive compulsive disorder and possibly social phobias.

It is well established that SSRIs selectively block 5-HT versus noradrenaline reuptake in vitro (e.g. Owens et al., 1997) and it is generally assumed their antidepressant effect is attributed to an increase in brain 5-HT function. However, recent preclinical studies indicate that the selectivity of SSRIs for 5-HT over noradrenaline might be less apparent in vivo. For example, in microdialysis studies several groups find that acute administration of the SSRI, fluoxetine, increases brain extracellular noradrenaline as well as 5-HT (Jordan et al., 1994; Hughes and Stanford, 1996; Gobert et al., 1997; Perry and Fuller, 1997). The selectivity of fluoxetine for 5-HT versus noradrenaline uptake is modest compared with that of other SSRIs (see Stanford, 1996). Recent microdialysis studies found that acute administration of citalopram, which has greater se-

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lectivity for 5-HT than fluoxetine (e.g. Owens et al., 1997), had no effect on extracellular noradrenaline in frontal cortex despite increasing 5-HT (Millan et al., 1999). In agreement, another recent study found that sertraline had no effect on noradrenaline when administered acutely (Thomas et al., 1998). However, in the latter study, sertraline increased extracellular noradrenaline when administered repeatedly (Thomas et al., 1998).

The latter microdialysis study suggests that SSRIs might alter noradrenaline function only following repeated administration. In support of this, a recent electrophysiological study found that the 2 week administration of paroxetine reduced the firing of noradrenaline neurones whereas acute administration had no effect (Szabo et al., 1999). The effect of acute or chronic administration paroxetine on extracellular noradrenaline is not currently known.

In the present microdialysis study, we have examined the effects of both acute and chronic treatment with paroxetine on extracellular noradrenaline in rat hippocampus. The effect of paroxetine was compared with that of the tricyclic antidepressant, desipramine, which is selective for noradrenaline versus 5-HT reuptake. A preliminary account of some of the findings was presented to the British Pharmacological Society (Hajós-Korcsok et al., 1999b).

2. Methods

2.1. Animals and antidepressant treatments

Male Sprague–Dawley rats (250–300 g, Harlan–Olac, Bicester, UK) were housed in groups of five to six under conditions of controlled temperature (21 ± 1°C) and lighting (lights on 0800–2000 h); food pellets and water were freely available.

Rats ($n = 4$–6/group) were injected s.c. for 14 days with one of the following four treatments: (i) paroxetine (5 mg/kg) twice daily (injections between 0800–0900 h and 1700–1800 h), (ii) paroxetine (5 mg/kg) once daily (injections between 1000–1200), (iii) desipramine (10 mg/kg) once daily, or (iv) vehicle (5% glucose) once daily. Microdialysis measurements were carried out during the day following the last injection.

2.2. Microdialysis

On the day of the last injection, rats were anaesthetized with halothane, and microdialysis probes (4-mm tip length) were implanted into the ventral hippocampus and fixed in position with dental cement. Stereotaxic co-ordinates were: rostro-caudal: −5.0 mm, medio-lateral: −4.6 mm, dorso-ventral: −8.5 mm, from bregma and dura surface (Paxinos and Watson, 1986). To allow administration of drugs with minimal handling, a subcutaneous cannula was also implanted at the back of the neck. After recovery, animals were returned to their home cage.

The day after surgery, animals were placed in a hemispherical Perspex bowl, and microdialysis probes were connected to perfusion pumps. Probes were perfused continuously (2 μl/min) with artificial cerebrospinal fluid. Perfusates were collected every 30 min (total volume of 60 μl), and samples were divided and immediately analyzed for noradrenaline and 5-HT (see below).

After establishing stable basal levels of noradrenaline and 5-HT (2–3 h after commencing perfusion), animals received a challenge injection of paroxetine (5 mg/kg), desipramine (10 mg/kg) or vehicle, as appropriate. The effect of the challenge injection was followed for a further 3 h.

2.3. Measurement of dialysate 5-HT and noradrenaline

Perfusate samples were analyzed for noradrenaline and 5-HT using high-performance liquid chromatography (HPLC) with electrochemical detection. Noradrenaline was separated using a Rainin Dynamax HPLC column (4.6 × 100 mm, Microsorb C_{18} 5 μm particles) with a mobile phase comprising 0.1 M NaH_2PO_4, 1.8 mM sodium octane sulphonate, 0.5 mM EDTA and 12% (v/v) methanol (final pH 4.0, flow rate 1.2 ml/min).

5-HT was separated using a Rainin Dynamax HPLC column (4.6 × 150 mm, Microsorb C_{18} 5 μm particles) and a mobile phase comprising 0.12 M NaH_2PO_4, 0.01 mM sodium octane sulphonate, 0.1 mM EDTA and 12.5% (v/v) methanol (final pH 3.8, flow rate 1.1 ml/min). Electrochemical detection (BAS LC-4 potentiometer) was by a glassy carbon electrode (+0.7 V versus Ag/AgCl reference electrode).

2.4. Measurement of plasma paroxetine levels

In about half of the paroxetine-treated rats, the level of plasma paroxetine was measured. In these cases, after completing the dialysis experiment animals were returned to their home cage and a second injection of paroxetine was administered at the usual time (1700–1800 h) according to whether the animals were on the once- or twice-daily regimen. The following day (i.e. either 12 or 24 h after the last injection of paroxetine), animals were killed and trunk blood was collected into plastic lithium heparinised tubes. Samples were centrifuged ($1300 \times g$, 4°C, 15 min) and the plasma was removed and stored (−20°C) until analysis. Plasma paroxetine levels were analyzed by HPLC with coulometric detection (Clement et al., 1998).

2.5. Data analysis

Data are presented as absolute amounts of noradrenaline and 5-HT (fmol/30 μl sample). Between group analysis was performed using two-way analysis of variance (ANOVA) with repeated measures. The effect of an acute

drug challenge was analyzed within group by one-way ANOVA with repeated measures.

Basal levels of noradrenaline and 5-HT were calculated as the average of the last four samples collected before drug or vehicle administration. Between group baseline data were analyzed statistically using one-way ANOVA followed by Dunnett's *t*-test. The correlation between plasma paroxetine concentrations and noradrenaline or 5-HT levels was analyzed by linear regression. Probability levels of 5% or less were considered statistically significant.

3. Results

3.1. Effect of acute and repeated administration of paroxetine on dialysate noradrenaline

A single injection of paroxetine (5 mg/kg s.c.) had no significant effect on dialysate noradrenaline levels in the hippocampus of control rats (vehicle twice daily for 14 days, one-way ANOVA, $F(8,24) = 1.72$; Fig. 1).

In contrast, in rats treated repeatedly with paroxetine (5 mg/kg s.c. twice daily for 14 days), basal noradrenaline levels were two-fold higher than vehicle-treated controls (Fig. 1 and Table 1). In these animals, challenge dose of paroxetine (5 mg/kg s.c.) had no further effect on noradrenaline (one-way ANOVA, $F(8,48) = 1.01$; Fig. 1).

In animals treated once daily for 14 days with paroxetine (5 mg/kg s.c.), basal levels of noradrenaline were not statistically different from vehicle-treated controls (Fig. 1 and Table 1). However, a further injection of paroxetine (5 mg/kg s.c.) caused a modest (+58% at $t = 90$ min) but significant increase in noradrenaline when compared with pre-drug levels (one-way ANOVA, $F(8,32) = 3.39$, $p < 0.006$; Fig. 1).

Table 1
Summary of the basal levels of 5-HT, 5-HIAA and noradrenaline in dialysates collected from the hippocampus of rats treated with paroxetine (5 mg/kg), desipramine (10 mg/kg) or vehicle

	5-HT (fmol/sample)	5-HIAA (pmol/sample)	Noradrenaline (fmol/sample)
Treatment-naive	15.5 ± 3.72	3.98 ± 0.23	19.6 ± 4.21
Repeated vehicle	15.5 ± 2.15	3.68 ± 0.43	17.0 ± 2.48
Repeated paroxetine once daily	21.7 ± 3.32	2.73 ± 0.49	14.9 ± 1.72
Repeated paroxetine twice daily	30.4 ± 4.31[a]	1.38 ± 0.14[a]	30.1 ± 2.98[a]
Repeated desipramine once daily	13.9 ± 2.28	3.67 ± 0.55	75.7 ± 10.41[a]

Values are mean ± S.E.M. values ($n = 6$–9).
[a] $P < 0.05$ compared to repeated vehicle-treated rats (one-way ANOVA, post-hoc Dunnett's test).

3.2. Effect of acute and repeated administration of paroxetine on dialysate 5-HT

The same doses of paroxetine examined above were tested for their effect on dialysate 5-HT. Acute injection of paroxetine (5 mg/kg s.c.) caused a doubling of dialysate 5-HT levels in the hippocampus of control rats (vehicle

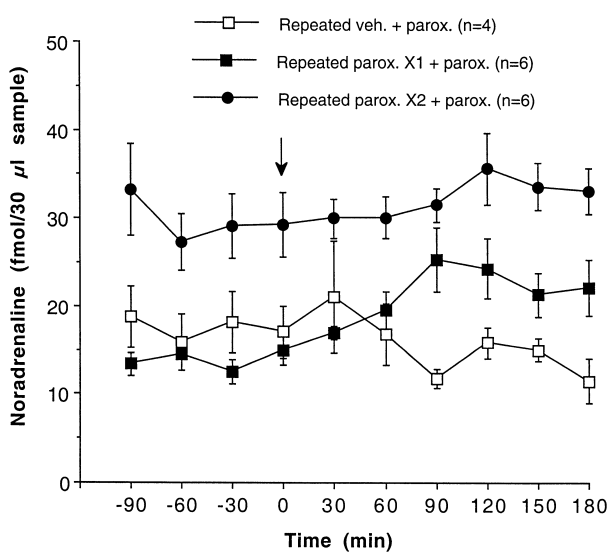

Fig. 1. Effect of repeated administration of paroxetine on dialysate noradrenaline levels in the hippocampus. Data are expressed as absolute amount of noradrenaline (fmol/30 µl dialysate). Paroxetine (5 mg/kg s.c.) was administered as indicated by the arrow. Each time point is a mean ± S.E.M. value. Two-way ANOVA revealed significant treatment ($F(2,13) = 11.45$, $p < 0.001$), but not time ($F(8,16) = 1.61$) effect.

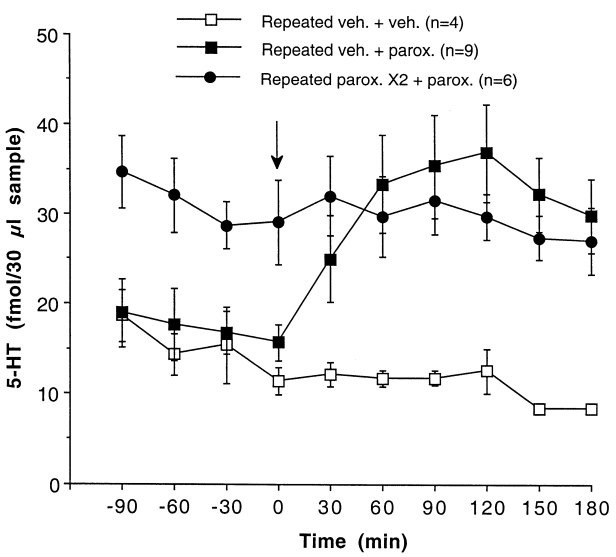

Fig. 2. Effect of repeated administration of paroxetine on dialysate 5-HT levels in the hippocampus. Data are expressed as absolute amount of 5-HT (fmol/30 µl dialysate). Paroxetine (5 mg/kg s.c.) or 5% glucose vehicle was administered as indicated by the arrow. Each time point is a mean ± S.E.M. value. Two-way ANOVA revealed a significant treatment x time interaction ($F(24,184) = 3.34$, $p < 0.0001$). For further statistical analysis, see Section 3.2.

once daily for 14 days; one-way ANOVA, $F(8,72) = 10.25$, $p < 0.0001$; Fig. 2 and Table 1). Levels of 5-HT were also elevated two-fold by twice (but not once) daily injection of paroxetine (5 mg/kg s.c. for 14 days) compared to vehicle-treated controls (Fig. 2 and Table 1).

3.3. Plasma levels of paroxetine after repeated treatments

Plasma levels of paroxetine were negligible 24 h after the drug (5 mg/kg s.c.) was administered either once only or once daily for 15 days (4.1 ng/ml ($n = 2$) and 7.3 ± 1.4 ng/ml ($n = 6$), respectively). In contrast, plasma paroxetine levels were readily detectable in animals 12 h after 5 mg/kg s.c. paroxetine administered twice daily for 15 days (213.5 ± 74.4 ng/ml, range 54.6–572.7, $n = 6$). This

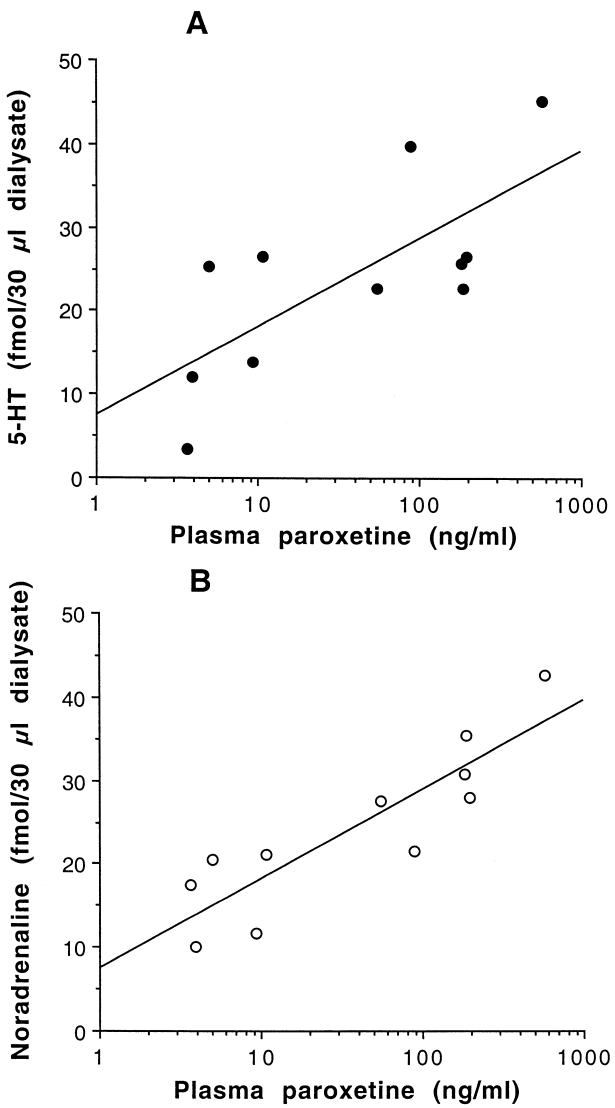

Fig. 3. Relationship between plasma levels of paroxetine and dialysate 5-HT (A) and noradrenaline (B). Rats were injected with paroxetine (5 mg/kg s.c.) once or twice daily for 14 days. Basal 5-HT and noradrenaline levels in the hippocampus are shown. Each point represents absolute data (fmol/sample) from one rat. For statistical analysis, see Section 3.3.

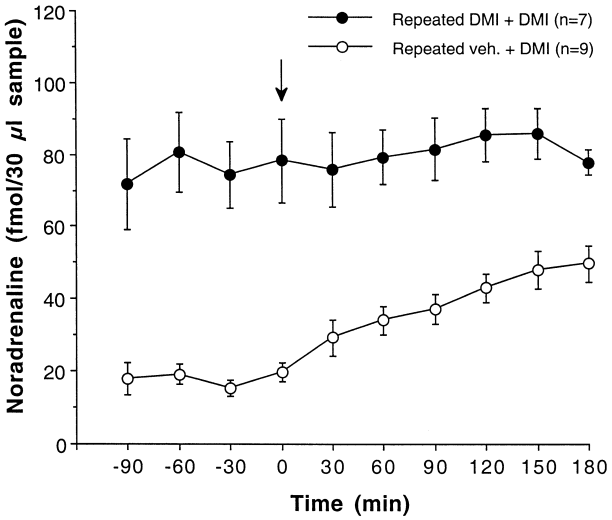

Fig. 4. Effect of repeated administration of desipramine on dialysate noradrenaline levels in the hippocampus. Data are expressed as absolute amount of noradrenaline (fmol/30 µl dialysate). Desipramine (10 mg/kg s.c.) was administered as indicated by the arrow. Each time point is a mean ± S.E.M. value. Two-way ANOVA revealed a significant treatment × time effect ($F(8,120) = 5.51$, $p < 0.0001$). For further statistical analysis, see Section 3.4.

was taken to indicate that the twice-daily injection regime more effectively sustained plasma paroxetine levels over the 24 h period.

As shown in Fig. 3, there was a positive correlation between plasma concentrations of paroxetine and dialysate levels of both noradrenaline ($r = 0.85$, $p < 0.001$) and 5-HT ($r = 0.69$, $p < 0.05$).

3.4. Effect of acute and repeated desipramine treatment on dialysate noradrenaline and 5-HT

Acute injection of desipramine (10 mg/kg s.c) caused a two-fold increase in dialysate noradrenaline levels above pre-drug values (one-way ANOVA, $F(8,72) = 24.09$, $p < 0.0001$; Fig. 4). Noradrenaline levels increased about four-fold after repeated injection of desipramine (10 mg/kg s.c. once daily for 14 days; Fig. 4 and Table 1). In the same experiments, desipramine had no effect on 5-HT levels (Table 1).

4. Discussion

This microdialysis study determined the effect of paroxetine on extracellular noradrenaline in the hippocampus of the awake rat. Paroxetine was selected for the study for several reasons: (i) it is the most potent inhibitor of the 5-HT transporter currently available, (ii) it has high selectivity for the 5-HT versus noradrenaline transporter in rat and human (1180- and 1307-fold, respectively) (Owens et al., 1997) and (iii) in the rat it has a long half-life (~ 8 h,

e.g. Owens et al., 2000) which makes it particularly useful for repeated administration. Administration of paroxetine (5 mg/kg s.c.) twice daily for 14 days caused a sustained, two-fold increase in dialysate levels of noradrenaline. This effect was related both to frequency and the duration of treatment. Thus, once daily paroxetine did not elevate basal noradrenaline but a further paroxetine challenge caused a modest increase. No increase in noradrenaline increase was found after acute paroxetine administration. The paroxetine dose regimen used in these experiments was validated in terms of increasing extracellular 5-HT and achieving plasma levels of the drug around the working therapeutic range (approximately 10–200 ng/ml) (Eap et al., 1998; Owens et al., 2000; cf. Fig. 3).

Few studies have examined the effect of chronic SSRI administration on extracellular noradrenaline. Recently, Thomas et al. (1998) reported an increase in extracellular noradrenaline in frontal cortex of rats treated repeatedly (14 days) with sertraline, although no changes were found in the hippocampus. In contrast, Shachar et al. (1997) found no change in cortical extracellular noradrenaline following repeated (21 days) treatment with fluvoxamine. It is possible that there are differences between individual SSRIs in terms of their effects on noradrenaline. However, these studies did not report either extracellular 5-HT levels or drug plasma levels in the SSRI treated animals, which makes it difficult to assess whether dosing was optimal. Given the current finding that noradrenaline (and 5-HT) only increased in the presence of significant plasma levels of the paroxetine, inadequate dosing may be an important factor.

The finding that *acute* paroxetine did not increase extracellular noradrenaline agrees with other studies using the SSRIs, sertraline, fluvoxamine and citalopram (Shachar et al., 1997; Thomas et al., 1998; Millan et al., 1999). Although fluoxetine increases extracellular noradrenaline after a single injection (Perry and Fuller, 1997; Jordan et al., 1994; Hughes and Stanford, 1996; Gobert et al., 1997), the drug is the least selective SSRI for 5-HT versus noradrenaline reuptake (Stanford, 1996; Owens et al., 1997).

Interestingly, a recent electrophysiological study found that paroxetine administered chronically (10 mg/kg/day for 21 days via osmotic minipump) but not acutely, reduces the noradrenergic cell firing (Szabo et al., 1999). While there are methodological differences between the present study and that of Szabo et al. (specifically, the route and duration of paroxetine administration), it is entirely plausible that the increase in extracellular noradrenaline seen here is associated with the inhibition of noradrenergic activity observed by Szabo et al. (1999). Thus, noradrenergic cell firing would decrease as a result of increased extracellular noradrenaline and the activation of somatodendritic α_2-adrenoceptor autoreceptors that follows. It is well established that these events occur following administration of noradrenaline uptake inhibitors such as desipramine (cf. Nybäck et al., 1975; L'Heureux et al., 1986).

Several lines of evidence suggest make it unlikely that the increase in extracellular noradrenaline after paroxetine is due to noradrenaline reuptake blockade. Paroxetine has low affinity for the rat noradrenaline uptake site in vitro (Buus Lassen, 1978; Thomas et al., 1987; Owens et al., 1997), and ex vivo studies estimate that the ED_{50} of paroxetine for blockade of noradrenaline uptake in the rat exceeds 30 mg/kg while for 5-HT reuptake it is 1.9 mg/kg (Thomas et al., 1987). The fact that paroxetine did not increase noradrenaline after acute administration (whereas desipramine did), also argues against a role for noradrenaline reuptake blockade. Interestingly, however, following the submission of this manuscript Owens et al. (2000) reported occupancy of the noradrenaline transporter in the brain of rats treated with paroxetine for one week. While a contribution of noradrenaline reuptake blockade cannot be excluded, it should be pointed out that this effect of paroxetine was modest (21% occupancy at high plasma concentrations [100–500 ng/ml]), highly variable between animals, and not detected by all the methods used.

An alternative to the latter explanation is that noradrenaline increases after paroxetine as a result of an interaction between 5-HT and noradrenaline. In favour of this, certain 5-HT receptors subtypes, specifically 5-HT_{1A} (Done and Sharp, 1994; Matsumoto et al., 1995; Hajós-Korcsok and Sharp, 1996; Hajós-Korcsok et al., 1999a) and 5-HT_3 (Blandina et al., 1991; Mongeau et al., 1994) have been found to exert a facilitatory influence on noradrenaline release. However, the increase in noradrenaline only occurred after repeated administration of paroxetine while extracellular 5-HT in hippocampus already increased after a single injection. Therefore, if an interaction between 5-HT and noradrenaline is involved it is likely to be via a neuroadaptive mechanism rather than a simple 5-HT receptor modulation of noradrenaline release. If the effect of paroxetine on noradrenaline reflects a 5-HT–noradrenaline interaction, other SSRIs will also raise extracellular noradrenaline. Clearly this is an important topic for further work.

It should be pointed out that although both paroxetine and desipramine increased extracellular noradrenaline the drugs were clearly distinct in their actions. Unlike desipramine, paroxetine did not increase extracellular noradrenaline after acute administration. Furthermore, unlike paroxetine, desipramine had no effect extracellular 5-HT. Overall these differences between the 5-HT and noradrenaline reuptake inhibitor may have functional significance.

Is there a role for increased extracellular noradrenaline in the therapeutic effect of paroxetine and other SSRIs? In this study, paroxetine increased extracellular noradrenaline at plasma levels around the therapeutic range (e.g. Eap et al., 1998). Furthermore, there are a several reports that noradrenaline metabolite levels are lowered in the CSF of patients taking paroxetine and other SSRIs (Potter et al.,

1985; Lundmark et al., 1994; Sheline et al., 1997). This decrease in metabolite levels could well arise as a consequence of adrenergic autoreceptor activation (see above). Although it is reported that patients treated with SSRIs do not relapse following inhibition of catecholamine synthesis (Delgado et al., 1993), recent data show that the latter manipulation lowers the mood of patients with a history of depression (Berman et al., 1999). An increase in noradrenaline during SSRI treatment may therefore help protect these vulnerable patients from relapse.

In conclusion, the present study found that repeated but not acute treatment with the selective 5-HT uptake inhibitor, paroxetine, causes an increase in extracellular noradrenaline (and 5-HT) in the rat hippocampus. This facilitatory effect of paroxetine on noradrenaline may reflect a 5-HT–noradrenaline interaction, in which case other SSRIs should have a similar effect. An increase in noradrenaline function may contribute to the antidepressant effect of paroxetine, and possibly other SSRIs.

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