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Inhibition of Hippocampal 5-HT Synthesis by Fluoxetine and Paroxetine: Evidence for the Involvement of Both 5-HT_{1A} and 5-$HT_{1B/D}$ Autoreceptors

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KEY WORDS hippocampus; raphe nuclei; 5-HT synthesis; 5-HT_{1A}; 5-$HT_{1B/1D}$ receptors; fluoxetine; paroxetine

ABSTRACT Hippocampal serotonin (5-hydroxytryptamine, 5-HT) synthesis, as determined by the accumulation of 5-hydroxytryptophan (5-HTP) following inhibition of L-aromatic amino acid decarboxylase with NSD 1015, was inhibited by systemic administration of the selective serotonin reuptake inhibitors fluoxetine (10 mg/kg i.p.) and paroxetine (3 mg/kg i.p.). Pretreatment of rats with the selective 5-HT_{1A} receptor antagonist WAY 100635 for a period of 7 days using subcutaneously implanted osmotic minipumps (1 mg/kg/day) was sufficient to block the inhibition of 5-HT synthesis following the 5-HT_{1A} receptor agonist 8-OH-DPAT (0.3 mg/kg s.c.), but failed to inhibit the decrease of hippocampal 5-HT synthesis by fluoxetine (10 mg/kg i.p.) or paroxetine (3 mg/kg i.p.). Similarly, pretreatment of rats with GR 127935 (5 mg/kg i.p.), an antagonist with high affinity for 5-$HT_{1B/D}$ receptors, blocked the reduction of hippocampal 5-HT synthesis following the 5-HT receptor agonist TFMPP (3 mg/kg s.c.) without affecting the reduction of hippocampal 5-HT synthesis by either fluoxetine or paroxetine. In contrast, pretreatment with WAY 100635 (1 mg/kg/day, for 7 days s.c. in osmotic minipumps) in combination with GR 127935 (5 mg/kg i.p.) significantly attenuated the decrease of hippocampal 5-HT synthesis by both fluoxetine and paroxetine. These results indicate that both 5-HT_{1A} and 5-$HT_{1B/1D}$ receptors, which function in the rat as inhibitory somatodendritic and nerve terminal autoreceptors, independently regulate hippocampal 5-HT synthesis and must be simultaneously blocked to prevent the inhibition of 5-HT synthesis by selective serotonin reuptake inhibitors which increase 5-HT availability at both nerve terminals in hippocampus and 5-HT cell bodies in the raphe nuclei. **Synapse 31:13–19, 1999.**

INTRODUCTION

It is now generally accepted that selective serotonin reuptake inhibitors (SSRIs) decrease brain serotonin (5-hydroxytryptamine, 5-HT) neuronal firing (Chaput et al., 1986; Arborelius et al., 1995; Gartside et al., 1995), synthesis (Carlsson and Lindquist, 1978; Moret and Briley, 1992), and increase the extracellular concentration of 5-HT in brain regions, particularly in the raphe nuclei (Perry and Fuller, 1992; Adell and Artigas, 1991; Bel and Artigas, 1992; Rutter and Auerbach, 1993; Malagie et al., 1995), which contain a high density of 5-HT reuptake sites (Hrdina et al., 1990).

The use of selective 5-HT_{1A} receptor agonists and antagonists has clearly demonstrated the importance of 5-HT_{1A} receptors, located in the raphe nuclei (Weissman-Nanopoulos et al., 1985), which function as autoreceptors in the regulation of 5-HT neuronal firing, 5-HT synthesis, metabolism, and release (Hjorth et al., 1982; Sprouse and Aghajanian, 1987; Hutson et al., 1987; Sinton and Fallon, 1988; Fletcher et al., 1996). Therefore, as there is a marked increase of extracellular 5-HT in the raphe nuclei following the systemic administration of SSRIs it is not unreasonable to assume that the inhibitory effects of SSRIs are mediated by an indirect action at somatodendritic 5-HT_{1A} autoreceptors. This appears to be the case for the inhibition of 5-HT neuronal firing by SSRIs, an effect which is blocked by pretreatment with WAY 100635, a selective 5-HT_{1A}

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receptor antagonist (Gartside et al., 1995). Furthermore, blockade of these inhibitory autoreceptors facilitates the increase of 5-HT in the extracellular space of forebrain regions following SSRIs (Hjorth, 1993, 1996; Hjorth and Auerbach, 1994; Gartside et al., 1995). Therefore, as 5-HT synthesis is inhibited by 5-HT_{1A} receptor agonists and by SSRIs it might be anticipated that this effect of SSRIs is also mediated via indirect activation of 5-HT_{1A} receptors. Surprisingly, pretreatment with the selective 5-HT_{1A} receptor antagonist WAY 100635 failed to reverse the inhibition of 5-HT synthesis by the SSRI citalopram (Moret and Briley, 1997), suggesting that the inhibition of brain 5-HT synthesis by SSRIs is independent of 5-HT_{1A} receptors.

However, 5-HT autoreceptors also exist on serotonin nerve terminals in many brain regions, including the dorsal raphe nucleus. These receptors belong to the 5-$HT_{1B/1D}$ subtypes and have been shown to regulate 5-HT release within the dorsal raphe nucleus, where their location, i.e., on dendrites or recurrent collaterals, is unclear, (Starkey and Skingle, 1993; Davidson and Stamford, 1995) and brain 5-HT synthesis (Hjorth et al., 1995). The potential role of 5-$HT_{1B/1D}$ autoreceptors in the regulation of 5-HT neuronal function by SSRIs has been suggested (Hjorth, 1993). Consistent with this idea, recent studies have demonstrated that the substantial increase of extracellular 5-HT concentration induced by SSRIs in combination with a 5-HT_{1A} receptor antagonist is also observed following the co-administration of an SSRI and a 5-HT_{1D} receptor antagonist (Rollema et al., 1996) and further enhanced by co-administration of SSRIs with selective 5-HT_{1A} and 5-$HT_{1B/1D}$ receptor antagonists (Gobert et al., 1997; Sharp et al., 1997). As both somatodendritic and terminal autoreceptors can independently regulate brain 5-HT synthesis, and as SSRIs increase the extracellular 5-HT concentration in the raphe nuclei and in forebrain regions such as the hippocampus, it is conceivable that both receptor subtypes are involved in the inhibition of brain 5-HT synthesis by SSRIs. Therefore, in the present study we determined if blockade of either or both 5-HT_{1A} and 5-$HT_{1B/1D}$ autoreceptors is required to attenuate the inhibition of hippocampal 5-HT synthesis by the selective SRIs fluoxetine and paroxetine. A preliminary report of this study, in abstract form, was made to the British Pharmacological Society (Barton and Hutson, 1997).

MATERIALS AND METHODS

Animals

Male Sprague Dawley rats (Bantin and Kingman, U.K., Ltd), weight range 250–300 g were housed on a 12-h light/dark cycle (lights on 07:00, off 19:00) with food and water available ad libitum. All procedures were carried out in accordance with the U.K. Home Office Animals (Scientific Procedures) Act, 1986.

Implantation of osmotic minipumps

Animals were anaesthetised with isofluorane and under aseptic conditions a small incision was made in the skin between the shoulder blades. An osmotic minipump (2ML4, Charles River, Alzet) prefilled with distilled water or water containing WAY 100635 (1 mg/kg/day) was then inserted under the skin and the incision sutured. Following recovery from anaesthesia, rats were transferred to single cages until termination of the experiment.

Drug treatment and determination of hippocampal 5-HT synthesis

Hippocampal 5-HT synthesis was determined by measuring the accumulation of 5-hydroxytryptophan (5-HTP) following inhibition of L-aromatic amino acid decarboxylase, essentially as described by Carlsson et al. (1972). Animals were pretreated acutely with either saline (1 ml/kg i.p. or s.c.), WAY 100635 (1 mg/kg s.c.), or GR 127935 (5 mg/kg i.p.) followed 30 min later by saline (1 ml/kg i.p. or s.c.), fluoxetine (10 mg/kg i.p.), paroxetine (3 mg/kg i.p.), 8-OH-DPAT (0.3 mg/kg s.c.), or TFMPP (3 mg/kg s.c.). In a second study, animals implanted 7 days previously with osmotic minipumps containing either vehicle (1 ml/kg/day) or WAY 100635 (1 mg/kg/day) were treated with saline (1 ml/kg s.c. or i.p.), 8-OH-DPAT (0.3 mg/kg s.c.), fluoxetine (10 mg/kg i.p.), or paroxetine (3 mg/kg i.p.). In a third study, rats were implanted with osmotic minipumps containing either vehicle or WAY 100635 (1 mg/kg/day), and 7 days later groups of rats were given either saline (1 ml/kg i.p.) or GR 127935 (5 mg/kg i.p) followed 30 min later by saline (1 ml/kg i.p.), fluoxetine (10 mg/kg i.p), or paroxetine (3 mg/kg i.p). All animals received NSD 1015 (100 mg/kg i.p.) 60 min after the last drug treatment and were humanely killed 30 min later. The hippocampi were removed, frozen on dry ice, and stored at -70°C until required for analysis of 5-HTP concentration.

Biochemical analysis

Hippocampal 5-HTP was determined essentially as described by Hutson et al. (1991). Briefly, brain samples were homogenised in 10 volumes of 0.4 M perchloric acid containing 0.02% L-cysteine, 0.02% ascorbic acid, and 0.0035% sodium EDTA. Following centrifugation at 10,000*g* for 10 min, aliquots were analysed for 5-HTP concentration by HPLC with electrochemical detection. The system comprised an HPLC Technology Techsphere 3 µm ODS column (4.6 mm × 7.5 cm). The mobile phase consisted of 0.07 M KH_2PO_4, 0.0035% EDTA Na, 0.023% sodium octyl sulphate, and 12.5% methanol, pH 2.75, pumped at a flow rate of 1 ml/min. 5-HTP was determined with an amperometric electrochemical detector (Antec Ltd., Netherlands) using a glassy carbon working electrode set at a potential of +0.7 V with respect to a silver / silver chloride reference

electrode. Under these conditions, retention times for 5-HTP, 5-HT, and 5-HIAA were 25, 19.8, and 5.4 min, respectively.

Statistical analysis

Data were analysed by two-way ANOVA followed where appropriate by Tukey's *t*-test. A value of $P < 0.05$ was considered significant.

Drugs used

8-OH-DPAT, 8-hydroxy-di-propylaminotetralin hydrobromide; TFMPP, N-(3-trifluoromethylphenyl) piperazine hydrochloride; NSD 1015, 3-hydroxy benzylhydrazine hydrochloride, (RBI, U.K.), WAY 100635, (N-[2-[4-(2-methoxyphenyl)-1-piperazinyl]-N-(2-pyridinyl) cyclo-hexanecarboxamide hydrochloride), GR 127935, 2-methyl-4-(5-methyl-[1,2,4]oxadiazol-3-yl)-biphenyl-(4-carboxylic acid [4-methoxy-3-(4-methyl-piperazine-1-yl)-phenyl]-amide were synthesised by the medicinal chemistry department, Merck Sharp and Dohme, Terlings Park, U.K. Drugs were dissolved in water when given by osmotic minipump or in 0.9% NaCl and injected in a volume of 1 ml/kg by the specified route.

RESULTS

Effects of acute administration of WAY 100635 on the inhibition of hippocampal 5-HT synthesis by fluoxetine and paroxetine

Hippocampal 5-HTP accumulation was significantly ($P < 0.05$) decreased to approximately 30% and 40% of control by fluoxetine (10 mg/kg i.p.) and paroxetine (3 mg/kg i.p.), respectively. Pretreatment with WAY 100635 given acutely (1 mg/kg s.c.) did not affect hippocampal 5-HTP accumulation per se, and also did not affect the reduction of hippocampal 5-HTP accumulation caused by fluoxetine or paroxetine (Fig. 1a,b).

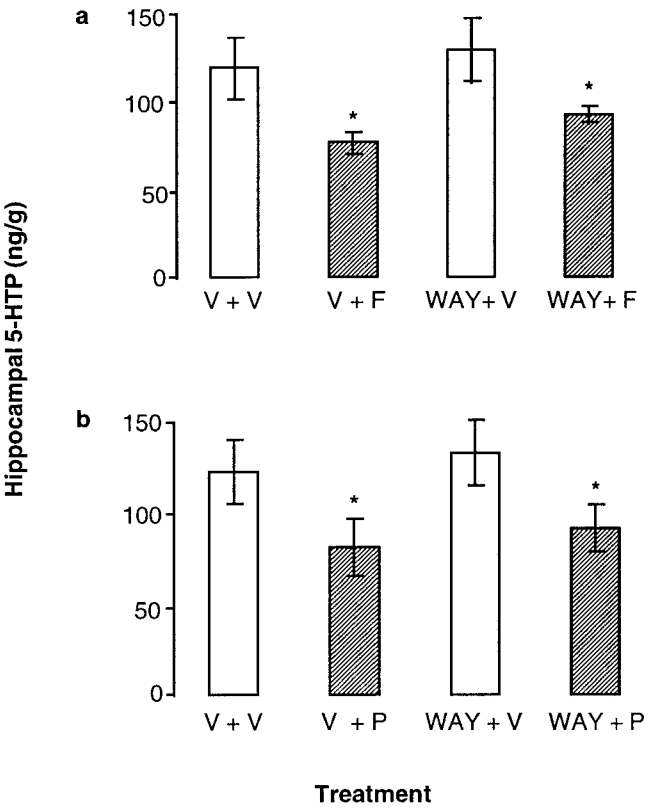

Fig. 1. Effects of pretreating animals with either vehicle (V; 1 ml/kg s.c.) or WAY 100635 (WAY; 0.3 mg/kg s.c.) on the decrease of hippocampal 5-HTP accumulation by (**a**) fluoxetine (F; cross-hatched columns) (10 mg/kg i.p.) and (**b**) paroxetine (P; cross-hatched columns) (3 mg/kg i.p.). Values are means ± SEM, n = 5/6 animals per group. * $P < 0.05$ compared with appropiate vehicle treated animals by Tukey's *t*-test.

Effects of WAY 100635 (7 days) or GR 127935 (acute) on the inhibition of hippocampal 5-HT synthesis by 8-OH-DPAT and TFMPP

Acute administration of the 5-HT $_{1B/1D}$ receptor antagonist GR 127935 (5 mg/kg i.p.) blocked the decrease of hippocampal 5-HTP accumulation induced by TFMPP (10 mg/kg i.p.) without affecting hippocampal 5-HTP accumulation per se (Fig. 2a). Administration of WAY 100635 (1 mg/kg/day) for 7 days in s.c.-implanted osmotic minipumps did not affect hippocampal 5-HTP accumulation per se, but significantly ($P < 0.05$) blocked the decrease of hippocampal 5-HTP accumulation following 8-OH-DPAT (0.3 mg/kg s.c.) (Fig. 2b).

Effects of WAY 100635 (7 days) on the decrease of hippocampal 5-HTP accumulation by fluoxetine and paroxetine

Fluoxetine (10 mg/kg i.p.) and paroxetine (3 mg/kg i.p.) significantly ($P < 0.05$) decreased hippocampal 5-HTP accumulation by approximately 40% of control values. Administration of WAY 100635 (1 mg/kg/day for 7 days) by s.c.-implanted osmotic minipump did not significantly affect basal 5-HTP accumulation and also did not affect the reduction of 5-HTP accumulation by either fluoxetine (10 mg/kg i.p.) or paroxetine (3 mg/kg i.p.) (Fig. 3a,b).

Effects of GR 127935 on the inhibition of hippocampal 5-HT synthesis by fluoxetine and paroxetine

Pretreatment with GR 127935 (5 mg/kg i.p.), a dose which had no effect on hippocampal 5-HTP accumulation per se, did not significantly affect the inhibition of hippocampal 5-HTP accumulation induced by either fluoxetine (10 mg/kg i.p.) or paroxetine (3 mg/kg i.p.) (Fig. 4a,b).

Effects of WAY 100635 (7 days) in combination with GR 127935 (acute) on the inhibition of hippocampal 5-HT synthesis by fluoxetine and paroxetine

Hippocampal 5-HTP accumulation in rats pretreated with WAY 100635 (1 mg/kg/day s.c.) for 7 days in

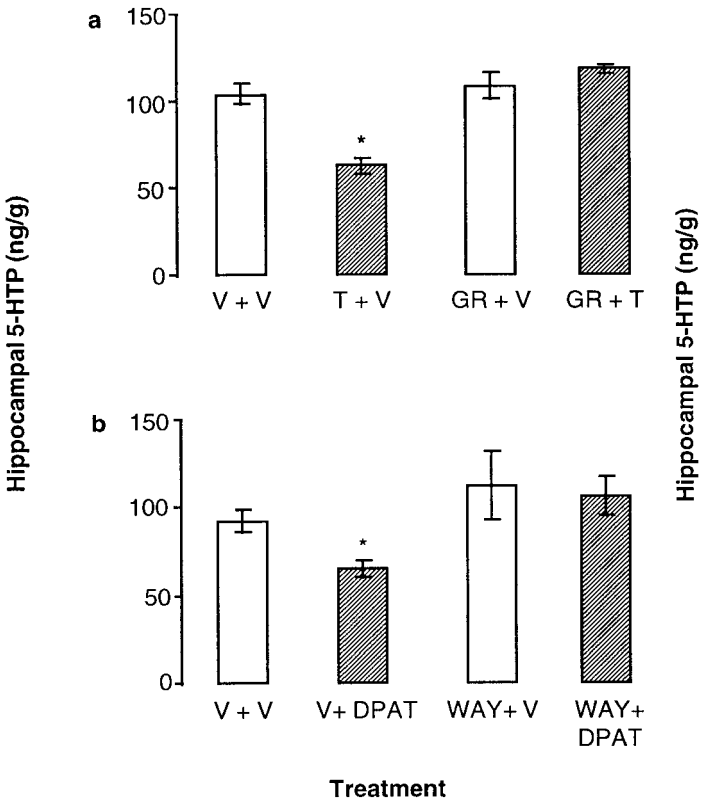

Fig. 2. Effects of (**a**) pretreating animals with either vehicle (V; 1 ml/kg i.p.) or GR 127935 (GR; 5 mg/kg i.p.) on the reduction of hippocampal 5-HTP accumulation by TFMPP (T; 10 mg/kg i.p.) (cross-hatched columns) and (**b**) pretreating rats with either vehicle (V; 1 ml/kg/day s.c.) or WAY 100635 (WAY; 1 mg/kg/day s.c.) for 7 days s.c. in osmotic minipumps on the decrease of hippocampal 5-HTP accumulation by 8-OH-DPAT (DPAT; 0.3 mg/kg s.c.) (cross-hatched columns). Values are means ± SEM, n = 5/6 animals per group, * $P <$ 0.05 compared with appropriate vehicle-treated animals by Tukey's *t*-test.

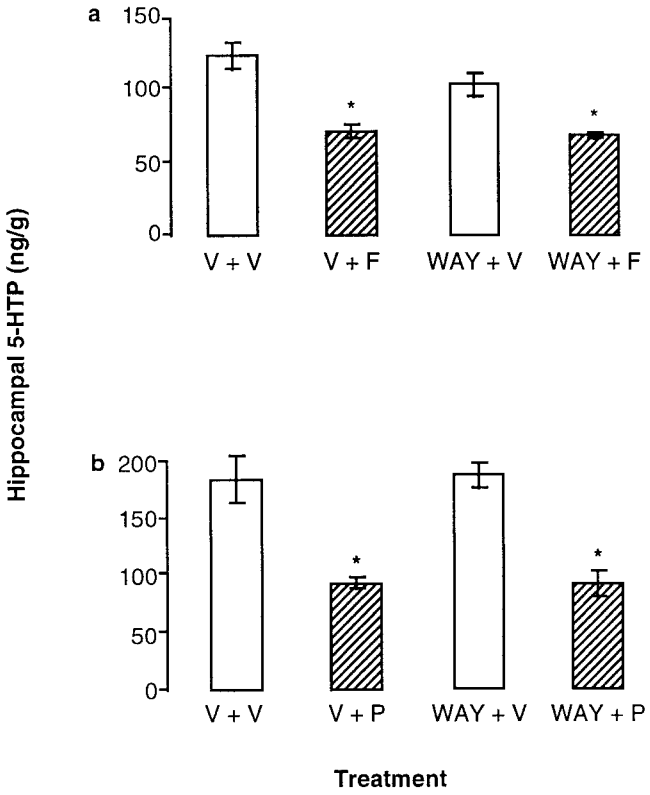

Fig. 3. Effects of pretreating animals with either vehicle (V; 1 ml/kg/day) or WAY 100635 (WAY; 1 mg/kg/day) for 7 days s.c. in osmotic minipumps on the decrease of hippocampal 5-HTP accumulation by (**a**) fluoxetine (cross-hatched columns) (F; 10 mg/kg i.p.) and (**b**) paroxetine (cross-hatched columns) (P; 3 mg/kg i.p.). Values are means ± SEM, n = 5/6 animals per group, * $P <$ 0.05 compared with appropriate control groups using Tukey's *t*-test.

combination with an acute dose of GR 127935 (5 mg/kg i.p.) was not significantly different from vehicle-treated control rats (Fig. 5a,b). However, in contrast to the lack of effect when given separately, the combination of WAY 100635 (1 mg/kg/day s.c.) for 7 days and an acute dose of GR 127935 (5 mg/kg i.p.) completely blocked the reduction of hippocampal 5-HTP accumulation induced by fluoxetine (10 mg/kg i.p.) or paroxetine (3 mg/kg i.p.) (Fig. 5a,b).

DISCUSSION

Results in the present study confirm established findings that SSRIs, including fluoxetine and paroxetine, inhibit brain 5-HT synthesis as estimated by the accumulation of 5-HTP following inhibition of L-aromatic amino acid decarboxylase with NSD 1015 (Carlsson and Lindqvist, 1978; Moret and Briley, 1992). However, the mechanism by which this occurs has not been fully characterised.

The inhibition of 5-HT neuronal firing and 5-HT release from cortex or hippocampus by SSRIs appear to be mediated by inhibition of somatodendritic 5-HT_{1A} autoreceptors located on 5-HT cell bodies in the raphe nuclei. Thus, the highly selective and silent 5-HT_{1A} receptor antagonist WAY 100635 blocked the inhibition of 5-HT cell firing by 8-OH-DPAT and the SSRI paroxetine (Gartside et al., 1995; Fletcher et al., 1996). Similarly, the inhibition of 5-HT release by citalopram and paroxetine was blocked by pretreatment with 5-HT_{1A} receptor antagonists pindolol and WAY 100135 (Hjorth and Auerbach, 1994). In the present study, acute administration of WAY 100635 at a dose previously shown to block the effects of 5-HT_{1A} receptor agonists or SSRIs did not affect the reduction of 5-HT synthesis by either fluoxetine or paroxetine, confirming recent findings that the reduction of 5-HT synthesis by citalopram was unaffected by an acute dose of WAY 100635 (Moret and Briley, 1997). It could be argued that after the acute administration of WAY 100635, insufficient drug was available at 5-HT_{1A} receptors over the time required for fluoxetine and paroxetine to decrease 5-HT synthesis. Therefore, in a separate study WAY 100635 was administered continuously in s.c.-implanted osmotic minipumps for a period of 7 days,

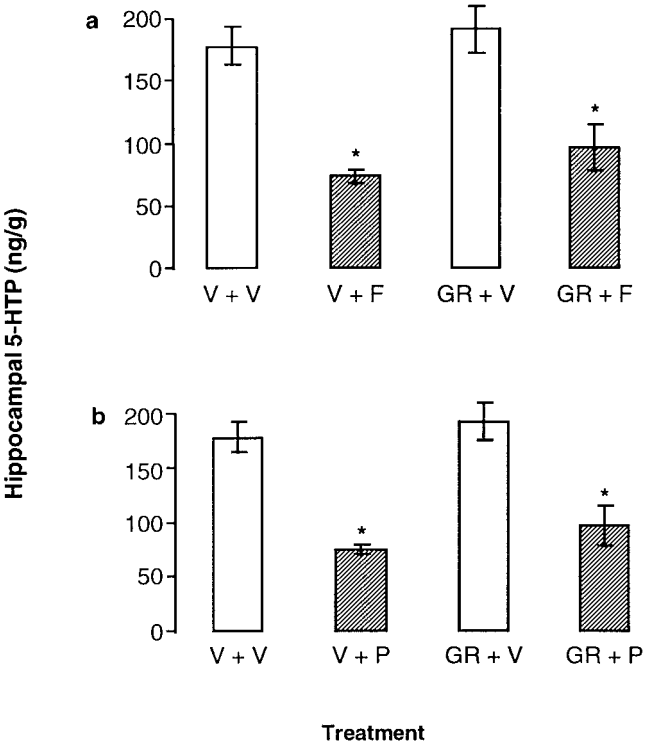

Fig. 4. Effects of pretreating rats with either vehicle (V; 1 ml/kg i.p.) or GR 127935 (GR; 5 mg/kg i.p.) on the reduction of hippocampal 5-HTP accumulation by (**a**) fluoxetine (cross-hatched columns) (F; 10 mg/kg i.p.) and (**b**) paroxetine (cross-hatched columns) (P; 3 mg/kg i.p.). Values are means ± SEM, n = 5/6 animals per group. * $P < 0.05$ compared with appropriate control groups using Tukey's *t*-test.

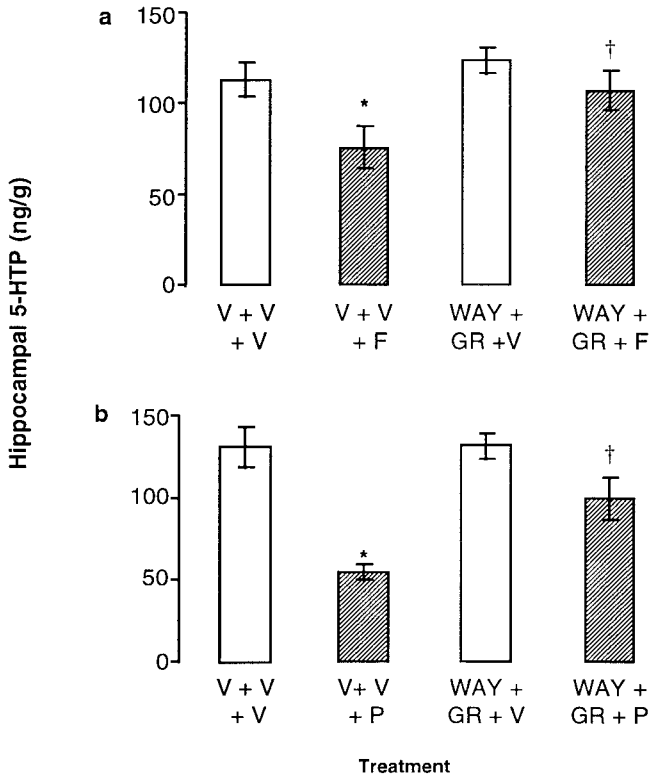

Fig. 5. Effects of pretreating rats with either vehicle (V; 1 ml/kg/day) or WAY 100635 (WAY; 1 mg/kg/day) for 7 days s.c. in osmotic minipumps in combination with either vehicle (V; 1 ml/kg i.p.) or GR 127935 (GR; 5 mg/kg i.p.) on the decrease of hippocampal 5-HTP accumulation by (**a**) fluoxetine (cross-hatched columns) (F; 10 mg/kg i.p.) or (**b**) paroxetine (cross-hatched columns) (P; 3 mg/kg i.p.). Values are means ± SEM, n = 5/6 animals per group, * $P < 0.05$ compared with vehicle/vehicle treated rats, † $P < 0.05$ compared with fluoxetine/vehicle or paroxetine/vehicle-treated rats by Tukey's *t*-test.

thereby ensuring the long-term presence of the antagonist. As the reduction of hippocampal 5-HT synthesis following the 5-HT_{1A} receptor agonist 8-OH-DPAT was blocked at 7 days, it was assumed that this dose of WAY 100635 was sufficient to block 5-HT_{1A} receptors. However, 7-day administration of WAY 100635 (1 mg/kg/day) was also ineffective in blocking the inhibitory effects of fluoxetine or paroxetine on hippocampal 5-HT synthesis suggesting, in agreement with Moret and Briley (1997), that 5-HT_{1A} receptors are not involved in this response.

5-HT synthesis (Hjorth et al., 1995) and release (Davidson and Stamford, 1995) may also be regulated by 5-HT_{1B} and/or 5-HT_{1D} receptor subtypes. GR 127935 has high affinity for both 5-HT_{1B} and 5-HT_{1D} receptors (Pauwels, 1996) and functionally it attenuated the inhibition of 5-HT release induced by 5-HT in vitro (Starkey and Skingle, 1993) and either decreased (Skingle et al., 1995) or was without effect (Hutson et al., 1995) on 5-HT efflux in guinea pig cortex at doses up to 5 mg/kg in vivo. In the present study, consistent with an antagonist action at 5-$HT_{1B/1D}$ receptors and with the suggestion by Hjorth et al. (1995) that 5-HT_{1B} autoreceptors regulate brain 5-HT synthesis, GR 127935 (5 mg/kg) blocked the reduction of hippocampal 5-HT synthesis by the 5-HT receptor agonist TFMPP without affecting hippocampal 5-HT synthesis per se. However, the same dose of GR 127935 did not affect the reduction of 5-HT synthesis by either fluoxetine or paroxetine, suggesting that 5-$HT_{1B/1D}$ autoreceptors are also not exclusively involved in the inhibition of hippocampal 5-HT synthesis by SSRIs.

Recent studies have shown that the combination of an SSRI with WAY 100635 and GR 127935 produced an even greater increase of extracellular 5-HT concentration than when the SSRI was administered with each antagonist separately (Gobert et al., 1997; Sharp et al., 1997). This implies that not all the inhibitory influences on serotonin neuronal function by SSRI administration are reversed by treatment with a selective 5-HT_{1A} or 5-$HT_{1B/1D}$ receptor antagonist. In the present study, the combination of WAY 100635 and GR 127935 at doses which blocked both 5-HT_{1A} and 5-$HT_{1B/1D}$ receptor agonist-mediated effects in vivo attenuated the inhibition of hippocampal 5-HT synthesis by both fluoxetine and paroxetine. Interestingly, acute or 7-day treatment with WAY 100635, acute treatment with GR 127935, or the combination of both compounds failed to signifi-

cantly affect hippocampal 5-HT synthesis per se, suggesting that both receptor subtypes are subjected to very little endogenous tone under physiological conditions. However, under conditions of increased 5-HT tone, i.e., in the presence of serotonin reuptake blockade, it would appear that both somatodendritic and nerve terminal 5-HT autoreceptors act independently to regulate 5-HT synthesis and that both must be simultaneously blocked to completely reverse the inhibitory effects of SSRIs on hippocampal 5-HT synthesis.

This observation may be of interest in light of recent findings that brain 5-HT efflux following SSRIs is enhanced when combined with 5-HT_{1A} receptor antagonists (Hjorth, 1993; Gartside et al., 1995; Sharp et al., 1997). Clearly, this effect occurs while 5-HT synthesis is still inhibited, even though the inhibition of 5-HT neuronal firing is reversed, and suggests that if only somatodendritic or terminal autoreceptors are blocked, the increase of 5-HT by SSRIs can still activate autoreceptors which inhibit 5-HT synthesis. Enhanced 5-HT release can presumably only be sustained if 5-HT synthesis is also maintained, and from the present study this would not be the case unless both types of autoreceptor are blocked. Therefore, the advantage gained from combining SSRIs with 5-HT_{1A} receptor antagonists may be short-lived, as synthesis inhibition may limit the time for enhanced 5-HT release. However, it is also conceivable that enhanced 5-HT availability from the combination of an SSRI and a 5-HT_{1A} receptor antagonist may be sustained if, under these conditions, 5-$HT_{1B/1D}$ autoreceptors were sufficiently desensitised by the continued presence of a high concentration of extracellular 5-HT, thereby diminishing their inhibitory effect on 5-HT synthesis.

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