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Co-administration of fluoxetine and WAY100635 improves short-term memory function

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Abstract

The aim of this study was to determine whether the action of the antidepressant fluoxetine or the anxiolytic buspirone could be modified by specific 5-hydroxytriptamine (5-HT_{1A}) receptor blockade in a short-term memory paradigm. Male Wistar rats were trained to perform the putative short-term memory task, delayed non-matching to position. WAY100635, a selective 5-HT_{1A} receptor antagonist (0.15 mg/kg), was administered 15 min before either the selective serotonin reuptake inhibitor fluoxetine (3 mg/kg), or the partial 5-HT_{1A} receptor agonist and dopamine D2 receptor antagonist, buspirone (0.3 mg/kg). 8-Hydroxy-di-*n*-propylamino tetralin (8-OH-DPAT), a full 5-HT_{1A} receptor agonist (0.3 mg/kg), was also included in the study as a positive control. WAY100635 alone had no effect on any behavioural parameter measured (response accuracy, delay lever press activity and trial completion). 8-OH-DPAT impaired response accuracy in a delay-dependent manner, an effect reversed by WAY100635. Fluoxetine also impaired response accuracy delay-dependently. WAY100635 pretreatment not only reversed this deficit but improved response accuracy, in the presence of a significant deficit in trial completion. At the dose used, buspirone showed no significant differences compared to the control group. The data suggest that fluoxetine impairs short-term memory function by the indirect activation of 5-HT_{1A} receptors, but that its co-administration with WAY100635 improves short-term memory function.

Keywords: Short-term memory; 5-HT_{1A} receptor; Fluoxetine; Buspirone; 8-OH-DPAT (8-hydroxy-di-*n*-propylamino tetralin); WAY100635

1. Introduction

It is well established that the serotonin system plays an important role in mood disorders such as depression and anxiety. Accordingly, selective serotonin/5-hydroxytryptamine (5-HT) reuptake inhibitors have become the most frequently used class of drugs for treatment of major depression. Improvement of mood in patients taking these agents is generally assumed to result from increased serotonergic synaptic transmission. Serotonin reuptake inhibitors (SSRIs) block the main pathway for clearance of released 5-HT, increasing endogenous 5-HT at serotonergic nerve terminals. This increase in 5-HT also activates inhibitory somatodendritic 5-HT_{1A} autoreceptors, which limit the increase in extracellular 5-HT elicited by the serotonin re-uptake inhibitors (Artigas et al., 1996). It has been hypothesised that concurrent antagonism of somatodendritic 5-HT_{1A} receptors with 5-HT reuptake inhibition should result in a more rapid and effective antidepressant treatment (Artigas, 1993; Artigas et al., 1996; Hjorth et al., 2000). In support of this hypothesis, clinical studies suggest that the non-selective 5-HT_{1A} receptor antagonist pindolol may accelerate the antidepressant effects of fluoxetine and paroxetine when co-administered (Pérez et al., 1997; Tomé et al., 1997; Zanardi et al., 1997). Besides antidepressant properties, SSRIs have lately been implicated in cognitive function. Studies in both humans and animals have shown an enhancement of cognitive function by SSRIs (Altman et al., 1984; Meneses and Hong, 1995; Hasbroucq et al., 1997; Harmer et al., 2002). Since 5-HT_{1A} receptor activation impairs short-term memory function (e.g. Pache et al., 2000) and 5-HT_{1A} receptor blockade might improve the antidepressant properties of the SSRIs, one of the objectives of this study was to determine whether this combination also enhances cognitive function.

In addition to depression, the serotonergic system is also implicated in anxiety. For instance, non-benzodiazepine

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azapirone agents, which act as 5-HT_{1A} partial agonists, such as buspirone (Buspar®, Coplan et al., 1995) are a therapeutic option for the treatment of anxiety. Buspirone is an atypical anxiolytic sharing clinical efficacy with conventional benzodiazepines, but is considered to possess less deleterious side-effects (Riblet et al., 1982; Boulenguer et al., 1989). Buspirone, as a partial 5-HT_{1A} agonist, could be expected to exert a negative effect on mnemonic function. Thus, buspirone has been reported to impair memory of healthy volunteers (Bourin et al., 1989; Greenblatt et al., 1994). However, Lucki and Rickels (1988) in addition to Hart et al. (1991) concluded that buspirone did not affect cognition in normal elderly and anxious subjects, respectively. Studies in animals, however, have shown an impairment of memory following buspirone treatment (e.g. Bass et al., 1992; Pache et al., 2003). Pharmacologically, buspirone not only acts on the serotonergic system but also as a partial dopamine D2 receptor antagonist (McMillen et al., 1983). Moreover, its metabolite can block central α_2-adrenoceptors (Enberg, 1988).

In the present experiments, performance in the putative short-term memory paradigm, delayed non-matching to position, was compared in subjects treated with either fluoxetine or buspirone only, or when co-administrated with the selective 5-HT_{1A} antagonist *N*-{2-[4-(2-methoxyphenyl)-1-piperaziny]ethyl}-*N*-(2-pyridinyl) cyclohexanecarboxamide trihydrochloride (WAY100635; Fletcher et al., 1996). The dose of WAY100635 was chosen on the basis of behavioural data previously described (e.g. Fletcher et al., 1996) and confirmed by assessing its activity against a positive control: the selective 5-HT_{1A} agonist, 8-hydroxy-di-*n*-propylamino tetralin (8-OH-DPAT). The dose of fluoxetine was chosen for the current study because it is considered approximately equivalent to the clinical dose of 20 mg used in the treatment of depression (Hervás et al., 2001).

2. Materials and methods

2.1. Animals

Twelve male Wistar rats (Harlan, UK) weighing between 120 and 150 g at the start were used for this study. Animals were housed in triads in standard laboratory cages under a 12 h : 12 h light–dark cycle with an ambient room temperature of 21–23 °C. They were maintained at 85–90% of their free-feeding weights by restricting food access to 1 h per day from Monday to Friday and then allowing free access to food over the weekend. Water was available at all times. All experiments were performed in accordance with a project license issued under the authority of the Home Office Animals (Scientific Procedures) Act 1986 and approved by the local Ethical Review Process.

2.2. Apparatus

Three operant conditioning chambers (Campden Instruments, UK) were employed. The boxes were equipped with two non-retractable levers sited 6.5 cm above the grid floor on one (front) wall, either side of a central food magazine, these represented the sample levers (right and left). Each box was modified such that there was also a single non-retractable lever on the rear wall opposite the pair of levers and food magazine, representing the delay lever. This delay lever was positioned 9.5 cm from the grid floor. All boxes had three functioning lights: one above each of the levers (bulbs were rated at 1.0 V). Equipment was controlled by a BBC Master computer via a SPIDER interface (Paul Fray Ltd.) with software written by D. M. Pache.

2.3. Procedure

The procedure used in this experiment was a modification of the delayed matching to position paradigm originally published by Dunnett (1985). Animals were initially acclimatised to the operant chambers and collecting 45 mg precision food pellets (Campden Instruments, UK) from the central magazine. They were then trained to respond to the rear (delay) lever, and also the left and right levers on either side of the food magazine when the lights over those levers were switched on. Each appropriate lever press resulted in the delivery of a food pellet (continuous reinforcement schedule). Once consistent lever pressing had been established, the animals were trained to respond first to the sample lever, either right or left, and then to the delay lever to earn the food reward. Subsequently a delayed non-matching to position schedule was introduced. Animals were required to press one of two pseudorandomly determined sample levers, identified by switching on the light above either the left or right lever at the start of a trial. Once the sample lever was pressed the sample light stimulus was extinguished and the lever deactivated. During the subsequent 1 s delay interval, the delay lever light was switched on and the animals were required to respond on the delay lever until the delay period expired. The first delay lever response following the expiry of the delay interval caused the delay lever light to be switched off, both sample lever lights to switch on and the sample levers reactivated. In order to obtain a small food reward animals then had to respond on the choice lever. This could be identified as being the lever that had not been illuminated at the sample stage of the trial. Over the course of several sessions delays were gradually increased from 1 s using an 8 s intertrial interval to a range comprising: 1, 4, 8, and 16 s using 32 s as the intertrial interval. Trial sequences that controlled the order of sample lever presentation and delay period for any given session were randomised at the start of a session. Sessions finished when either 64 trials had been completed or 60 min had elapsed. Within four complete sets of 16 trials during the course of a session each combination of sample lever and delay was presented twice.

Once total response accuracy had reached asymptote (80 %) using 1, 4, 8 and 16 s delays with 32 s as the intertrial interval, experimental sessions were started. Training continued on Mondays and Thursdays, whilst experimental sessions were conducted on Tuesdays and Fridays. Wednesdays, Saturdays and Sundays were rest days.

2.4. Drugs

All drugs were obtained from Sigma Poole (UK), dissolved in vehicle (normal saline) and injected subcutaneously using a dose

volume of 0.5 ml/kg. Vehicle or WAY100635 was injected 15 min prior to vehicle or the 5-HT mimetic (fluoxetine, 8-OH-DPAT or buspirone). The treatment protocol was as follows: saline/saline, saline/mimetic, WAY100635/mimetic. Animals were placed in the operant chambers 1 h after the last injection.

2.5. Data analysis

Response accuracy was expressed as a percentage of correct responses against total number of trials conducted according to individual delays. Delay lever press activity was obtained by calculating the lever press rate per second during each delay. For both response accuracy and delay lever press activity, the data were analysed according to discrete treatment groups based on each serotonergic (fluoxetine, 8-OH-DPAT or buspirone) and WAY100635 using two-way analysis of variance (ANOVA) with both factors, treatment and delay, repeated (SPSS 10.0). Where significance was observed, post hoc multiple comparisons were made using Student–Newman–Keuls test on data at the longest delay, 16 s, for response accuracy and overall delay lever press activity. Overall delay lever press activity was obtained by pooling data across the delays and dividing it by the total number of seconds that the animals were allowed to press the delay lever, i.e. 1, 4, 8 and 16 s. Total number of trials completed was analysed using a one-way ANOVA with treatment as a single repeating factor. Thus, comparisons were made between three treatment profiles: saline/saline, saline/serotonergic and WAY100635/serotonergic. To include an animal in the data analysis, at least 20 trials must have been completed (5 per delay). Two animals failed to reach the training criteria and were excluded from the experiment. Treatments were randomised over the time scale of the complete experiment.

3. Results

3.1. Effect of WAY100635 (0.15 mg/kg) on delayed non-matching to position

WAY100635 had no significant effect in comparison to saline-treated animals on any of the behavioural parameters measured: response accuracy ($F(1,9)=0.2$), delay press activity ($F(1,9)=2.7$) and trial completion ($F(1,18)=0.4$).

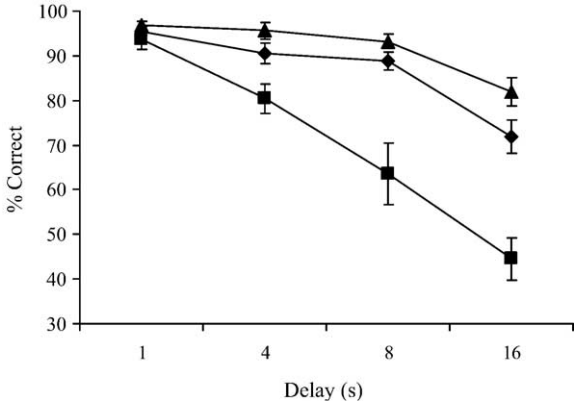

Fig. 1. Response accuracy following 8-OH-DPAT (0.3 mg/kg) and WAY100635 (0.15 mg/kg) treatments ($n=10$). Key: ♦ saline/saline; ■ saline/8-OH-DPAT (0.3 mg/kg); ▲ WAY100635 (0.15 mg/kg)/8-OH-DPAT (0.3 mg/kg).

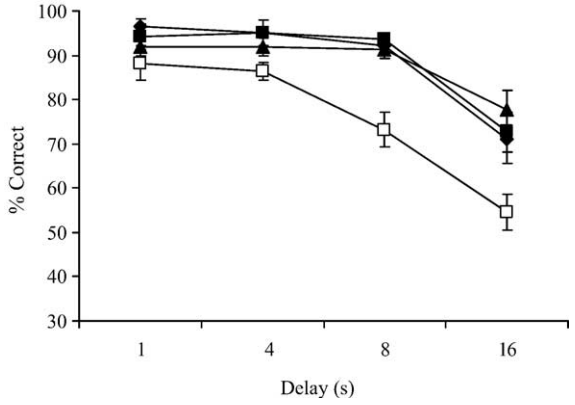

Fig. 2. Response accuracy following buspirone (0.3 and 1.0 mg/kg) and WAY100635 (0.15 mg/kg) treatments ($n=10$). Key: ♦ saline/saline; ■ saline/buspirone (0.3 mg/kg); □ saline/buspirone (1.0 mg/kg); ▲ WAY100635 (0.15 mg/kg)/buspirone (0.3 mg/kg).

3.2. Effect of WAY100635 plus 8-OH-DPAT (0.3 mg/kg) treatment on delayed non-matching to position

8-OH-DPAT treatment significantly impaired response accuracy in a delay-dependent manner as indicated by the significant main effect of treatment ($F(2,18)=43.2$, $P<0.001$) and the significant interaction between treatment and delay ($F(6,54)=9.0$, $P<0.001$, Fig. 1). Subsequent post hoc analysis showed differences between 8-OH-DPAT-only treatment and both saline control and the combination of WAY100635 plus 8-OH-DPAT. Delay lever press activity was also significantly affected ($F(2,18)=37.3$, $P<0.001$), with post hoc analysis identifying differences between the same groups as in response accuracy, i.e. 8-OH-DPAT-only treatment and both saline control and the combination of WAY100635 plus 8-OH-DPAT. Thus, WAY100635 reversed the impairments imposed by 8-OH-DPAT for both response accuracy and delay lever press activity. No significant main effect of treatment was observed on trial completion ($F(2,27)=1.4$).

3.3. Effect of WAY100635 plus buspirone (0.3 and 1.0 mg/kg) treatment on delayed non-matching to position

Two-way ANOVA identified a significant main effect of treatment on response accuracy following buspirone treatment ($F(3,27)=10.5$, $P<0.001$, see Fig. 2) and an interaction between treatment and delay ($F(9,81)=2.8$, $P<0.01$). Subsequent post hoc analysis showed differences between saline and buspirone 1.0 mg/kg (indicating the effect of buspirone 1.0 mg/kg to be delay dependent). The combination of WAY100635 (0.15 mg/kg) plus buspirone (1.0 mg/kg) completely inhibited responding in all animals. Thus, the dose of busiprone was reduced to 0.3 mg/kg. Using this dose of buspirone, no significant effect was observed on response accuracy between the three treatment profiles, but there was a slight impairment of delay lever response activity ($F(2,18)$

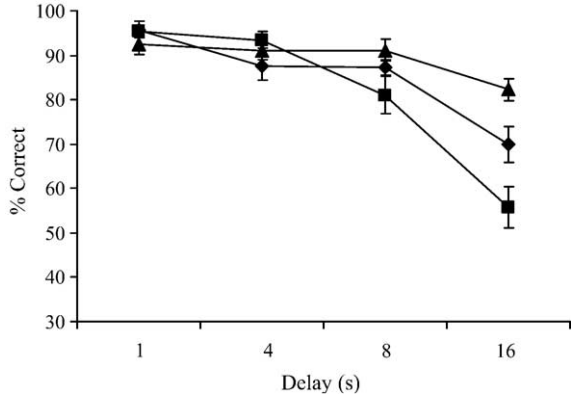

Fig. 3. Response accuracy following fluoxetine (3.0 mg/kg) and WAY100635 (0.15 mg/kg) treatments ($n=10$). Key: ◆ saline/saline; ■ saline/fluoxetine (3.0 mg/kg); ▲ WAY100635 (0.15 mg/kg)/fluoxetine (3.0 mg/kg).

$=6.0$, $P<0.05$). Subsequent post hoc test analysis following one-way ANOVA on total delay lever press activity failed to identify differences between treatments. No significant effect was observed on the total number of trials completed ($F(2,27)=0.9$).

3.4. Effect of WAY100635 plus fluoxetine treatment on delayed non-matching to position

Two-way ANOVA using delay and treatment as repeating factors identified a significant main effect of treatment on response accuracy ($F(2,18)=5.5$, $P<0.05$; Fig. 3) and an interaction between treatment and delay ($F(6,54)=12.2$, $P<0.001$). Subsequent one-way ANOVA followed by post hoc analysis conducted on the 16 s delay data identified differences between saline control and both fluoxetine-only treatment and the combination of WAY100635 plus fluoxetine. Therefore, fluoxetine impaired the delay non-matching to position paradigm in a delay-dependent manner and WAY100635, not only reversed that impairment, but significantly improved response accuracy. Treatment induced a significant change in delay lever press activity ($F(2,18)=16.4$), but subsequent post hoc analysis failed to identify differences between treatment groups. Trial completion data indicated a significant difference between fluoxetine plus WAY100635 treatment and both saline control and fluoxetine groups ($F(2,27)=6.2$, $P<0.01$).

4. Discussion

This study examined the potential for the selective 5-HT_{1A} receptor antagonist WAY100635 to modify the cognitive properties of two clinically relevant compounds, the anxiolytic buspirone (Buspar®) and the selective serotonin reuptake inhibitor, fluoxetine (Prozac®). Although not known for its potential to induce mnemonic dysfunction (e.g. Lucki and Rickels, 1988), it has been reported that buspirone impairs cognition (e.g. Bass et al., 1992). Furthermore, we have recently established that buspirone can impair delayed matching/non-matching to position performance (Pache et al., 2003). The majority of literature regarding fluoxetine supports the premise that it can enhance cognitive performance (Levkovitz et al., 2002).

WAY100635 was found to be inert in the delayed non-matching to position paradigm, a finding that coincides with previous reports that this compound has no inherent ability to affect cognitive function (Fletcher et al., 1996; Meneses and Hong, 1995; Liang, 1999; Helsley et al., 1998). Nevertheless, WAY100635 inhibited the mnemonic impairment caused by 8-OH-DPAT, indicating that the dose of WAY100635 employed was sufficient to block 5-HT_{1A} receptors. Consistent with our data, Helsley et al. (1998) also found that WAY100635 reversed 8-OH-DPAT-induced impairment of working memory in the radial arm maze. Earlier, Carli and Samanin (1992) suggested that 8-OH-DPAT at a dose identical to that currently utilized (0.3 mg/kg) did not affect motor behaviour or motivation but impaired spatial navigation. These data support the contention that 5-HT_{1A} receptor activation impairs short-term memory function, whereas 5-HT_{1A} receptor blockade has no effect on memory.

Previous work in this laboratory has demonstrated that buspirone (1.0 mg/kg) can impair delayed non-matching to position performance in a delay-dependent manner (Pache et al., 2003) and at this dose level and up to 3 mg/kg it does not possess sedative effects (Lerman et al., 1986). Combining this dose of buspirone with WAY100635 disrupted lever responding to such an extent that insufficient trials were completed for analysis. Therefore, the dose of buspirone chosen for the combination experiment was reduced to 0.3 mg/kg. At this level no interference with either cognition or sensorimotor function was observed when given either alone or in combination with WAY100635. Buspirone is primarily a 5-HT_{1A} partial agonist, but it also exerts dopamine D2 receptor antagonist activity. A plausible explanation for the immobility induced by the higher dose of buspirone when combined with WAY100635 is the increased amount of buspirone available for dopamine D2 antagonism following 5-HT_{1A} receptor blockade. Thus, the combination of WAY100635 and buspirone suggests that blockade of dopamine D2 receptors does not impair delayed non-matching to position performance. This result agrees with Bushnell and Levin (1993) who also concluded no impairment of this paradigm following treatment with the dopamine D2 receptor antagonist raclopride. Furthermore, Steckler et al. (1998) reported that noradrenergic mechanisms have little or no role in the mediation of short-term memory in rats. Hence, the noradrenaline α_2-adrenoceptor blockade by the 1-PP (the buspirone metabolite, Enberg, 1988) is unlikely to play a role in buspirone mnemonic impairment. Together, these results support the contention that the serotonergic component of the action of buspirone is responsible for its ability to induce cognitive impairment.

Fluoxetine (3.0 mg/kg) impaired performance in the paradigm in a delay-dependent manner, which reflects an impairment of short-term memory function. This impairment was not associated with any concomitant sensorimotor deficits and this concurs with the report that fluoxetine at a higher dose (20 mg/kg) decreased the number of immobility counts in the rat forced swimming test (Bianchi et al., 2002). Taken together, the

effect on these parameters indicates that mobility was not a factor in the observed deficit in response accuracy. This result contrasts with that of Janssen and Andrews (1994) who concluded that fluoxetine did not affect the delayed non-matching to position task. However, our result is not unique. For example, Nelson et al. (1997) demonstrated that fluoxetine disrupted the ability of rats to avoid foot shocks.

Interestingly, WAY100635 plus fluoxetine, increased response accuracy in comparison to the saline control group. This combination induced no deficit of delay lever press activity, but decreased trial completion. Thus, 5-HT_{1A} receptor activation appears to play a role in the impairment elicited by fluoxetine on short-term memory function, but, more interesting is the observation that fluoxetine can actually improve short-term memory function when 5-HT_{1A} receptors are blocked.

One of the potential mechanisms by which 5-HT_{1A} receptors might influence short-term memory function may be associated with 5-HT levels in areas involved with cognitive processes such as the prefrontal cortex and hippocampus. Thus, 5-HT_{1A} receptor activation causes a general decrease of extracellular 5-HT levels in the forebrain frontal cortex and hippocampus (Casanovas et al., 1997), which possibly underlies the short-term memory impairment observed by 8-OH-DPAT and buspirone in this experiment. The same authors also found that WAY100635 did not change 5-HT levels, but prevented the decrease induced by 5-HT_{1A} receptor activation in the midbrain. Therefore the maintenance of normal 5-HT levels should be behind the reestablishment of acute response accuracy observed with the combined treatment of WAY100635 plus 8-OH-DPAT.

The fluoxetine mechanism that leads to an impairment of short-term memory function is not clear. Although fluoxetine increases 5-HT levels in the forebrain (Malagie et al., 1996; Dawson and Nguyen, 1998; Li et al., 1999), a greater enhancement of 5-HT levels is observed following the co-administration of WAY100635 plus fluoxetine (Malagie et al., 1996; Hervás and Artigas, 1998; Li et al., 1999), leading to memory improvement. Therefore, the 5-HT increase elicited by fluoxetine does not appear to be the cause of memory impairment on the delayed non-matching to position task. The cognitive deficit might be attributable to the indirect action of 5-HT general enhancement on other neurotransmitter systems, such as the dopaminergic (Fernandez-Perez, 2003).

In contrast with fluoxetine, the improvement on short-term memory function following the combined treatment of WAY100635 plus fluoxetine appears to be related to an increase in forebrain 5-HT levels. This effect could be attributed to the action of WAY100635 at presynaptic 5-HT_{1A} autoreceptors in the raphe nuclei, which augments the action of serotonin reuptake inhibitors (Romero et al., 1996; Dawson and Nguyen, 1998). However, postsynaptic 5-HT_{1A} receptor activity should not be dismissed due to their location in brain areas strongly linked to cognitive function, such as the prefrontal cortex and hippocampus (Burnet et al., 1997; Barnes and Sharp, 1999). Interestingly, the work of Sprouse et al. (2001) demonstrated that fluoxetine not only inhibited hippocampal cell firing in a WAY100635 sensitive manner but also increased hippocampal 5-HT levels which were likely to activate postsynaptic 5-HT_{1A} receptors. It is therefore possible that 5-HT_{1A} receptors in the hippocampus might also play a role in the enhanced mnemonic function induced by the combination of WAY100635 plus fluoxetine.

In conclusion, our data support the contention that 5-HT_{1A} receptor activation impairs short-term memory function, which underlies the memory deficit observed following fluoxetine treatment. It is also suggested that specific 5-HT_{1A} receptor antagonism in conjunction with the selective serotonin reuptake inhibitor, fluoxetine improves the potential for cognitive benefit during the treatment of clinical depression. Furthermore, this approach may be of use in the treatment of age-associated memory impairment.

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