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Acceleration of onset of action in schedule-induced polydipsia: combinations of SSRI and 5-HT_{1A} and 5-HT_{1B} receptor antagonists

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Abstract

Onset of action is a key unmet need in the treatment of depression. However, very few preclinical models in which the effects of antidepressants can be shown are suitable for screening for onset. In this context, previous literature suggests that a slow onset of action of selective serotonin reuptake inhibitors (SSRIs) is observed in schedule-induced polydipsia (SIP). The current investigation was performed to determine the latency to reduce SIP of the SSRI, fluoxetine, and of two treatments known to facilitate 5-HT neurotransmission to a greater extent than an SSRI alone. These treatments included interaction studies for fluoxetine + the 5-HT_{1A} antagonist, WAY 100635, and for fluoxetine + the 5-HT_{1B} partial agonist, GR 127935. Food-restricted rats were trained on a fixed interval schedule with drinking water freely available. Once water intake was stable, rats were randomly assigned to vehicle of treatment groups. Daily treatment was continued for 3 (interaction studies) or 18 days (fluoxetine alone study). Fluoxetine significantly reduced SIP after 5–6 days of treatment, with the maximal effect evidenced after 8 days. WAY 100635 and GR 127935 accelerated the onset of action of fluoxetine, with significant effects observed on treatment day 1. These data suggest that SIP may be useful to assess the onset of action of serotonin enhancers.

Keywords: Schedule-induced polydipsia; SSRI; Fluoxetine; WAY 100635; GR 127935; Fast onset

1. Introduction

Selective serotonin reuptake inhibitors (SSRIs) are generally considered to be slow acting, taking at least 2–4 weeks to reduce symptoms of clinical depression, 8–12 weeks to reduce symptoms of obsessive compulsive disorder (e.g., Wagstaff et al., 2002), and 1–2 weeks to reduce panic attacks (e.g., Asnis et al., 2001). As such, it is of particular interest to develop SSRI-related compounds with a faster onset of action (e.g., Artigas et al., 1994; Blier and Bergeron, 1995; Maes et al., 1996). However, the preclinical models that that have been proposed to assess onset latency are limited to chronic mild stress (CMS) in rats (Willner, 1997) and mice (Przegalinski et al., 1995), olfactory bulbectomy (OB) (Kelly et al., 1997), and the rat resident–intruder paradigm (Mitchell and Redfern, 1997). While the latter model has shown a high level of predictive validity and has been shown to be suitable for the study of onset of action (Mitchell and Redfern, 1997), the CMS model reportedly lacks reliability (Willner, 1997) and the OB model has shown limited sensitivity to clinically active fast onset treatments (Cryan et al., 1998, 1999).

The current report examines the potential for using the phenomenon of schedule-induced polydipsia (SIP) to assess the onset of action of SSRI-related antidepressant compounds. SIP belongs to a group of so-called "adjunctive" behaviors that are elicited in circumstances when motivation is impeded (Falk, 1961; Tazi et al., 1986). Other examples of adjunctive behaviors include bar biting, pica, and increased grooming (Wallace and Singer, 1976). SIP can be induced both by conditional and nonconditional food administration to food-restricted rats (Hudson and Singer, 1979). In the present procedure, food-deprived rats exposed to a fixed interval food schedule exhibit enhanced drinking (Falk, 1961). This behavior shows species generality, with reports of SIP described in humans (Wallace and Singer, 1976; Wallace et al., 1975) and a broad range of other

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species (Palfai et al., 1971; Porter and Bryant, 1978; Dantzer and Mormede, 1981; Wilson and Spencer, 1975; Hudson and Singer, 1979; Porter and Kenshalo, 1974). It is important to note that the drinking or adjunctive behavior observed in this model is thought to represent a stress control or displacement reaction and is observed in non-thirsty rats, which have free access to water in their home cages (and are dosed orally with water prior to testing). This paradigm has been proposed as a model of obsessive–compulsive disorder with selective sensitivity to serotinergic enhancers being observed; the slow onset of action of SSRIs in reducing SIP (Woods et al., 1993; but see Martin et al., 2002) suggests that the model may be useful in assessing the onset of SSRI-related compounds (irrespective of indication).

The clinical effects of acute SSRI treatment are widely believed to be retarded by an initial 5-HT_{1A} autoreceptor-mediated inhibition of 5-HT cell firing (Blier and de Montigny, 1994) limiting SSRI-induced increases in extracellular 5-HT concentrations (Gardier et al., 1995; Artigas et al., 1996). In contrast, chronic SSRI treatment desensitizes 5-HT_{1A} autoreceptors, thus attenuating the feedback inhibition of cell firing (Svensson, 1978; Chaput et al., 1996; Jolas et al., 1994) and producing higher increases in 5-HT concentrations in postsynaptic regions (Bel and Artigas, 1993; Rutter et al., 1994; Kreiss and Lucki, 1995; Cremers et al., 2000; but see Hjorth and Auerbach, 1994; Bosker et al., 1995). This hypothesis was derived from clinical reports that the 5-HT_{1A}/β adrenoceptor antagonist, pindolol, reduces the latency for the antidepressant therapeutic effect of SSRIs (Artigas et al., 1994; Blier and Bergeron, 1995; Maes et al., 1996; Perez et al., 1997; Bakish et al., 1997; Tome et al., 1997; but see Dinan and Scott, 1997; Berman et al., 1997). In this context, preclinical data in behavioral models are sparse and contradictory, with 5-HT_{1A} receptor antagonism reportedly accelerating the onset of SSRI-induced aggression in the rat resident–intruder procedure (Mitchell and Redfern, 1997) but having no impact on SSRI-induced reductions in hyperactivity in the OB paradigm (Cryan et al., 1998, 1999).

The evidence suggesting that SSRIs combined with 5-HT_{1B} receptor antagonists may produce a rapid onset antidepressant effect (via antagonism of 5-HT_{1B} terminal autoreceptors) and show greater efficacy compared to SSRI treatment alone is equivocal. Thus, electrophysiological studies suggest that chronic SSRI treatment down-regulates (O'Connor and Kruk, 1994) and desensitizes (Blier and Bouchard, 1994; Chaput et al., 1991; Blier et al., 1998) 5-HT_{1B} receptors and facilitates SSRI-enhanced serotonergic neurotransmission (Davidson and Stamford, 1995). However, microdialysis studies have generally failed to confirm that 5-HT_{1B} autoreceptors desensitize following chronic SSRI treatment (Chaput et al., 1996; Auerbach and Hjorth, 1995; Bosker et al., 1995; Moret and Briley, 1996; Davidson and Stamford, 1997; Cremers et al., 2000). Nevertheless, SSRI-induced increases in 5-HT are reportedly greater in mice pretreated with 5-HT_{1B} receptor antagonists (Roberts et al., 1998; Rollema et al., 1996; Gobert et al., 1997; Hervas et al., 2000) and in 5-HT_{1B} receptor knockout mice (Knobelman et al., 2001). The behavioral evidence is inconsistent, with reports that relative to wild-type mice, SSRIs produce an enhanced response in 5-HT_{1B} receptor knockout mice in the tail suspension test (Mayorga et al., 2001) and no effect in the forced swim test (Trillat et al., 1998). Furthermore, in apparent support of the latter finding, the 5-$HT_{1B/1D}$ receptor antagonist GR 127935 has been reported to block the effects of paroxetine in the tail suspension test (O'Neill et al., 1996). However, this blockade could also be a 5-HT_{1D}-mediated effect.

The purpose of the current group of studies was to confirm the slow onset of action of fluoxetine in inhibiting SIP and to determine whether this onset of action can be accelerated by cotreatment with the 5-HT_{1A} or the 5-HT_{1B} receptor antagonists, WAY 100635, and GR 127935, respectively. Thus, the utility of the SIP model for the behavioral assessment of the fast onset potential of SSRI-augmentation strategies would be assessed.

2. Materials and methods

2.1. Animals

Subjects were male Wistar WU rats (weighing 150–175 g on arrival; Møllegård, Denmark) housed two per cage (Macrolon III type) for at least 1 week prior to SIP training. All animals were housed for at least 7 days prior to testing and maintained in a temperature (21 ± 1 °C)-, humidity (55 ± 5%)-, and air-exchange (16 times/h)-controlled environment under a 12:12-h light–dark cycle (lights on: 06:00 h). Animals were kept on a food-restricted diet in which they were permitted to eat ad libitum for 90 min/day following the training or test session, while water was freely available at all times. This feeding regimen maintained rats at 80–90% of their free-feeding body weight.

2.2. Apparatus

Four sound-attenuated Skinner boxes (Campden Instruments) were used (64 × 38 × 38 cm) with two dark, one-way observation windows (d = 16.5 cm) on the doors. The boxes contained an electric fan (providing ventilation and a constant level of background noise), an operant chamber (dimensions: 24 × 24 × 20 cm; materials: aluminum, Plexiglas), and a grid floor. Each operant chamber contained a pellet dispenser and a food tray covered by a hinged Plexiglas flap. In order to gain access to the pellets (Noyes, 45 mg), rats were required to push the flap up. A stainless steel spout protruded into the chamber. This was positioned 4 cm above floor level and on the wall 10 cm to the left of the food tray. The spout was attached to a graduated burette

filled with 100 ml of water, permitting water intake to be recorded to the nearest 0.1 ml.

2.3. Procedure

Rats were trained (4–5 times/week) in an operant chamber on a fixed schedule (1 food pellet/60 s, 30-min trial), during which drinking water (which was freely available) was recorded. Following 3 weeks of training, water intake was stable (approximately 12 ml/rat/30 min) and the animals were randomly allocated to vehicle or drug groups ($n = 7–9$/group). Daily treatment was continued for 3 (combination studies) or 18 days (fluoxetine study).

The combination studies were conducted to determine whether combinations of (1) fluoxetine and WAY 100635 and (2) fluoxetine and GR 127935 would interact synergistically to reduce SIP. In this context, synergism is defined as a drug combination treatment that produces a significant effect compared with control and either drug alone.

The amount of home cage water intake was recorded for the 3 days following the polydipsia experiment in rats that had been treated with vehicle, fluoxetine, WAY 100635, and the fluoxetine–WAY 100635 combination. In addition, the number of food pellets consumed by animals was monitored.

2.4. Drugs

The doses, pretreatment times, and routes of administration of WAY 100635 and GR 127,935 were selected on the basis of previous literature (Stanhope and Dourish, 1996; de Almeida et al., 2001; Mayorga et al., 2001; Martin et al., 1998, 2002). The dose of fluoxetine was selected following pharmacokinetic studies in which the oral bioavailability was determined to be approximately 20% (in this rat strain from the present supplier); thus, the daily dose is equivalent to approximately 6–7 mg/kg sc. In addition, preliminary behavioral experiments showed a reduction in consumption of food pellets at doses higher than 50 mg/kg po. Fluoxetine hydrochloride (Tocris, Ballwin, USA), WAY 100635, and GR 127935 (synthesized at Department of Medicinal Chemistry at H. Lundbeck) were prepared freshly on test days. Fluoxetine was administered orally (per os) 60 min prior to testing in a volume of 5 ml/kg, whereas WAY 100635 and GR 127935 were given subcutaneously. GR 127935 was dissolved in 2-OH-Br-beta cyclodextrin, whereas all other compounds were dissolved in 0.9% saline. Control animals received injections of the appropriate vehicle in a volume of 5 ml/kg. All compounds doses are presented as mg base/kg body weight.

2.5. Statistical analysis

The amount of water consumed during tests sessions was analyzed by two-factor (Experiment 1) or three-factor (Experiments 2 and 3) repeated measures ANOVA and Tukey's follow-up tests. These data were expressed as a percentage of baseline prior to statistical analysis. For the home cage water intake study, data were analyzed by 2×2 factor ANOVAs and a single-factor ANOVA with Tukey's post hoc test.

2.6. Body weight

The rats were weighed every day for the 3 days prior to and the duration of drug treatment.

3. Results

3.1. Experiment 1

Fig. 1 shows the effects of chronic treatment with fluoxetine (27 mg/kg/day po) on water intake. ANOVA yielded a significant Fluoxetine × Day interaction term for water intake [$F(7,79) = 4.1$, $P < .001$]. Post hoc analysis indicated that fluoxetine reduced SIP after 5–6 days of treatment. The maximal effect was observed after 8 days. In addition, ANOVA revealed significant main effects for fluoxetine [$F(1,79) = 17.56$, $P < .001$] and day [$F(7,79) = 11.14$, $P < .001$].

3.2. Experiment 2

ANOVA revealed significant Fluoxetine × WAY 100635 [$F(3,33) = 14.37$, $P < .01$] and Fluoxetine × Day [$F(3,99) = 17.15$, $P < .01$] interactions for water consumption. In contrast, the Fluoxetine × WAY 100635 × Day interaction term approached significance [$F_{crit} = 4.50$; $F(3,33) = 4.15$, NS] for water consumption, while there

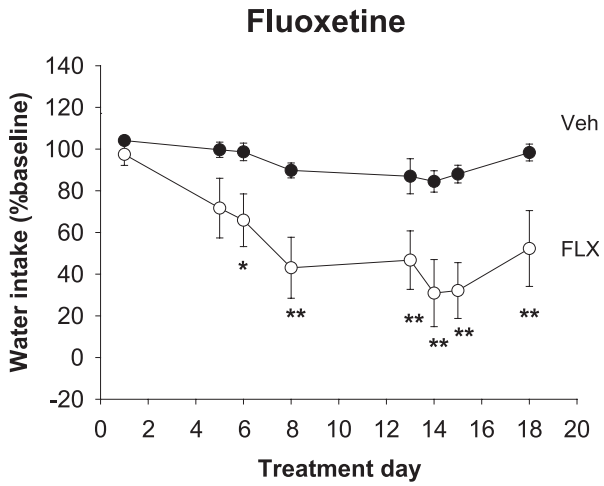

Fig. 1. The effect of chronic treatment with fluoxetine (27 mg/kg/day po) on water intake in the SIP model. Data are presented as means ± S.E.M. of water intake represented as percentage of baseline (predosing). * $P < .05$, ** $P < .01$ versus Day 1 vehicle and same-day vehicle control. Veh = vehicle; FLX = fluoxetine.

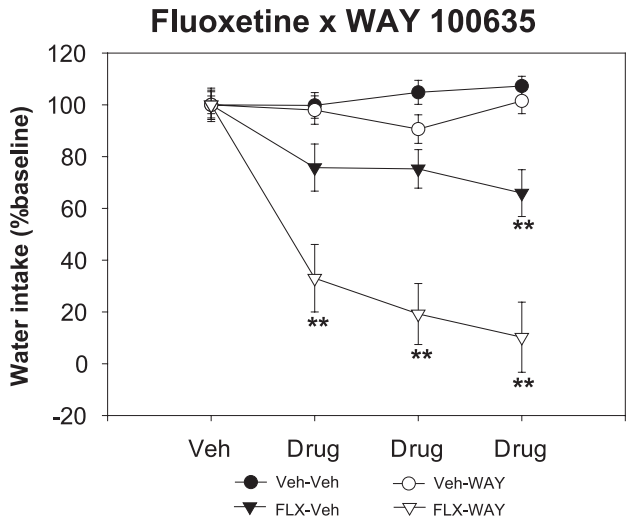

Fig. 2. The effects of fluoxetine (27 mg/kg/day po) alone and in combination with WAY 100635 (0.52 mg/kg/day sc) on water intake in the SIP model. Rats were treated with vehicle on the first day of treatment (veh) and with the appropriate compounds on subsequent consecutive days (marked drug). Data are presented as means ± S.E.M. of water intake represented as percentage of baseline (predosing). * * $P < .01$ versus Day 1 vehicle and same day vehicle control. Veh = vehicle; FLX = fluoxetine; WAY = WAY 100635.

was no significant WAY 100635 × Day interaction [$F(3,99) = 3.48$, NS]. As shown in Fig. 2, follow-up tests indicated that while fluoxetine and WAY 100635 were without intrinsic effects, combination treatment with these compounds significantly reduced SIP on treatment days 1–3.

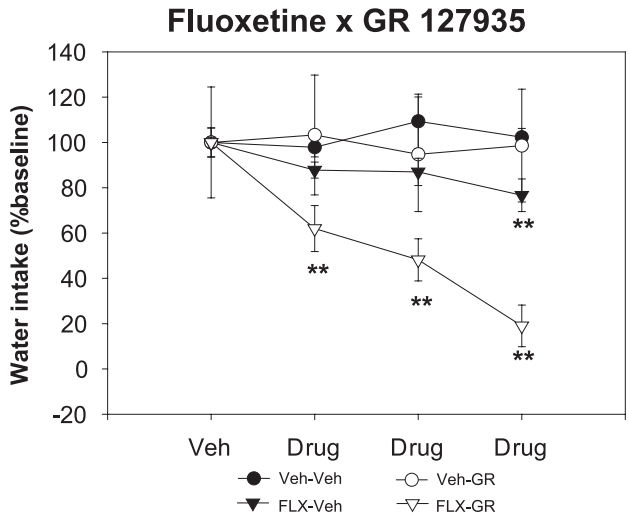

Fig. 3. The effects of fluoxetine (27 mg/kg/day po) alone and in combination with GR 127935 (4.5 mg/kg/day sc) on water intake in the SIP model. Rats were treated with vehicle on the first day of treatment (veh) and with the appropriate compounds on subsequent consecutive days (marked drug). Data are presented as means ± S.E.M. of water intake represented as percentage of baseline (predosing). * * $P < .01$ versus Day 1 vehicle and same day vehicle control. Veh = vehicle; FLX = fluoxetine; GR = GR 127935.

Table 1
The effects of fluoxetine (27 mg/kg/day po), WAY 100635 (0.52 mg/kg/day sc), and combination on home cage water intake (ml) over 3 days in rats

	Vehicle	Fluoxetine
Vehicle	46.7 ± 2.4	60.2 ± 2.9
WAY 100635	52.7 ± 3.5	62.0 ± 6.3

3.3. Experiment 3

ANOVA yielded a significant Fluoxetine × GR 127935 × Day interaction term [$F(3,90) = 9.02$, $P < .01$]. Furthermore, pairwise comparisons indicated that while fluoxetine and GR 127935 were without significant effect when administered alone, the combination produced a significant reduction in SIP on all 3 days tested (see Fig. 3).

3.4. Home cage water intake

The effect of fluoxetine, WAY 100635, and the combination on home cage water intake is shown in Table 1. Interestingly, a main effect for fluoxetine was indicated by ANOVA [$F(1,12) = 7.73$, $P < .05$], with post hoc tests indicating that this reflected an increase in home cage water intake compared to animals that did not receive the SSRI ($P < .05$). There was no main effect for WAY 100635 [$F(1,12) = .92$, NS] nor a Fluoxetine × WAY 100635 interaction effect [$F(1,12) = 0.26$, NS] on this parameter.

All subjects consumed all the food pellets that were delivered during the experiments.

3.5. Body weights

There were no differences in body weight between the vehicle- and drug-treated rats at any time; prior to, during, or at the completion of the studies reported here (data not shown).

4. Discussion

The present investigation suggests that SIP may be useful for predicting the onset of antidepressant drug treatment. While the SSRI fluoxetine significantly reduced SIP after 5–6 days of treatment, significant reductions in water intake were observed on Day 1 of drug treatment following coadministration of fluoxetine with silent doses of the 5-HT_{1A} receptor antagonist, WAY 100635, or the 5-$HT_{1B/1D}$ receptor antagonist, GR 127935. Importantly, all animals in the studies consumed all the pellets that were delivered during the test session, suggesting that the appetitive behaviors remained intact and indicating that the animals are active. In addition, the doses used here did not reduce home cage water consumption indicating that the reduction in water intake observed was specific to the context of SIP testing. Comparable doses of all the compounds used in the

current report have produced behaviorally specific effects in the literature. Thus, similar and higher doses of fluoxetine have been used in the polydipsia model (Martin et al., 1998, 2002). Furthermore, WAY 100635 has been shown to possess behavioral effects in the absence of sedative or neurotoxic effects at doses ranging from 0.3 to 3.0 mg/kg (e.g., Mayorga et al., 2001; Stanhope and Dourish, 1996). Moreover, studies suggest that doses of GR 127935 block 5-$HT_{1B/D}$ receptors at a wide dose range (0.056–10 mg/kg ip) and are without sedative effects at these doses (Mayorga et al., 2001; de Almeida et al., 2001).

Electrophysiological and microdialysis evidence indicates that SSRI/5-HT_{1A} (Svensson, 1978; Chaput et al., 1996; Jolas et al., 1994; Bel and Artigas, 1993; Rutter et al., 1994; Kreiss and Lucki, 1995) and SSRI/5-HT_{1B} receptor antagonist (Knobelman et al., 2001; Roberts et al., 1998; Rollema et al., 1996; Gobert et al., 1997; Hervas et al., 2000) combinations produce a greater enhancement in serotonergic neurotransmission relative to SSRI treatment alone. It is therefore suggested that serotonergic mechanisms are highly important in the reduction of SIP effects. Indeed, the speed with which the reductions in water intake were observed and the specificity of the effect to SSRIs (Woods et al., 1993) suggest that the SIP model is sensitive to direct postsynaptically 5-HT-mediated effects rather than the complex plasticity changes thought to underlie the alleviation of OCD and other SSRI-sensitive states.

The present finding that fluoxetine took several days to reduce polydipsia agrees with a previous report (Woods et al., 1993) but apparently contrasts with a more recent reports in which acute doses of fluoxetine reduced SIP (Martin et al., 1998, 2002). However, it is noteworthy that the lowest orally administered dose of fluoxetine that was active in the studies conducted by Martin et al. (1998, 2002) was 60 mg/kg ip, while 30 mg/kg ip was without effect. In our own hands, doses higher than 50 mg/kg po (probably equivalent to approximately 10 mg/kg ip) fluoxetine disrupted the intake of food pellets, the effects of such doses on water intake were therefore considered to be nonspecific. Furthermore, it is notable that significant reductions in SIP were observed on Day 5 in the current study and Day 15 in the study conducted by Woods et al. (1993). This difference may be due to the higher dose administered (27 mg/kg/day po) in the present experiment relative to the report of Woods et al. (1993) (5 mg/kg/day ip), though our pharmacokinetic data suggest that our dose equates to approximately 6–7 mg/kg/day ip. In addition, such differences may be due to procedural differences between the two studies; we tested rats several times per week, whereas Woods et al. (1993) tested their animals 1 day per week. A low test frequency would necessarily reduce the sensitivity to temporal factors.

The reduction in the onset latency for the decrease in SIP produced by cotreatment with the 5-HT_{1A} receptor antagonist, WAY 100635, and fluoxetine supports the view that the fast onset response observed in the clinic following pindolol/SSRI treatment (Artigas et al., 1994; Blier and Bergeron, 1995; Maes et al., 1996; Perez et al., 1997; Bakish et al., 1997; Tome et al., 1997; but see Dinan and Scott, 1997; Berman et al., 1997) derives from the 5-HT_{1A} receptor antagonist properties of pindolol. In addition, it is noteworthy that the fluoxetine/WAY 100635 treatment combination appeared to show enhanced efficacy in the model relative to fluoxetine alone. This observation is consistent with reports of the 5-HT_{1A} receptor antagonist, WAY 100135 (Da-Rocha et al., 1997), and low doses of the 5-HT_{1A} receptor partial agonist, buspirone (Redrobe and Bourin, 1998), potentiating SSRI effects in the forced swim test.

The finding that the 5-HT_{1B} receptor antagonist accelerated fluoxetine-induced suppression of SIP is the first report on the effects of SSRI-5-HT_{1B} receptor antagonist combinations in a model in which SSRI-induced behavioral effects are observed only following chronic administration. As with the fluoxetine–WAY 100635 data, this SSRI-5-HT_{1B} receptor antagonist combination also appeared to increase the efficacy compared to the maximal response obtained with fluoxetine. This observation concurs with a report of an augmented fluoxetine-induced antiimmobility response in the tail suspension test in 5-HT_{1B} receptor knockout mice (Mayorga et al., 2001), though it contrasts with reports that 5-HT_{1B} receptor knockout mice are insensitive to paroxetine in the forced swim test (Trillat et al., 1998) and that GR 127935 blocks the effects of paroxetine in the tail suspension test (O'Neill et al., 1996). In this context, it is feasible that 5-HT_{1B} receptors are essential for SSRI-induced antiimmobility responses in the background strain of mice used in the forced swim test. Nevertheless, the GR 127935-induced acceleration of the anti-SIP effects of fluoxetine findings suggest that down-regulation and/or desensitization observed in electrophysiological studies (O'Connor and Kruk, 1994; Blier and Bouchard, 1994; Chaput et al., 1991; Blier et al., 1998), albeit not in microdialysis studies (Auerbach and Hjorth, 1995; Bosker et al., 1995; Moret and Briley, 1996; Davidson and Stamford, 1997; Cremers et al., 2000), may be an important mechanism in potentiating SSRI-enhanced serotonergic neurotransmission (Davidson and Stamford, 1995). To the knowledge of the current authors, SSRI/5-HT_{1B} receptor antagonist combinations have not been tested in clinically depressed patients. Clearly, present data suggest that combining 5-HT_{1B} receptor antagonism with SSRI may be an interesting target for developing a fast acting antidepressant/anxiolytic.

To summarize, the present investigation represents a preliminary validation of SIP as a model to measure the onset of action of SSRIs. In this paradigm, fluoxetine had a slow onset of action that could be reduced by the putative fast onset treatment combination of fluoxetine and a 5-HT_{1A} receptor antagonist (WAY 100635) and the combination of an SSRI and a 5-HT_{1B} receptor antagonist (GR 127935). These data suggest that the SIP model has potential in assessing the onset of action of 5-HT enhancers though it should be stressed that the present data do not address the

utility of the SIP model to look at antidepressant effects per se. The utility of SIP model for assessing the onset of action of both serotonergic and nonserotonergic compounds warrants further investigation.

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