Dose-dependent influence of buspirone on the activities of selective serotonin reuptake inhibitors in the mouse forced swimming test

Abstract Recent clinical data suggest that buspirone may enhance the efficacy and/or reduce the latency to therapeutic effect of selective serotonin reuptake inhibitors (SSRIs) in unipolar major depressive disorder. The present study, using the mouse forced swimming test, was performed to investigate further the mechanisms involved in the potential antidepressant-enhancing effects of buspirone. Prior administration of buspirone (0.06 mg kg⁻¹, IP) significantly enhanced the anti-immobility effects of subactive doses of fluvoxamine (4 mg kg⁻¹, IP; P < 0.01), paroxetine (4 mg kg⁻¹, IP; P < 0.01), citalopram (4 mg kg⁻¹, IP; P < 0.01) and sertraline (2 mg kg⁻¹, IP; P < 0.01) in the forced swimming test. However, pretreatment with buspirone did not induce antidepressant-like effects when tested in combination with fluoxetine (4 mg kg⁻¹, IP). Each antidepressant tested reduced immobility time in the forced swimming test [citalopram (16 mg kg⁻¹, IP; P < 0.01), fluoxetine (32 mg kg⁻¹, IP; P < 0.01), fluvoxamine (32 mg kg⁻¹, IP; P < 0.01), paroxetine (16 mg kg⁻¹, IP; P < 0.01) and sertraline (16 mg kg⁻¹, IP; P < 0.01)]. Pretreatment with buspirone (0.5 mg kg⁻¹, IP), or its major metabolite 1-PP (0.5 mg kg⁻¹, IP), attenuated all SSRI-induced anti-immobility effects (P < 0.01). Concomitant studies of locomotor activity ruled out any stimulant or sedative effects of the interactions. The results of the present study suggested that low dose buspirone enhanced the activity of subactive doses of SSRIs in the mouse forced swimming test, probably via an action at 5-HT₁A receptors. On the other hand, a high dose of buspirone attenuated the antidepressant-like effects of active doses of these drugs, possibly via the generation of an active metabolite (1-PP) acting at alpha₂-adrenoceptors.

Key words Buspirone · 1-PP · Selective serotonin reuptake inhibitor · Mouse forced swimming test

Introduction

Recent clinical data suggest that pindolol (Artigas et al. 1994; Blier and Bergeron 1995) and buspirone (Jacobsen 1991; Jöfe and Schuller 1993) may enhance the efficacy and/or reduce the latency to therapeutic effect of selective serotonin reuptake inhibitors (SSRIs) in unipolar major depressive disorder. Pindolol and buspirone have been shown to possess high affinity for central 5-HT₁A receptors (Hoyer 1988) and may be classified as antagonist, and partial agonist/antagonist, respectively (Lucki 1992; Hjorth 1996). However, pindolol has also been shown to possess agonist activity at 5-HT₁A receptors (Hjorth and Carlsson 1986) under conditions when low endogenous or exogenous agonist competitor prevail. It has been demonstrated that 5-HT₁A receptor agonists induced antidepressant-like effects in the mouse forced swimming test (Hascoet et al. 1994). Previously, it has been shown that (±) pindolol potentiated the antidepressant-like effects of subactive doses of SSRIs in the mouse forced swimming test (Redrobe et al. 1996). These effects were proposed to be the result of enhanced presynaptic 5-HT₁A receptor function by preventing the self-inhibitory actions of serotonin (5-HT) on the firing and release of serotonergic neurones (Artigas 1995). This, however, may not be pindolol’s sole mechanism of action (Bourin et al. 1998).

The underlying mechanism of action of buspirone is unclear. A member of the azapirone class of
anxiolytics, buspirone, together with other members of this class of compounds (e.g. gepirone, ipsapirone), has been reported as being effective in several animal models of depression, including the forced swim test in rats, the stress-induced suppression of locomotor activity test, chronic mild stress model of depression and the learned helplessness model (Kennett et al. 1985; Cervo and Samanin 1987; Giral et al. 1988; Kennett and Curzon 1989; Robinson et al. 1989; Martin 1991; Przegalinski et al. 1995). On the other hand, buspirone has recently been reported to attenuate the activity of antidepressants in the mouse forced swimming test, an effect proposed to be a result of stimulation of presynaptic 5-HT1A autoreceptors (Da Rocha et al. 1997).

It is now known that 5-HT1A agonists such as buspirone, but not 8-hydroxy-(di-n-propylamino)tetralin (8-OH-DPAT), are metabolised and major metabolites have been identified and quantified, particularly for buspirone (Jajoo et al. 1989). The major metabolite, 1-(2-pyrimidinyl)-piperazine (1-PP or 1-PmP), is rapidly and abundantly formed in humans and rodents and tends to accumulate in brain (Caccia et al. 1985). 1-PP has been shown to act as an alpha2-adrenoreceptor antagonist in vitro and in vivo (Caccia et al. 1986; Rimele et al. 1987) and has no affinity for alpha1-adrenoreceptors and dopamine receptors (Rimele et al. 1987). In addition, 1-PP does not bind to 5-HT1A receptors (Caccia et al. 1986). Alpha2-adrenoreceptor antagonists have since been shown to attenuate the anti-immobility effects of antidepressants in the forced swimming test (Cervo et al. 1990). In the learned helplessness paradigm, buspirone exhibited a bihapasic action: at low doses, it showed an antidepressant-like effect, but this action progressively disappeared as the doses were increased (Martin 1991). These results suggested that 1-PP may alter the effects of 5-HT1A agonists in this test.

The present study, using the mouse forced swimming test and locomotor activity apparatus, was performed to investigate further the mechanisms involved in the potential antidepressant-enhancing effects of buspirone. The mouse forced swimming test is a behavioural model developed to predict the efficacy of antidepressant drugs in humans, and is sensitive to compounds acting on 5-HT systems (Porsolt et al. 1977). This model has also been used to investigate the mechanism of action of antidepressant drugs (see Borsini 1995 for review). Two doses of buspirone were chosen (low and high) for interaction studies with SSRIs. Interactions of 1-PP with SSRIs were also performed to investigate any effect this metabolite might have on the action of buspirone. Concomitant studies in the locomotor activity apparatus were performed to rule out any stimulant or sedative effects of the interactions. Drugs used in the present study included: the SSRIs fluoxetine, fluvoxamine, citalopram, paroxetine and sertraline; the partial 5-HT1A receptor agonist buspirone, and its metabolite 1-(2-pyrimidinyl)-piperazine.

### Materials and methods

#### Animals

Naive male Swiss mice (Centre d’Élevage Janvier, France) weighing 20–24 g were used throughout this study. They were housed in groups of 20 on a 12:12-h light:dark cycle (lights on 0700 hours) and had free access to food and water. The ambient temperature of the room was maintained at 21 ± 1°C. Each experimental group consisted of ten randomly chosen mice. Mice were only used once. All experiments were performed within the guidelines of the French Ministry of Agriculture for experiments with laboratory animals (law No 87 848).

#### Dose-response experiments

Dose-response experiments were performed in the forced swimming test and locomotor activity apparatus to determine the appropriate doses of buspirone and 1-PP for use in interaction studies. Drugs were administered to mice 45 min prior to placement in a photo-cell activity meter (OSYS) for 10 min, and testing in the forced swimming test. Sub-active/active doses of antidepressants were based on previous results (Redrobe et al. 1996; Redrobe and Bourin 1997).

#### Drugs and treatment

The following drugs were used in the study: fluoxetine HCl (Lilly), fluvoxamine maleate (Duphar), citalopram HBr (Lundbeck), paroxetine HCl (SmithKline Beecham), sertraline HCl (Pfizer), buspirone HCl (Bristol-Myers), 1-(2-pyrimidinyl)-piperazine HCl (1-PP or 1-PmP) (Aldrich).

All drugs were dissolved in distilled water except sertraline, which was dissolved in a 1% aqueous solution of Tween 80 (Merck). Buspirone/1-PP and antidepressants were injected IP in a constant volume of 0.5 ml/20 g body weight, 45 and 30 min, respectively, prior to testing. Control animals received vehicle only. Doses used refer to the salt form of the drug. Measurement of the pH of solutions indicated that sertraline was the most acidic (4.25) < fluvoxamine (4.70) < fluoxetine (5.31) < paroxetine (6.15) < citalopram (6.65) < vehicle (6.73).

#### Measurement of locomotor activity

Buspirone/1-PP and antidepressants were injected IP in a constant volume of 0.5 ml/20 g body weight, 45 and 30 min, respectively, prior to testing in the spontaneous locomotor activity apparatus (Boissier and Simon 1965). Control animals received vehicle only. Animals were placed in activity monitors to which photoelectric cells were attached, allowing locomotor activity to be recorded over a 10-min testing period.

#### Measurement of immobility time

The forced swimming test employed was essentially similar to that described elsewhere (Porsolt et al. 1977). Briefly, mice were dropped individually into glass cylinders (height: 25 cm, diameter: 10 cm) containing 10 cm water, maintained at 23–25°C, and left there for 6 min. A mouse was judged to be immobile when it floated in an upright position, and made only small movements to keep its head above water. The duration of immobility was recorded during the last 4-min of the 6-min testing period.