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Stimulus properties of venlafaxine in a conditioned taste aversion procedure

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ABSTRACT

Conditioned stimulus properties of venlafaxine are still unknown. In the present study, the discriminative stimulus properties of venlafaxine by using a conditioned taste aversion procedure were investigated. Swiss Webster mice were allowed to reach water from 2 pipettes for 20 min (09:00–11:30 h), plus 30 min (15:30–16:00 h), daily. During the 4 days, the test drugs [fluoxetine, escitalopram, tianeptine, reboxetine, and *N*ω-nitro-L-arginine methyl ester (L-NAME)] were injected to mice at least 1 h after they had first water session. On day 5, they consumed glucose solution (5% w/v) and immediately injected with conditioning drug (venlafaxine 32 mg/kg). On day 8, mice were allowed to make a choice between water and glucose solution. The amount of glucose consumption as a percentage of total fluid intakes was calculated for each animal. Significant reduction in glucose choice was defined as conditioned taste aversion. Venlafaxine (32 mg/kg) induced a robust conditioned taste aversion in mice. Pre-exposure to tianeptine (2.5–10 mg/kg), fluoxetine (10 mg/kg), escitalopram (32 mg/kg), and reboxetine (5 mg/kg) substituted for venlafaxine by preventing the conditioned taste aversion induced by venlafaxine. L-NAME did not substitute for venlafaxine. Substitution of venlafaxine by fluoxetine, tianeptine, escitalopram, and reboxetine provides further evidence that both 5-HT and noradrenaline reuptake inhibition may play an important role in the stimulus effect of venlafaxine.

1. Introduction

Evaluating the discriminative stimulus properties of antidepressant agents have long been proven useful in investigating the behavioral effects of these compounds, and their underlying neuronal and receptor mechanisms (Dekeyne and Millan, 2003). Drug discrimination, which is an operant two-lever procedure, and the most frequently used method to characterize discriminative stimulus properties of drugs, has been extensively used in the investigation of the pharmacological effects of antipsychotics (Goudie and Smith, 1999), anxiolytics (Goudie and Leathley, 1993), and drugs of abuse (Glennon, 1991). However, because of the toxicity associated with the prolonged exposure to tricyclic antidepressants (Shearman et al., 1978; Filip et al., 1993), and unsuitable pharmacokinetic characteristics (e. g., their long half-lives) of some of the selective serotonin reuptake inhibitors (SSRI), including fluvoxamine (Olivier et al., 1993) and fluoxetine (Marona-Lewicka and Nichols, 1998), studies successfully establishing and characterizing the stimulus properties of antidepressants in this procedure have been comparatively limited in number and in the recent past (see Dekeyne and Millan 2003 for a review).

Previous research investigating the stimulus properties of antidepressant agents in several laboratories have successfully demonstrated that, irrespective of their long-term therapeutic utility, substitution is observed almost exclusively between drugs of similar acute pharmacological properties in both operant drug discrimination and conditioned taste aversion procedures. For example, indicating the role of 5-HT reuptake inhibition in the stimulus effects of SSRIs, paroxetine substituted for the discriminative stimulus effect of citalopram (Millan et al., 1999) and sertraline, whereas desipramine (a noradrenaline reuptake inhibitor) failed to substitute for both of these drugs (Marona-Lewicka and Nichols, 1998). In addition, a cross-substitution was observed between the two SSRIs, fluoxetine and fluvoxamine, in a conditioned taste aversion procedure (Gommans et al., 1998). In pigeons, fluoxetine and citalopram, but not nisoxetine, another noradrenaline reuptake inhibitor, substituted for the discriminative stimulus effect of LW233708, which is another SSRI (Wolf and Leander, 1999). Similarly, noradrenaline reuptake inhibition seems to underlie the discriminative stimulus effects of noradrenaline reuptake inhibitors, because two selective noradrenaline reuptake inhibitors, desipramine and maprotiline, completely substituted for reboxetine, whereas the SSRIs paroxetine, citalopram and sertraline,

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dopamine reuptake inhibitors GBR12935 and bupropion failed (Dekeyne et al., 2001a). Further, the serotonin–noradrenaline reuptake inhibitors, venlafaxine and S33005, substituted for both citalopram and reboxetine with a comparable potency (Dekeyne et al., 2001a,b).

An alternative possibility to investigate the stimulus properties of antidepressant agents is conditioned taste aversion, and research has shown that both fluoxetine (Berendsen and Broekkamp, 1994) and fluvoxamine (Gommans et al., 1998) have stimulus properties when measured in this procedure. Conditioned taste aversion procedure is based on the assumption that drugs induce aversion as a result of novelty rather than the intrinsic aversive stimulus of the drug effect (Grant, 1987). Animals will, then, associate a taste with a drug effect when both are novel experiences, and develop avoidance response to the taste. However, this avoidance response will be prevented if the animals are pre-exposed to the drug prior to the taste-drug pairing. An important implication is that the avoidance will be prevented not only by the pre-exposure to the drug itself, but to other drugs with similar discriminative stimulus cues, thus allowing comparison of the stimulus properties of drugs (De Beun et al., 1993).

Venlafaxine is the first member of a new class of antidepressants currently referred as serotonin–noradrenaline reuptake inhibitors. In vitro, venlafaxine blocks the synaptosomal uptake of both serotonin and noradrenaline (Mendlewicz, 1995). It has a 30-fold higher affinity for serotonin transporters than noradrenaline transporters (Tran et al., 2003). Venlafaxine is also a weak inhibitor of dopamine reuptake transporter and has no significant affinity for muscarinic, alpha1-adrenergic, or histaminergic receptors, which may account for its better tolerability profiles compared to the tricyclic antidepressants. For the clinical proof of its antidepressant efficacy, the conclusion one can draw from available findings is that venlafaxine is significantly more effective than placebo, and at least as effective as various tricyclics and SSRIs (Holliday and Benfield, 1995; Andrews et al., 1996). There is, indeed, recent evidence that it can be a more effective antidepressant than fluoxetine (Thase et al., 2001; Smith et al., 2002). Moreover, venlafaxine has also been dose-dependently active in various animal models of depression (Llyod et al., 1992; Redrobe et al., 1998). However, the stimulus properties of this antidepressant has not been investigated yet, except in one study, where it was used as a testing drug and substituted for both reboxetine, a noradrenaline reuptake inhibitor, and citalopram, an SSRI (Dekeyne et al., 2001a,b).

In the present study, we aimed to investigate a conditioned taste aversion procedure by the stimulus effects of venlafaxine in mice. In addition, a number of drugs, including tianeptine (a serotonin reuptake enhancer), fluoxetine and escitalopram (SSRIs), reboxetine (a noradrenaline reuptake inhibitor) and *N*ω-nitro-L-arginine methyl ester [(L-NAME), a nitric oxide synthase (NOS) inhibitor], were also tested as pre-exposure drugs to determine whether this effect was mediated by serotonergic, noradrenergic or nitrergic mechanisms.

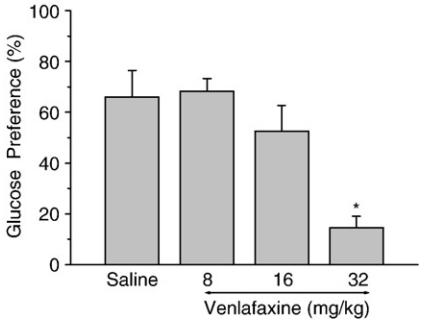

Fig. 1. Taste aversion producing effect of venlafaxine [*$P<0.0001$, Dunnett's test, significantly different from saline, $n=8$ for each group].

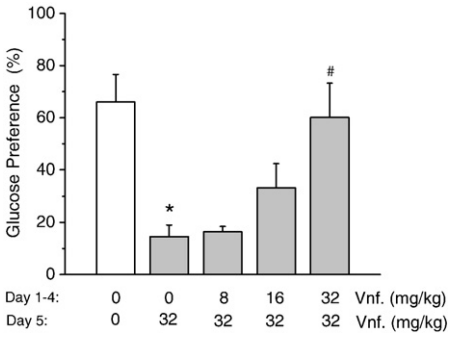

Fig. 2. Effect of venlafaxine pre-treatment on the taste aversion induced by the drug itself at 32 mg/kg [Vnf.=venlafaxine; *$P=0.001$, Student's t test, significantly different from the saline-treated group on the conditioning day; #$P=0.002$, Dunnett's test, significantly different from the saline-pretreated venlafaxine group, $n=8$ for each group].

2. Materials and methods

2.1. Subjects and laboratory

All procedures in the present study were performed in accordance with the rules in the Guide for the Care and Use of Laboratory Animals adopted by National Institutes of Health (USA) and the Declaration of Helsinki. Adult male Swiss Webster mice, weighting 25–33 g, were subjects. They were assigned to the groups ($n=8$) randomly, and each group of mice was housed separately in Plexiglas cages. They were placed in a quiet and temperature and humidity controlled room (20±2 °C and 60±5%, respectively) in which a 12/12 h light–dark cycle was maintained (07:00–19:00 h light). Food was available *ad libitum*, but access to tap water was restricted to 20 min daily during the experimental sessions (between 09:00 and 11:30 h) and an additional daily period of 30 min in their home cage from 15:30 till 16:00. All experiments were performed at the same time period of the day (09:00–12:00 h).

2.2. Drugs

Reboxetine, tianeptine, escitalopram and venlafaxine were generous gifts from Pfizer (UK), Servier (Turkey), Lundbeck (Denmark) and Wyeth (Turkey), respectively. Fluoxetine HCl and L-NAME were purchased from Sigma Chemical (USA). All drugs were dissolved in 0.9% saline and injected intraperitoneally (i.p.). Drug solutions were prepared freshly in every morning.

2.3. Procedure

Following a day of water deprivation, during the first 4 days (pre-exposure days) every morning mice were placed individually in an experimental cage equipped with two pipettes filled with water. They were allowed to drink for 20 min, and the amount of water consumed from both pipettes was recorded. These drinking sessions ran between 09:00 and 11:30 h. At least 1 h after they had water, mice were injected with a test drug i.e. venlafaxine (8–32 mg/kg), fluoxetine (1.25–10 mg/kg) escitalopram (2–32 mg/kg), reboxetine (5–20 mg/kg), L-NAME (15–120 mg/kg), and tianeptine (0.313–10 mg/kg) or saline. From 15:00 to 16:00 h, all mice had free access to water in their home cages. On day 5 (conditioning day) both pipettes were filled with a 5% w/v glucose solution; mice were injected with the conditioned taste aversion-inducing reference drug, venlafaxine (32 mg/kg) or saline immediately after they did drink from glucose. From day 5 until day 7, mice were left in their home cages where they had free access to water. On day 7 (11:00 h), the water bottles were removed again. On