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Effect of dopamine and serotonin receptor antagonists on fencamfamine-induced abolition of latent inhibition

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ABSTRACT

The purpose of this investigation was to verify the role of dopamine and serotonin receptors in the effect of fencamfamine (FCF) on latent inhibition. FCF is a psychomotor stimulant with an indirect dopaminergic action. Latent inhibition is a model of attention. Latent inhibition is blocked by dopaminergic agents and facilitated by dopamine receptor agonists. FCF has been shown to abolish latent inhibition. The serotonergic system may also participate in the neurochemical mediation of latent inhibition. The selective dopamine D_1 receptor antagonist SCH 23390 (7-chloro-3-methyl-1-phenyl-1,2,4,5-tetrahydro-3-benzazepin-8-ol), D_2 receptor antagonists pimozide (PIM) and methoclopramide (METH), and serotonin 5-HT $_{2A/C}$ receptor antagonist ritanserin (RIT) were used in the present study. Latent inhibition was evaluated using a conditioned emotional response procedure. Male Wistar rats that were water-restricted were subjected to a three-phase procedure: preexposure to a tone, tone-shock conditioning, and a test of the effect of the tone on licking frequency. All of the drugs were administered before the preexposure and conditioning phases. The results showed that FCF abolished latent inhibition, and this effect was clearly antagonized by PIM and METH and moderately attenuated by SCH 23390. At the doses used in the present study, RIT pretreatment did not affect latent inhibition and did not eliminate the effect of FCF, suggesting that the FCF-induced abolition of latent inhibition is not mediated by serotonin 5-HT $_{2A/C}$ receptors. These results suggest that the effect of FCF on latent inhibition is predominantly related to dopamine D_2 receptors and that dopamine D_2 receptors participate in attention processes.

1. Introduction

Fencamfamine (FCF) is a dopaminergic agent whose pharmacological and behavioral effects are related to an indirect activation of dopamine systems in the central nervous system (DeLucia and Planeta, 1990; DeLucia et al., 1997; Planeta et al., 1995; Scavone et al., 1985). FCF is characterized by a profile similar to amphetamine and particularly cocaine. In fact, behavioral studies have shown that FCF increases locomotion, rearing, and sniffing and provokes anorexia; at high doses, it induces stereotyped behavior (Aizenstein et al., 1983; Planeta et al., 1989). In vivo neurochemical studies have shown that the drug increases dopamine levels in both the caudate-putamen and nucleus accumbens (Kuczensky et al., 1991), which likely results from the blockade of synaptic dopamine reuptake (Seyfried, 1983). Evidence indicates that FCF acts as a positive reinforcer. It is self-administered by monkeys and dogs (Estrada-Robles, 1974; Risner and Cone, 1986). In rats, it substitutes for cocaine in a drug discrimination procedure (Risner et al., 1985) and exhibits reinforcing properties in place preference conditioning (Planeta et al., 1995). FCF has been marketed as an antifatigue medication (Reynolds, 1982) and has been abused by students and athletes (Delbeke and Debackere, 1981; Gorenstein et al., 1983).

Particularly relevant to the present experiments, FCF abolishes latent inhibition, as shown in this laboratory (Alves et al., 2002). Latent inhibition is a behavioral paradigm in which previous nonreinforced exposure to a stimulus impairs subsequent conditioning to that stimulus (Lubow, 1973; Weiner and Arad, 2009). Presumably stimuli that do not predict reinforcement are treated as irrelevant by the organism. As a model of attention, latent inhibition reflects the organism's ability to learn to ignore irrelevant stimuli. Latent inhibition is considered a privileged

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model of the distortion of attention observed in schizophrenia because it is reduced in schizophrenia patients (Baruch et al., 1988; Thornton et al., 1996). It also mimics the difficulty that these patients have been ignoring irrelevant stimuli, and it is abolished by dopamine receptor agonists and facilitated by antipsychotic dopamine receptor antagonists in animals and humans (Aguiar et al., 2011; Alves and Silva, 2001; Alves et al., 2002; Thornton et al., 1996; Weiner and Arad, 2009; Weiner and Feldon, 1987). The serotonergic system has also been suggested to be involved in latent inhibition. Dopaminergic drugs elevate serotonin levels (Lyon, 1991). Serotonin receptor agonists abolish latent inhibition (Cassaday et al., 1993; Hitchcock et al., 1997), and serotonin antagonists facilitate latent inhibition (Alves and Silva, 2001; Hitchcock et al., 1997).

The aim of the present study was to extend the investigation of the role of dopaminergic and serotonergic systems in the abolition of latent inhibition induced by FCF. The dopamine D_2 receptor antagonists pimozide (PIM) and methoclopramide (METH), the selective dopamine D_1 receptor antagonist SCH 23390 (7-chloro-3-methyl-1-phenyl-1,2,4,5-tetrahydro-3-benzazepin-8-ol), and the serotonin 5-HT2 $_{A/C}$ receptor antagonist ritanserin (RIT) were tested in the latent inhibition model. Given the involvement of dopamine and serotonin receptors in latent inhibition, verifying the eventual predominance of one of these amines might be an important contribution to understanding the neurotransmitter systems involved in latent inhibition and attention.

2. Methods

2.1. Animals

The experiments were conducted according to the recommendations of the National Institutes of Health Guide for the Care and Use of Laboratory Animals. Naive male Wistar rats that weighed approximately 300 g at the beginning of the experiment were used. During the first week of each experiment, the animals were housed in groups of five in $40 \times 33 \times 17$ cm polyethylene cages under a 12 h/12 h reverse light/dark cycle (lights on at 7:00 PM) and controlled temperature (21 ± 1 °C). At the end of that week, each rat was transferred to individual Inox cages ($24.5 \times 18 \times 19$ cm). Food (Purina food pellets) was freely available throughout the experiment.

2.2. Drugs

The drugs, doses, routes of administration, and pretreatment intervals followed a protocol routinely used in our laboratory (Planeta et al., 1995). FCF (Merck), METH (Pharmacotherapy American Laboratory), SCH 23390 (Sigma-Aldrich), and RIT (Sigma-Aldrich) were dissolved in a 0.9% NaCl solution (SAL). PIM (Janssen) was dissolved in a small amount of 1% tartaric acid. Control solutions were prepared with SAL. FCF, METH, RIT, and PIM were injected intraperitoneally. SCH 23390 was administered subcutaneously. SAL was injected by the same route as the drug with which it was associated. All of the solutions were injected in a volume of 1 ml/kg.

2.3. Apparatus

Four operant conditioning chambers ($32 \times 25 \times 21$ cm) encased in sound-attenuating isolation boxes were used. All of the equipment was obtained from Med Associates (St. Albans, VT, USA). A ventilation fan (ENV-025F28) provided background noise. A removable drinking bottle was located on one wall of the box. Licks were detected by a lickometer circuit (ENV-25 A). Tone stimuli (10 s, 70 dB, 2.8 kHz) were generated by a Sonalert module (SC-628). Shock stimuli (0.85 mA, 1 s) were supplied by a shock generator (ENV-410A) and scrambler (ENV-412) applied via 0.25 cm diameter stainless steel bars spaced 1.5 cm apart. A 486-IBM personal computer was programmed to control stimulus presentation and data acquisition.

2.4. Procedure

The experimental procedure was based on Weiner et al. (1996) and consisted of four phases conducted during the same AM or PM period of the day.

2.4.1. Baseline training (days 1–5)

The animals were individually placed in the experimental chamber with water available in the lickometer and remained there for 20 min. Each rat was then returned to its home cage and allowed to drink for 30 min, after which no water was provided until the next day.

2.4.2. Preexposure (day 6)

The bottle was removed, and each subject was placed in the experimental chamber. The preexposed (PE) animals received 40 presentations of a 10 s tone, with an intertrial interval (ITI) of 50 s. The nonpreexposed (NPE) animals were confined to the chamber for an identical length of time (2400 s), but they did not receive the tone.

2.4.3. Conditioning (day 7)

Each animal was again placed in the experimental chamber with the water bottle removed. Five minutes later, the rat was given two tone-shock pairings spaced 5 min apart. The tone was identical to the one used during the preexposure phase. Each tone presentation was immediately followed by a scrambled footshock (0.85 mA, 1 s). The animals were removed from the box 5 min after the second shock.

2.4.4. Testing (day 8)

The water bottle was replaced, and each animal was allowed to drink freely. When the rat had completed 50 licks, the tone was presented. The tone continued until an additional 25 licks had been made. If the rat failed to complete these 25 licks within 300 s, then the session was terminated. The suppression ratio was calculated as the time between licks 50 and 75 (pre-conditioned stimulus (CS) period) divided by the time between licks 50 and 100 (pre-CS period+CS period). A complete suppression of responding would be indicated by a ratio that is close to zero (i.e., no latent inhibition), whereas a ratio of 0.5 would indicate no change from the period prior to stimulus presentation (i.e., latent inhibition). Latent inhibition was defined as a suppression ratio that was greater in PE than in NPE rats.

2.5. Experimental design

Four experiments were conducted to study the effects of PIM, METH, SCH 23390, and RIT pretreatment on the FCF-induced abolition of latent inhibition. Each experimental group was subdivided into PE and NPE groups. Each of these groups had corresponding SAL+SAL and SAL+FCF control groups. These control groups received an equivalent volume of SAL or FCF 15 min before the experimental session. All of the drugs, with the exception of SCH 23390, were injected intraperitoneally. SCH 23390 was administered subcutaneously in a volume of 1 ml/kg.