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Abstract

Cinnarizine, a drug known as a calcium channel blocker, is currently used for the treatment of migraine and vertigo. Induction of extrapyramidal signs by cinnarizine has been reported in the elderly, which is related to its moderate antagonistic properties at dopamine D2 receptors, resembling the mechanism of action of most antipsychotic drugs. Despite this effect, cinnarizine has never been tested as a putative antipsychotic drug. Here we evaluate the potential effect of cinnarizine in two pharmacological models of psychosis, namely amphetamine- and MK-801-induced hyperlocomotion, as well as its ability to induce catalepsy. Cinnarizine significantly counteracted MK-801 (0.25 mg/kg) and amphetamine (5 mg/kg) locomotor effects at doses as low as 20 mg/kg,

having no incremental effect at 60 or 180 mg/kg. Regarding side-effects, cinnarizine induced no catalepsy in mice at the effective dose of 20 mg/kg, inducing only mild catalepsy at the doses of 60 and 180 mg/kg. Based on these results and on the antagonist effect of cinnarizine on dopamine D2 receptors, we suggest that it has a potential antipsychotic effect with an atypical profile that should be evaluated clinically.

Keywords

cinnarizine, MK-801, amphetamine, catalepsy, locomotion, schizophrenia, psychosis, mice

Introduction

Diphenylpiperazines compounds, such as cinnarizine and flunarizine, are usually known for their ability to inhibit calcium channels, especially of the T-type, and have been clinically used in some European and South American countries for the treatment of migraine (Rossi *et al.*, 2003) and vertigo (Pianese *et al.*, 2002). Cinnarizine is usually well tolerated by most patients, but case reports showed that its chronic use may exacerbate and even induce extrapyramidal symptoms, especially when administered to the elderly (Daniel and Mauro, 1995). This effect is explained by its low-to-moderate dopamine D2 receptor antagonist effect in the striatum, leading to impairment of nigrostriatal transmission (Brucke *et al.*, 1995). Dopamine D2 receptor antagonism is the main mechanism of action of antipsychotic drugs, which can be divided in two distinct groups: typical (or first generation) and atypical (or second generation) antipsychotics. Typical antipsy-

chotics act mainly on positive symptoms of schizophrenia (hallucinations and delusions), induce more intense extrapyramidal symptoms, tend to induce higher prolactin secretion and act through a potent dopamine D2 receptor blockade (Seeman *et al.*, 1997). In contrast, atypical antipsychotics exert only moderate blockade of dopamine D2 receptor and interfere with other neurotransmitter systems, resulting in broader symptomatic relief (including negative and disorganized symptoms) associated with milder or absent extrapyramidal and prolactin related symptoms (Seeman and Talerico, 1998; Kapur and Seeman, 2001).

Considering that the affinity of cinnarizine for blocking dopamine D2 receptor is similar to atypical antipsychotics, we hypothesized that cinnarizine would have such a profile in animal models, which could reinforce its putative therapeutic effects for the treatment of psychotic disorders and schizophrenia. In order to test this hypothesis we evaluated the effect of cinnarizine on MK-801 and amphetamine-induced hyperlocomotion, two pharmaco-

logical models of psychosis and schizophrenia, and tested its ability to induce catalepsy in mice as a model for extrapyramidal side-effects.

Material and methods

Animals

Experiments were performed with male adult albino mice (CF1) purchased from Fundação Estadual de Pesquisa em Saúde (FEPPS) when 21 days old and maintained in our own animal facilities under a controlled environment ($23 \pm 2^\circ\text{C}$, 12 hr light/dark cycle, free access to standard food and water) up to 3–4 months old (35–45 g). All behavioural experiments were in accordance with the Guidelines for Animal Care of our university. Different groups of animals were used in the distinct experiments. All experiments were conducted between 10 AM and 6 PM.

Drugs

MK-801 maleate and d-amphetamine sulphate were purchased from Sigma (St Louis, MO) and dissolved in fresh saline (0.9% NaCl) for acute administrations. Commercially available solutions for oral use of cinnarizine (Stugeron® – Janssen Cilag) and haloperidol (Haldol® – Janssen Cilag) were used. For all injections (oral – by gavage – and i.p.), a volume of 10 mL/kg was administered.

Locomotor activity experiments

Mice were treated orally with water or cinnarizine solution at different doses (6, 20, 60, 180 mg/kg). One hour later, their spontaneous locomotor activity was recorded for 1 h, followed by i.p. injection of either MK-801 (0.25 mg/kg) or amphetamine (5 mg/kg) and further recording for 3 h. A control group with oral water and i.p. saline was also included.

To assess locomotor activity, mice were randomly allocated to individual triangular boxes (50 cm \times 30 cm \times 30 cm, 50 cm high) with rounded corners, placed on the floor of a soundproof and diffusely illuminated room. Locomotor activity of eight mice was recorded simultaneously by a video-computerized system, with image analysis at four frames per second. The software (programmed by Tort ABL) tracked the animals by distinguishing their white colour from the black background of the floor, registering X and Y horizontal coordinates. The method was set to examine horizontal locomotor activity, ignoring small movements, such as breathing, head and tail actions, and tremors. Animals had not been previously habituated to the boxes and were observed for a total of 4 h (1 h habituation and 3 h after i.p. injection), with data divided in 10 min blocks.

Catalepsy experiment

Mice were orally treated with cinnarizine at different doses (6, 20, 60 and 180 mg/kg) or water, and had their catalepsy time deter-

mined 1.5 h and 3 h later. Mice treated with haloperidol (1 mg/kg p.o.) were used as positive controls.

Catalepsy time was measured after mice forepaws were placed over a horizontal glass bar (0.6 cm diameter), elevated 6 cm from the floor. The time mice maintained both forepaws over the bar and both hindpaws on the ground was recorded with a cut-off time of 180 s, allowing three immediate attempts to replace the animal in cataleptic position within the first 10 s. Mice that did not move their paws, but showed active body or head movements were not considered as cataleptic. The experimenter was blind to drug treatment. A control group with oral water treatment was also included.

Statistical analysis

Locomotor activities at different time points and groups were analysed using two-way ANOVA (General Linear Model) with time as the repeated measure. Duncan's post hoc test was used to determine differences among specific groups. Catalepsy time of different groups were analysed using the Kruskal-Wallis followed by the Mann-Whitney *U*-test due to use of a cut-off time. A value of $p < 0.05$ was considered statistically significant.

Results

Cinnarizine did not consistently affect spontaneous locomotor behaviour up to 60 mg/kg, as observed during the habituation period (Fig. 1, Fig. 2). MK-801 (0.25 mg/kg) significantly increased mice locomotor activity during approximately 120 min (Fig. 1). Cinnarizine pre-administration at the doses of 20 and 60 mg/kg, but not 6 mg/kg, significantly counteracted MK-801-induced hyperlocomotion. This effect was time-dose dependent ($F(68,459) = 1.582$; $p < 0.01$). The dose of 180 mg/kg inhibited spontaneous locomotion by around 40% and was not included in the analysis (Fig. 1).

Acute amphetamine (5 mg/kg) treatment induced a significant increment in mice locomotor behaviour (Fig. 2). Cinnarizine pre-treatment at the dose of 20 and 60 mg/kg, but not 6 mg/kg, produced a significant time-dose dependent ($F(68,187) = 2.087$; $p < 0.001$) attenuation of amphetamine effect (Fig. 2).

Cinnarizine 20, 60 and 180 mg/kg failed to induce cataleptic behaviour in mice 1.5 h after administration. However, the doses of 60 and 180 mg/kg produced significant catalepsy 3 hours after administration compared to saline, but significantly lower than haloperidol (Fig. 3). Haloperidol at the dose of 1 mg/kg induced significant catalepsy, near the ceiling point of 180 s at both time points (Fig. 3).

Discussion

The main finding of this study is that cinnarizine attenuated the psychostimulant effects of two pharmacological models of psychosis, MK-801 and amphetamine. This effect was present even at doses that did not elicit important extra-pyramidal effects in mice

Figure 1 Effect of cinnarizine on MK-801-induced hyperlocomotion. Cinnarizine (6, 20 and 60 mg/kg) or water was administered 1 h before the experiment, and MK-801 (0.25 mg/kg) or saline (control group) was administered after a 1-h habituation period. *denotes significant ($p < 0.05$) difference when compared to water group, which was also injected with MK-801. Data presented as mean \pm S.E.M. ($n = 8-10$ animals per group)

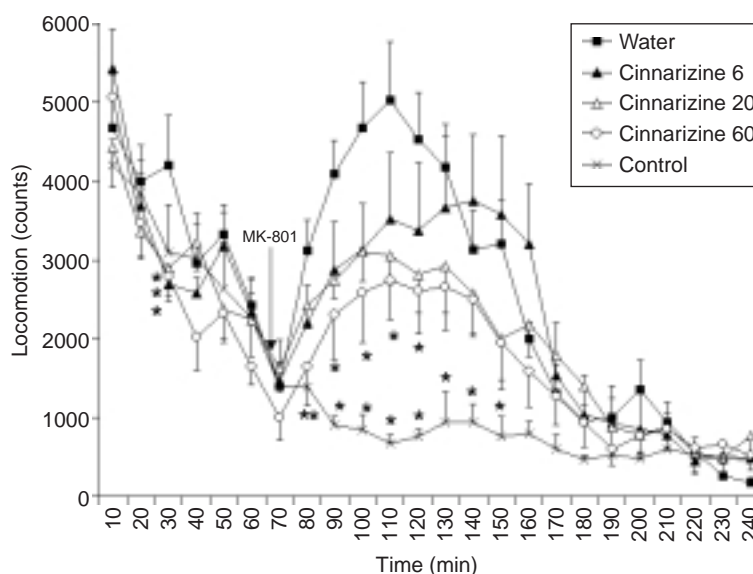
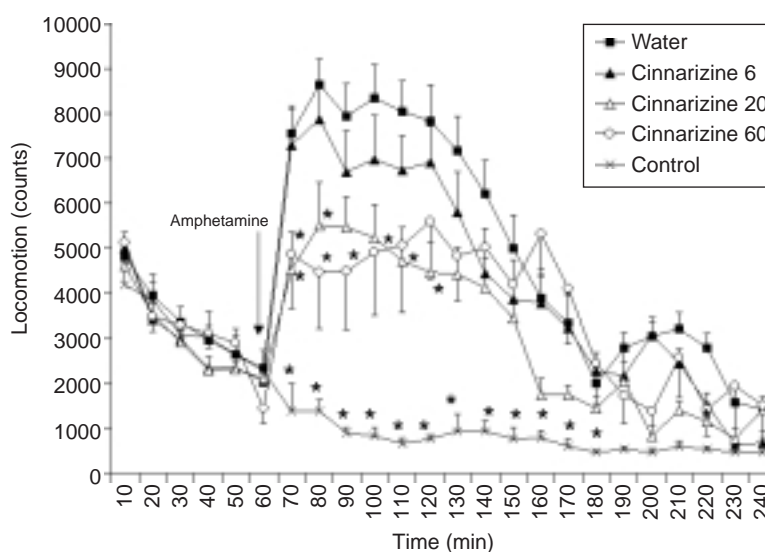


Figure 2 Effect of cinnarizine on amphetamine-induced hyperlocomotion. Cinnarizine (6, 20 and 60 mg/kg) or water was administered 1 h before the experiment, and amphetamine (5 mg/kg) or saline (control group) was administered after a 1-h habituation period. *denotes significant ($p < 0.05$) difference when compared to water group, which also received amphetamine. Data presented as mean \pm S.E.M. ($n = 8-10$ animals per group)



and without effects on spontaneous locomotion. These results, allied with existing data, suggest that cinnarizine exerts a behaviourally significant dopamine D2 receptor blockade, similar to atypical antipsychotics in these experimental models (Geyer and Ellenbroek, 2003).

Cinnarizine is clinically used for the treatment of vertigo and migraine, and extra-pyramidal side-effects such as rigidity and tremors that occasionally occur in elderly patients (Daniel and Mauro, 1995). Cinnarizine was also shown to aggravate Parkinson's disease (Fernandez *et al.*, 1988) and even induce parkinsonism in primates (Garcia Ruiz *et al.*, 1992), suggesting a relevant anti-dopaminergic effect. This was demonstrated by Brucke *et al.*

(1995), who showed around 40% striatal dopamine D2 receptor occupancy in patients using cinnarizine or flunarizine in a SPECT study, although extrapyramidal side-effects only occurred with higher occupancy rates. In comparison, occupancy level with atypical antipsychotics quetiapine (mean 550 mg/day), clozapine (mean 450 mg/day) and olanzapine (mean 18 mg/y) were 20, 33 and 74%, respectively, with the same radioligand (Tauscher *et al.*, 2002). *In vitro*, using the same radioligand, the affinity (K_i) of cinnarizine for dopamine D2 receptor was 13.2 nM, while haloperidol K_i is 0.125 or ~ 100 -fold lower (Kariya *et al.*, 1995). In the binding assays by Seeman *et al.* (1997), K_i for haloperidol (0.35 nM) is ten-fold lower than that for olanzapine (3.7 nM), but

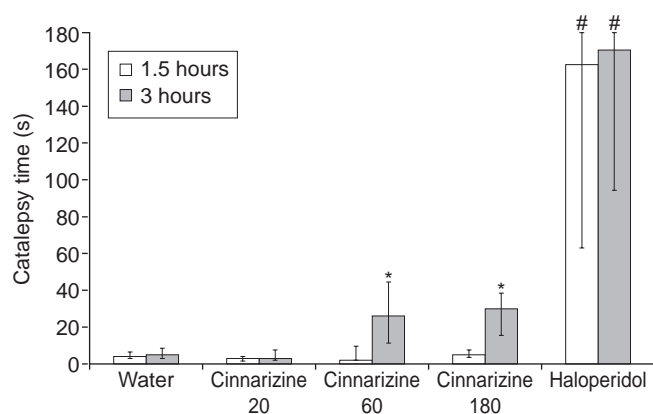


Figure 3 Effect of cinnarizine on catalepsy. Catalepsy time was determined 1.5 h and 3 h after treatment with water, cinnarizine (20, 60 or 180 mg/kg) or haloperidol (1 mg/kg). A cut-off time of 180 s was used. *denotes significant ($p < 0.05$) difference when compared to water group. # denotes significant difference from all other groups. Data presented as medians and interquartile range ($n = 8-10$ animals per group)

between 120- and 220-fold lower than clozapine (40 nM) and quetiapine (78 nM). Thus, based on its D2 receptor occupancy (*in vivo*) and affinity (*in vitro*), cinnarizine can be categorized as a dopamine D2 receptor antagonist of low-to-moderate affinity in between olanzapine and clozapine (Seeman *et al.*, 1997), therefore sharing the main mechanism of atypical antipsychotics, according to Seeman's proposal (Seeman and Tallerico, 1998; Kapur and Seeman, 2001). Importantly, extrapyramidal symptoms typically appear only in the elderly, who have a decreased dopaminergic tone (Brucke *et al.*, 1995). Furthermore, cinnarizine exerted a fairly potent antagonism of 5-HT₂ receptors *in vivo* (K_i 0.32 nM) (Okoro, 1999), an action shared with atypical antipsychotics such as olanzapine, risperidone and clozapine (Bymaster *et al.*, 1996).

Amphetamine-induced hyperlocomotion has long been used as a pharmacological model for psychosis in animals (Geyer and Ellenbroek, 2003) and is very useful in pre-clinical research for new antipsychotic drugs as it may mimic the hyperdopaminergic tone present in many schizophrenic patients (Kapur and Mamo, 2003). Cinnarizine was able to significantly counteract amphetamine-induced hyperlocomotion at doses as low as 20 mg/kg, a dose that neither interfered in spontaneous locomotion nor induced cataleptic behaviour in mice. At least part of this effect should result from cinnarizine antagonistic effect on dopamine D2 receptors, although other functions such as inhibition of glutamate (Terrian *et al.*, 1990) and dopamine release (Mena *et al.*, 1995) could be involved. These anti-dopaminergic mechanisms seem not to excessively decrease dopaminergic activity beyond a point to produce significant catalepsy and hypolocomotion, which occurred only in much higher doses than the ones effective against amphetamine induced hyperlocomotion, similarly to olanzapine (Ninan and Kulkarni, 1999). Importantly, catalepsy was not increased despite a three-fold dose increment up to 180 mg/kg,

indicating that the effective dose of cinnarizine would be unlikely to induce robust parkinsonism in humans, especially in younger psychiatric patients.

Glutamate NMDA receptor antagonists, such as phencyclidine and dizocilpine, have also been regarded as a pharmacological model for schizophrenia, producing both hyperlocomotion and cognitive deficits in rodents (Ninan and Kulkarni, 1999; Dall'Igna *et al.*, 2003). Of note, typical antipsychotics typically inhibit hyperactivity induced by NMDA receptor antagonists only at doses that inhibit spontaneous activity *per se*, contrary to the more effective and safe atypical antipsychotics with 5-HT₂ receptor antagonism (O'Neill and Shaw, 1999; Geyer and Ellenbroek, 2003). Here we have found that the cinnarizine effect on MK-801 hyperlocomotion is also similar to atypical antipsychotic profile, occurring at doses that do not affect spontaneous locomotion or induce catalepsy. NMDA receptor antagonists have been shown to indirectly activate non-NMDA glutamatergic receptors by an increase in glutamate release (Moghaddam *et al.*, 1997). Cinnarizine, mainly due to its ability to block calcium channels, inhibits glutamate release from intact synaptosomes (Terrian *et al.*, 1990), an action that *per se* could possibly prevent behavioural effects of NMDA receptor antagonists both in rodents (Moghaddam and Adams, 1998) and humans (Anand *et al.*, 2000). Another pharmacological action of cinnarizine is the blockade of sodium channels (Velly *et al.*, 1987), which is also a mechanism that prevents NMDA receptor antagonist neurotoxicity (Farber *et al.*, 2002). Also, cinnarizine has been shown to exert neuroprotective (Eichler *et al.*, 1994), antistress (Ossowska *et al.*, 1994) and neurotrophic effects (Tong and Rich, 1997), which are of potential interest for the treatment of schizophrenia and other psychotic disorders.

Based on its pharmacological profile in clinical practice (regarding tolerability) and in these models, cinnarizine has a putative antipsychotic action without major motor side-effects, similarly to atypical antipsychotics. Its mechanisms of action – dopamine D2 and 5-HT₂ receptor antagonism associated with inhibition of calcium and sodium channels – could give cinnarizine potential therapeutic advantage over other antipsychotics and is also an interesting pharmacological profile as a mood stabilizer. Clinical trials are necessary to investigate if the effect on animals models and the theoretical advantage of cinnarizine are relevant in the management of patients with psychotic disorders and schizophrenia.

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