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ORIGINAL INVESTIGATION

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Atypical antipsychotic profile of flunarizine in animal models

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Abstract *Rationale:* Flunarizine is known as a calcium channel blocker commonly used in many countries to treat migraine and vertigo. Parkinsonism has been described as one of its side-effects in the elderly, which is in agreement with its recently characterized moderate D_2 receptor antagonism. *Objectives:* To perform a pre-clinical evaluation of flunarizine as a potential antipsychotic. *Methods:* We evaluated the action of orally administered flunarizine in mice against hyperlocomotion induced by amphetamine and dizocilpine (MK-801) as pharmacological models of schizophrenia, induction of catalepsy as a measure for extrapyramidal symptoms and impairment induced by dizocilpine on the delayed alternation task for working memory. *Results:* Flunarizine robustly inhibited hyperlocomotion induced by both amphetamine and dizocilpine at doses that do not reduce spontaneous locomotion (3–30 mg/kg). Mild catalepsy was observed at 30 mg/kg, being more pronounced at 50 mg/kg and 100 mg/kg. Flunarizine (30 mg/kg) improved dizocilpine-induced impairment on the delayed alternation test. *Conclusions:* These results suggest a profile comparable to atypical antipsychotics. The low cost, good tolerability and long half-life (over 2 weeks) of flunarizine are possible advantages for its use as an atypical antipsychotic. These results warrant clinical trials with flunarizine for the treatment of schizophrenia.

Keywords Flunarizine · Amphetamine · Dizocilpine · Locomotion · Antipsychotic · Schizophrenia

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Introduction

Atypical antipsychotics were an important advance in the treatment of schizophrenia and other psychotic disorders (Meltzer et al. 2002). Their main advantages include better tolerability, especially regarding extrapyramidal symptoms, efficacy in a wider range of symptoms (Volavka et al. 2002) and increase in quality of life (Karow and Naber 2002). However, there are concerns about metabolic and cardiovascular side-effects that may affect morbidity and mortality of patients (Meltzer et al. 2002), added to the high cost of treatment, making them inaccessible for many patients, particularly in developing countries. Furthermore, except for injectable depot risperidone, atypical antipsychotics are not yet available in long-acting formulations, which facilitate adhesion to treatment.

Flunarizine, a piperazine derivative with chemical structure similar to the neuroleptic trifluoperazine, is a non-selective T-type, N-type and L-type calcium channel blocker, which has long been used in some countries for the treatment of migraine, vertigo and cerebrovascular disorders (Todd and Benfield 1989; Leone et al. 1991; Schmidt and Oestreich 1991). Flunarizine is usually well tolerated, but clinical reports showed aggravation and inducement of extrapyramidal motor signs secondary to chronic treatment with flunarizine, mainly in elderly patients (Chouza et al. 1986; Brücke et al. 1995). Accordingly, animal studies suggested that this side-effect could be due to moderate striatal D_2 receptor antagonism (Pani et al. 1990; Ambrosio and Stefanini 1991; Kariya et al. 1995; Haraguchi et al. 1998), which was in the low to moderate micromolar range. In humans, this was confirmed by Brücke et al. (1995), who found around 50% of D_2 receptor blockade in a SPECT study in patients chronically treated with flunarizine. Thus, based on its in vivo D_2 receptor occupancy and in vitro affinity, flunarizine can be categorized as a dopamine D_2 receptor antagonist of moderate affinity, in the range 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 after at least 6 months of treatment with flunarizine, which can be explained by its long-half life (around 15–20 days) (Kariya et al. 1995), leading to its accumulation due to daily administration up to the point when dopaminergic activity is excessively inhibited. Also, all patients who experienced extrapyramidal symptoms in the literature were older than 55 years, when the physiological dopaminergic tone is decreased (Brücke et al. 1995).

Despite these findings, flunarizine has not been proposed for the treatment of psychotic disorders or adequately tested in pre-clinical studies aiming at its putative antipsychotic actions. However, flunarizine, among other calcium channel blockers, has already been used as a pharmacological tool to study the role of calcium channels in the effects of amphetamine and NMDA receptor antagonists, which are pharmacological models with predictive validity for antipsychotics in pre-clinical studies. It was observed that flunarizine produced a significant inhibitory effect against behaviors induced by the indirect dopaminergic agonist amphetamine in rodents and monkeys (Grebb 1986; Rosenzweig-Lipson and Barrett 1995; Hori et al. 1998) and a borderline inhibitory effect against the NMDA receptor antagonist PCP (Grebb 1986; Hori et al. 1998). Of note, flunarizine also prevented, whereas haloperidol potentiated, the EEG effects of PCP (Popoli et al. 1992; Feinberg and Campbell 1998). Importantly, in all these studies flunarizine has been administered up to 30 min before testing, not taking into account the 2–4 h period to reach peak serum levels (Kariya et al. 1995).

In this study we investigated the profile of flunarizine as an atypical antipsychotic. To this end, we evaluated the effect of orally administered flunarizine on hyperactivity induced by systemic administration of the NMDA receptor antagonist dizocilpine (MK-801) and the indirect dopamine agonist amphetamine as pharmacological models of schizophrenia. The motor side-effects of flunarizine were also evaluated by testing the potency to reduce spontaneous locomotor activity and to induce catalepsy. Finally, cognitive impairment induced by dizocilpine on the delayed alternation task was used as a measure of working memory.

Materials and methods

Animals

Experiments were performed with male adult albino mice (CF1) purchased from Fundação Estadual de Pesquisa em Saúde (FEPS) when 21 days old and maintained in our own animal facilities under controlled environment (23±2°C, 12 h light/dark cycle, lights on at 7:00 a.m. with free access to standard food and water) up to 3–4 months old (35–45 g). All behavioral experiments were in accordance with the Guidelines for Animal Care of our university. Different groups of animals were used in the distinct experiments.

Locomotor activity experiments

Mice were orally treated at 8:00 a.m. with vehicle or flunarizine at different doses (1.0, 3.0, 10.0, 30.0 mg/kg). Three hours later, spontaneous locomotor activity was recorded for 1 h, followed by IP injection with dizocilpine (0.25 mg/kg) or amphetamine (5 mg/kg) and further recording for 3 h. A control group with oral vehicle (water) and IP saline was also included. For all injections (oral and IP), a volume of 10 ml/kg was administered.

To assess locomotor activity, mice were randomly allocated to individual triangular boxes (50 cm×30 cm×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 ABL Tort) tracked the animals by distinguishing their white color 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 IP injection), with data divided into 10 min blocks.

Catalepsy experiment

Mice were orally treated with flunarizine at different doses (3.0, 10.0, 30.0, 50.0 and 100.0 mg/kg) or vehicle, and had their catalepsy time determined 3 h and 6 h later. Mice treated with haloperidol 1 mg/kg PO 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 kept their paws over the bar, but showed active body or head movements were also not considered as cataleptic. The experimenter was blind to drug treatment.

Delayed alternation task

Delayed alternation performance was assessed in the T-maze task. The starting arm is 60 cm long, each side arm is 30 cm long, and both are 20 cm high and 10 cm wide, and the test was performed in a dimly illuminated room.

Mice were deprived from food until they achieved 80% of their initial weight. Then they were habituated in the T-maze for 4 days, receiving a food reward (Nescau cereal) at the end of the goal arms. In this habituation period, each mouse was placed in the start arm of the maze and permitted to explore it freely for 10 min, with the two open "goal" arms baited.

After these adaptation sessions, mice were trained as follows. In the first trial, food reward was presented in both goal arms. During the next 15 trials, the arm opposite to the one the animal had entered on the previous trial was baited with food reward, except when the animal had gone to the empty arm on the last trial. In this case, the food was left in the same place and the baited side was changed only after the animal had alternated. Sliding doors were used to keep the animal for a 10 s inter-trial interval in the starting arm, and to confine the mouse into the goal arm for 20 s, once it had entered in it. This training continued until the animal reached a criterion of at least 11 correct choices (score) in 15 trials on 3 consecutive days. A maximum of 10 blocks of 15 trials (10 days) was given to each mouse. Animals that failed to reach the criterion in these training sessions were discarded.

In the day after they matched the criterion, they received flunarizine (10 mg/kg or 30 mg/kg) or vehicle PO and after 3 h they were tested (15 trials). This first score was considered as predizocilpine. As soon as this session was over, they received

dizocilpine (0.4 mg/kg IP) and after 30 min they were retested. This second testing session was called post-dizocilpine.

Drugs

Dizocilpine maleate and *d*-amphetamine sulfate were purchased from Sigma (St Louis, Mo., USA) and were dissolved in fresh saline (0.9% NaCl) for acute administrations. Commercially available solutions for oral use of flunarizine (Flunarin, Asta Medica) and haloperidol (Haldol, Janssen) were used.

Statistical analysis

Comparisons of locomotor activities at different time points were analyzed using General Linear Model (GLM) repeated measure (drug treatment versus time) with time as the repeated measure. Duncan's post hoc was used to determine differences among specific groups. Catalepsy time and delayed alternation task performance were analyzed using the Kruskal–Wallis followed by the Mann–Whitney *U*-test due to cut-off time. A value of $P<0.05$ was considered statistically significant.

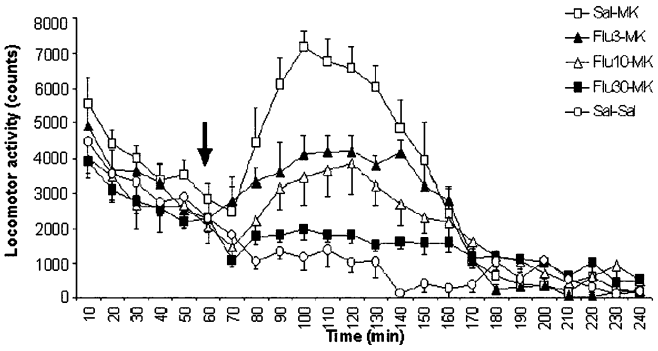

Fig. 2 Flunarizine inhibits hyperlocomotion induced by dizocilpine in mice. Flunarizine was orally administered to male adult albino mice 3 h before spontaneous locomotor recording in a computerized system. After 1-h habituation, mice were injected with 0.25 mg/kg dizocilpine or saline IP and locomotion was recorded for 3 h (n=6 per group). Results shown as mean±SEM. Statistics (two-way ANOVA with time as the repeated measure): no difference between groups at 0–60 min interval; saline > flu3=flu10 > flu30 at 70–240 min interval (P<0.05)

Results

Flunarizine dose-time-dependently inhibited amphetamine-induced hyperlocomotion [$F(85,612)=3.523$; $P<0.001$], with sal=1.0>3.0=10.0=30.0 mg/kg [between groups: $F(5,36)=7.205$; $P<0.001$] (Fig. 1). Against dizocilpine, flunarizine presented a dose-time-dependent inhibition of the hyperlocomotion induced by this NMDA receptor antagonist [$F(68,374)=7.779$; $P<0.001$], with sal >3.0=10.0>30.0 mg/kg [between groups: $F(4,22)=9.008$; $P<0.001$] (Fig. 2).

Regarding motor side-effects, considering the data of the 1 h habituation period in both trials, flunarizine 30 mg/kg presented, if anything, a mild inhibition of spontaneous locomotion (about 18% reduction), which was not statistically different from saline controls (P=0.08). Flunarizine caused catalepsy in a dose-dependent fashion, with no or minimal catalepsy up to 30.0 mg/kg (at 6 h: $Z=-2.747$; P=0.006), whereas the higher doses of 50.0 mg/kg and 100.0 mg/kg produced consistent catalepsy at both 3 h ($Z=-3.724$ for 50.0 mg/kg and −3.832 for 100.0 mg/kg; $P<0.001$) and 6 h ($Z=-3.592$ for 50.0 mg/kg and −3.622 for 100.0 mg/kg; $P<0.001$) after oral injections, but still less than 1 mg/kg haloperidol (at 3 h: $Z=-4.310$ and at 6 h $Z=-4.203$; $P<0.001$) [(Fig. 3)].

In the delayed alternation task, flunarizine 30 mg/kg attenuated the impairment provoked by dizocilpine ($Z=-1.983$; $P<0.05$), while the dose of 10 mg/kg did not achieve statistical significance ($Z=-1.512$; P=0.16) (Fig. 4).

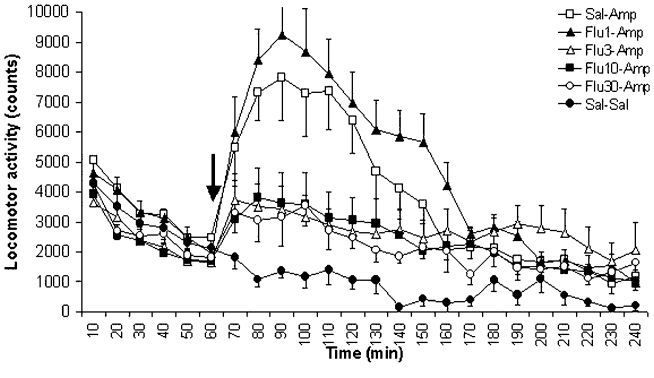

Fig. 1 Flunarizine inhibits hyperlocomotion induced by amphetamine in mice. Flunarizine was orally administered to male adult albino mice 3 h before spontaneous locomotor recording in a computerized system. After 1-h habituation, mice were injected with 5 mg/kg amphetamine or saline IP and locomotion was recorded for 3 h (n=6 per group). Results shown as mean±SEM. Statistics (two-way ANOVA with time as the repeated measure): no difference between groups at 0–60 min interval; sal=flu1 > flu3=flu10=flu30 at 70–240 min interval (P<0.05)

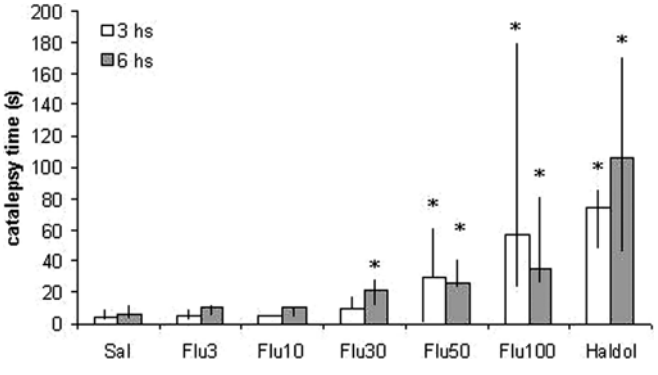

Fig. 3 Effect of flunarizine and haloperidol on catalepsy. Catalepsy time was determined 3 h and 6 h after treatment with vehicle, flunarizine or haloperidol PO. A cut-off time of 180 s was used. n=8 for all groups. Data presented as medians and interquartile range. * Denotes statistically significant (P<0.05) difference from control group

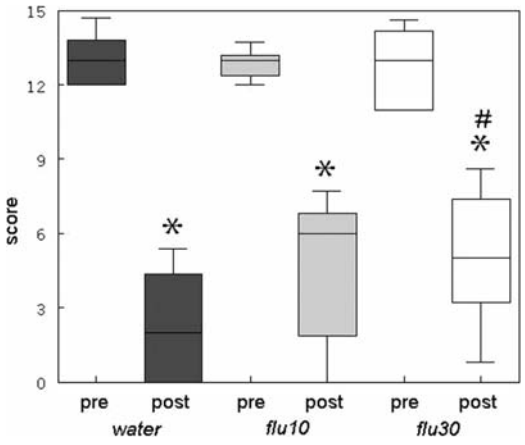

Fig. 4 Flunarizine attenuates dizocilpine induced impairment in the delayed alternation task. In mice previously trained to perform a delayed alternation task, flunarizine (10 mg/kg or 30 mg/kg) or vehicle PO was orally administered to male adult albino mice 3 h before testing 15 trials (*pre*). As soon as this session was over, they received dizocilpine (0.4 mg/kg IP) and after 30 min they were retested (*post*). n=8 for all groups, * denotes statistically significant (P<0.05) difference from its respective pre-test control, # denotes statistically significant (P<0.05) difference from saline post-test group

Discussion

The present work showed that flunarizine potently inhibited hyperlocomotion induced by amphetamine and dizocilpine, two models with predictive validity for antipsychotics, at doses that produced no hypolocomotion and cataleptic behavior, a characteristic suggestive of atypical antipsychotics (Ninan and Kulkarni 1999). Flunarizine also improved dizocilpine-induced impairment in the delayed alternation test at 30 mg/kg, a dose that caused only mild catalepsy. Such profile was observed with a 3-h pretreatment interval, which is more suitable to the pharmacokinetic profile of flunarizine, in contrast with previous studies, which typically administered flunarizine 15–30 min before the experiments (Grebb 1986; Sukhotina et al. 1999).

Among animal models to identify novel compounds with potential antipsychotic action, the indirect dopamine agonist amphetamine has been the most used pharmacological strategy for decades (Ellenbroek 1993). This model has gained further merit after direct evidence of increased dopaminergic activity in a high proportion of schizophrenic patients (for review, see Kapur 2003). Flunarizine potently inhibited amphetamine induced locomotion without a gradual dose response, since 1 mg/kg was ineffective and the doses of 3, 10 and 30 mg/kg were equally effective. Given the complex mechanism of action flunarizine, perhaps this effect may not be ascribed solely to its D_2 receptor antagonist properties. Inhibition of calcium and sodium channels by flunarizine (Holmes et al. 1984; Velly et al. 1987; Pauwels et al. 1991) can inhibit catecholamine release. Also, a possible increase in adenosine (Phillis et al. 1983; Popoli et al. 1990) by flunarizine treatment can also attenuate dopaminergic activity presynaptically by A1 receptors, which inhibit dopamine release, as well as post-synaptically by decreasing D_2 receptor affinity via A_{2a}–D_2 receptor interactions (Lara and Souza 2000). Nevertheless, these combined mechanisms seem not to excessively decrease dopaminergic activity based on its much lower potency to produce significant catalepsy and hypolocomotion, which is at least 1 order of magnitude distant from the effective doses against amphetamine and dizocilpine induced hyperlocomotion. A similar pattern has been observed for olanzapine (Ninan and Kulkarni 1999).

Age (especially >70 years old) was found to be a risk factor for developing extrapyramidal symptoms with flunarizine (Brücke et al. 1995), similarly to antipsychotics. This profile is probably due to the ontogenetic decay of dopaminergic tone (Brücke et al. 1995). To our knowledge, there is no report of extrapyramidal effect of flunarizine in patients younger than 55 years old. Long-term use (usually more than 6 months) was another risk factor, which is not unexpected considering flunarizine's long half-life (more than 2 weeks). This characteristic has been consistently overlooked in clinical practice, since it is normally prescribed at daily intakes. With such long half-life, rats treated daily with flunarizine presented an almost linear accumulation of the drug in plasma and striatum (Kariya et al. 1995), indicating that dose reduction or longer intervals between intakes should be considered to avoid motor side-effects. Apart from this side effect after long-term use, flunarizine is well tolerated even by the elderly.

Glutamate NMDA receptor antagonists, such as phencyclidine and dizocilpine, have also been used as a pharmacological model for schizophrenia, producing both hyperlocomotion and cognitive deficits in rodents (Ninan and Kulkarni 1999). Of note, typical antipsychotics typically inhibit hyperactivity induced by NMDA receptor antagonists at doses that inhibit spontaneous activity per se, contrary to atypical antipsychotics (O'Neill and Shaw 1999). Flunarizine produced a substantial dose-dependent effect in this model without significantly inhibit spontaneous locomotion. Flunarizine was also able to attenuate the cognitive impairment induced by dizocilpine in the delayed alternation test for working memory, which is thought to assess frontal lobe function (Le Marec et al. 2002). These results, therefore, further suggest an atypical profile of flunarizine, which may count with the contribution of other mechanisms of action, such as sodium channel blockade, which may also inhibit the effects of NMDA receptor antagonists (Farber et al. 2002).

Based on its pharmacological profile in clinical practice (regarding tolerability) and in these models, flunarizine has putative antipsychotic action without major motor side-effects, similarly to atypical antipsychotics. Moreover, after target symptoms have improved, flunarizine has the potential to be orally administered weekly or twice a month, which could considerably improve typically poor treatment compliance in psychotic patients (Perkins 2002). The long half-life also may prevent abrupt exacerbation of symptoms in the case of abandoning the treatment.

Conversely, if extrapyramidal side-effects occur, anticholinergic treatment would have to be initiated until plasma levels decrease significantly after dose adjustment. Another notable advantage of flunarizine is its very low cost, which is 10–40 times lower in comparison with atypical antipsychotics. It is also available in liquid formulation, which was used in this study. Taken together, these characteristics may increase treatment compliance with flunarizine in comparison with commercially available antipsychotics. Clinical trials with flunarizine for the treatment of schizophrenia and other psychotic disorders are therefore warranted to confirm its putative profile as a long-acting atypical antipsychotic.

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