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The antidepressant-like effect of 7-fluoro-1,3-diphenylisoquinoline-1-amine in the mouse forced swimming test is mediated by serotonergic and dopaminergic systems

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ABSTRACT

The aim of the present study was to investigate the role of monoaminergic system in the antidepressant-like action of 7-fluoro-1,3-diphenylisoquinoline-1-amine (FDPI), a derivative of isoquinoline class, in Swiss mice. The antidepressant-like effect of FDPI was characterized in the modified forced swimming test (FST) and the possible mechanism of action was investigated by using serotonergic, dopaminergic and noradrenergic antagonists. Monoamine oxidase (MAO) activity and [^{3}H]serotonin (5-HT) uptake were determined in prefrontal cortices of mice. The results showed that FDPI (1, 10 and 20 mg/kg, i.g.) reduced the immobility time and increased the swimming time but did not alter climbing time in the modified FST. These effects were similar to those of paroxetine (8 mg/kg, i.p.), a positive control. Pretreatments with *p*-chlorophenylalanine (100 mg/kg, i.p., an inhibitor of 5-HT synthesis), WAY100635 (0.1 mg/kg, s.c., 5-HT$_{1A}$ antagonist), ondansetron (1 mg/kg, i.p., a 5-HT$_3$ receptor antagonist), haloperidol (0.2 mg/kg, i.p., a non-selective D$_2$ receptor antagonist) and SCH23390 (0.05 mg/kg, s.c., a D$_1$ receptor antagonist) were effective to block the antidepressant-like effect of FDPI at a dose of 1 mg/kg in the FST. Ritanserin (1 mg/kg, i.p., a 5-HT$_{2A/2C}$ receptor antagonist), sulpiride (50 mg/kg, i.p., a D$_2$ and D$_3$ receptor antagonist), prazosin (1 mg/kg, i.p., an α1 receptor antagonist), yohimbine (1 mg/kg, i.p., an α2 receptor antagonist) and propranolol (2 mg/kg, i.p., a β receptor antagonist) did not modify the effect of FDPI in the FST. FDPI did not change synaptosomal [^{3}H]5-HT uptake. At doses of 10 and 20 mg/kg FDPI inhibited MAO-A and MAO-B activities. These results suggest that antidepressant-like effect of FDPI is mediated mostly by serotonergic and dopaminergic systems.

1. Introduction

Depression is one of the most prevalent neuropsychiatric disorders in our society characterized by modifications of mood and emotions. It affects approaching 15%–25% of the population (Nemeroff, 2007) and studies predict that in 2020, it will be the second largest global burden of disease, illustrating the severity and impact of the disorder (Manji et al., 2001).

Studies have demonstrated the involvement of numerous neural pathways in the pathophysiology of depression (Altamura et al., 2008). The monoaminergic system is one of the most important targets in this disorder (Elhwuegi, 2004; Steele et al., 2007). Furthermore, antidepressant compounds are now available, which probably act via different mechanisms, including the serotonergic, noradrenergic and dopaminergic systems (Goncalves et al., 2012).

Among the classical pharmacological treatments for depression currently available, three main classes can be cited: tricyclic antidepressants (TCAs), selective serotonin (5-HT) reuptake inhibitors (SSRIs) and monoamine oxidase inhibitors (MAOIs). However, it often takes more than 5–8 weeks until the patients respond to the treatment, beyond present adverse effects (Paez-Pereda, 2005). Thus, pursuing new pharmacotherapy, with elevated efficacy and fewer adverse side-effects, is an utmost clinical need.

Besides the well known involvement of monoamines, currently, large scale studies on the antidepressant mechanisms start to focus on the monoamine receptors. Different serotonergic receptors (5-HT$_{1A}$, 5-HT$_{1B/1D}$ and 5-HT$_{2C}$) (Cryan et al., 2005b; Wang et al., 2008), the three

Abbreviations: FDPI, 7-fluoro-1,3-diphenylisoquinoline-1-amine; FST, Forced Swimming Test; MAO, Monoamine oxidase; WAY 100635, N-[1]-N-(2-pyridinyl) cyclohexanecarboxamide; 5-HT, serotonin; TCAs, tricyclic antidepressants; SSRIs, selective serotonin reuptake inhibitors; MAOIs, monoamine oxidase inhibitors; NE, noradrenalin; i.g., intragastric; i.p., intraperitoneally; pCPA, p-Chlorophenylalanine; ANOVA, analysis of variance.

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families of adrenergic receptors, alpha1 (α1), alpha2 (α2) and beta (β) (Elhwuegi, 2004), and dopaminergic receptors (Joca et al., 2000) have been implicated in the etiology of depression.

The forced swimming test (FST), is the most widely used pharmacological model for assessing antidepressant efficacy (Cryan et al., 2002). It is based on the adoption of a passive response in a stress situation and suggested to have greater sensitivity (Porsolt et al., 1977a). The modification in the FST allows detecting active behaviors as either swimming, which is sensitive to serotonergic compounds such as the selective serotonin reuptake inhibitors (SSRIs), or climbing, which is sensitive to noradrenalin (NE)-selective uptake inhibitors (Cryan and Lucki, 2000; Detke et al., 1995).

Substituted isoquinolines represent a class of natural and synthetic compounds (Kulkarni and Dhir, 2010; Mantovani et al., 2014). 1-Methyl-1,2,3,4-tetrahydroisoquinoline (1MeTIQ) is an endogenous substance, which demonstrates antidepressant-like activity in the FST (Wasik et al., 2013). 1MeTIQ inhibits both monoamine oxidase A (MAO-A) and B (MAO-B) activities and increases monoamine neurotransmitter levels in the brain (Patsenka and Antkiewicz-Michaluk, 2004). Berberine, a yellow plant isoquinoline alkaloid, has multiple neuropharmacological properties, such as antidepressant and anxiolytic (Ye et al., 2009). 7-Fluoro-1,3-diphenylisoquinoline-1-amine (FDPI), a synthetic isoquinoline represented in Fig. 1, has antidepressant-like action in mice, non-selectively inhibits MAO activity and has antioxidant properties *in vitro* (Mantovani et al., 2014).

In view of the above considerations, the antidepressant-like effect of FDPI was investigated in the mouse modified FST. The hypothesis that serotonergic, dopaminergic and noradrenergic systems are involved in the antidepressant-like action of FDPI in the FST was evaluated.

2. Materials and methods

2.1. Animals

Behavioral experiments were conducted using male Swiss mice (25–35 g). Animals were maintained at 22–25 °C with free access to water and food, under a 12:12 h light/dark cycle, with lights on at 7:00 a.m. All manipulations were carried out between 08.00 a.m. and 04.00 p.m. All experiments were performed on separate groups of animals and each animal was used only once in each test. Animals were used according to the guidelines of the Committee on Care and Use of Experimental Animal Resources, of the Federal University of Santa Maria, Brazil. All efforts were made to minimize animal suffering and to reduce the number of animals used in the experiments.

2.2. Chemicals

FDPI (Fig. 1) was prepared and characterized in our laboratory by the method previously described (Mantovani et al., 2014). Analysis of the ^{1}H NMR and $^{13}CNMR$ spectra showed analytical and spectroscopic data in full agreement with its assigned structure. The chemical purity of the studied compound (99.9%) was determined by gas chromatography–mass spectrometry. All other chemicals were of analytical grade and obtained from standard commercial suppliers. To behavioral assays, all drugs were dissolved in saline except FDPI which was dissolved in canola oil. Mice received all drugs in a constant volume of 10 ml/kg body weight.

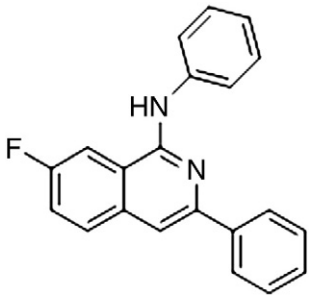

Fig. 1. Chemical structure of 7-fluoro-1,3-diphenylisoquinoline-1-amine (FDPI).

2.3. Behavioral tests

2.3.1. Forced swimming test (FST)

The FST was conducted as originally described by Porsolt et al. (1977a,b). In this test, mice were individually forced to swim in an open cylindrical container (diameter 10 cm, height 25 cm), containing 19 cm of water at 25 ± 1 °C. The total duration of immobility was recorded during the 6-min period. A decrease in the duration of immobility is indicative of an antidepressant-like effect.

The modified mouse FST was carried out as described by Detke et al. (1995) and Porsolt et al. (1977b), with some modifications (Can et al., 2013; Tanaka and Telegdy, 2008). This test permits to study the involvement of monoamines in the antidepressant-like effect of a compound.

Briefly, mice were individually forced to swim in an open cylindrical container (15 cm in diameter and 40 cm in height), containing 30 cm of water at 25 ± 1 °C. In the test, the time of climbing, swimming and immobility was measured during a 6-min period. Climbing behavior consisted of upward directed movements of the forepaws along the side of the swim chamber. Swimming behavior was defined as movement (usually horizontal) throughout the swim chamber, which also included crossing into another quadrant. Immobility was assigned when no additional activity was observed other than that required to keep the mice head above the water.

2.3.2. Effect of FDPI in the modified mouse FST

In this test, 30 min after the intragastric (i.g.) administration of FDPI (1, 10 and 20 mg/kg) or canola oil (vehicle), the animals were placed in the apparatus for 6 min and the behaviors were monitored. Pretreatment time of 30 min for the administration of FDPI was based on a previously published report (Mantovani et al., 2014). Paroxetine [8 mg/kg, intraperitoneally (i.p.), a selective serotonin reuptake inhibitor] (Gay et al., 2010), administered 45 min before the modified forced swimming test, was used as positive control.

2.3.3. The role of the serotonergic system in the antidepressant-like effect of FDPI in the FST

To address the role of the serotonergic system in the antidepressant-like effect of FDPI in the FST, distinct groups of animals were treated with different classes of drugs. Mice were pretreated with ondansetron, a selective 5-HT_3 receptor antagonist (1 mg/kg, i.p.) (Savegnago et al., 2007), ritanserin, a non-selective 5-$HT_{2A/2C}$ receptor antagonist (4 mg/kg, i.p.) (Wang et al., 2008), *N*-[1]-*N*-(2-pyridinyl) cyclohexanecarboxamide (WAY100635), a selective 5-HT_{1A} receptor antagonist [0.1 mg/kg, subcutaneous injection (s.c.)] (Savegnago et al., 2007; Villarinho et al., 2012) or saline (10 mg/kg, i.p.), 15 min before of FDPI (1 mg/kg, p.o.) or canola oil (10 ml/kg, i.g.). The FST was carried out 30 min after FDPI administration to mice.

p-Chlorophenylalanine (*p*CPA) is known to reduce the concentration of brain 5-HT by inhibiting its biosynthesis (Koe and Weissman, 1966). In the present experiments, mice were injected i.p. either with saline (control group) or with *p*CPA. *p*CPA was administered at a dose of 100 mg/kg once daily for 4 consecutive days (Machado et al., 2007). On the fifth day (24 h after the last *p*CPA administration), mice received canola oil (10 ml/kg, i.g.) or FDPI (1 mg/kg, i.g.) 30 min before the test.

2.3.4. The role of the dopaminergic system in the antidepressant-like effect of FDPI in the FST

To study the possible contribution of the dopaminergic system in the antidepressant-like action of FDPI, separate groups of animals were