and in the TST (dose range: 0.5–50 mg/kg). Given orally, 60 min earlier, guanosine produced an anti-immobility effect in the FST at a dose of 0.5 mg/kg and in the TST at the dose range 0.5–5 mg/kg. When given centrally (i.c.v. route), 15 min earlier, guanosine at a dose of 160 nmol/site was also able to reduce the immobility time in the FST. Besides that, the treatment of animals with guanosine by any route did not increase the locomotor activity in the open-field test. The pretreatment of mice with p-chlorophenylalanine methyl ester (PCPA; 100 mg/kg, i.p., an inhibitor of serotonin synthesis, for 4 consecutive days) significantly prevented the anti-immobility effect of either guanosine (5 mg/kg, i.p.) or fluoxetine (32 mg/kg, a preferential serotonin reuptake inhibitor, positive control) in the FST. In conclusion, our results firstly show that guanosine, administered systemically or centrally, produces a specific antidepressant-like effect in the FST and in the TST in mice, which seems to be dependent on an interaction with the serotonergic system. Financial support: CNPq, CAPES (Brazil).

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P.2.d.021 Chronic agomelatine and fluoxetine treatments induce antidepressant effects in H/Rouen mice, a new genetic mouse model of depression

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Purpose: Genetically-determined inter-individual variation in vulnerability to depressive disorder is a well-known phenomenon. Therefore, genetically- and/or environmentally-manipulated models would be closer to the clinical situation than models based on standard laboratory strains. Two research strategies are commonly assessed to study individual differences in rodents: (a) comparing features of individuals belonging to different strains of animals and (b) comparing features of individuals belonging to the same strain, screened on the basis of a particular feature (e.g. 'helpless' vs. 'non-helpless' mice). A third approach more closely matches the human situation: individuals displaying different behavioural traits that co-exist in an otherwise unselected outbred strain (e.g. CD1 mice) may be selectively bred and may represent two stable distinct types of individuals which normally occur in rodent population (e.g. H/Rouen and NH/Rouen lines of mice). The helpless line (H/Rouen), which is much more immobile in the tail suspension test (TST) than the so-called non helpless (NH/Rouen) line, may correspond to a new genetic model of depression (El Yacoubi et al., 2003). Mice have been selectively bred for high and low immobility in the TST.

Methods: Here, H/Rouen and NH/Rouen mice (from generation S20) were chronically (3 weeks) administered with agomelatine (S-20098, 50 mg/kg/day i.p.), a melatonergic agonist (Audinot et al., 2003) and a 5-HT2C antagonist (Millan et al., 2003) or fluoxetine (10 mg/kg/day i.p.), a Selective Serotonin Reuptake Inhibitor. The design of the study was as follows: immobility times in the TST (each trial lasts 360 seconds) were measured at different days (D) (D1, D2, D8, D15 and D22); locomotor activity (Digiscan®) was recorded at D18.

Results: Both fluoxetine (10 mg/kg i.p. daily) and agomelatine (50 mg/kg i.p. daily) were devoid of any effects in the TST in NH/Rouen mice at all tested days. In H/Rouen mice, both fluoxetine and agomelatine significantly ($p < 0.05$) reduced the immobility time at D8, D15 and D22. Locomotor activity in a novel environment was shown to be lower in H/Rouen than in NH/Rouen mice in a previous work (El Yacoubi et al., 2003) and in the present study. When tested on D18 of the chronic treatment, agomelatine and fluoxetine did not modify ($P > 0.05$) locomotor activity in any of the lines (H/Rouen and NH/Rouen mice). This result suggests that the reduction of immobility time observed in the TST after treatment with the two drugs is not influenced by motor activity since motor activity patterns were similar in control and treated mice.

Conclusion: Taken together, these data indicate that the novel antidepressant agomelatine is endowed with antidepressant-like properties in H/Rouen mice, a new genetic model of depression.

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P.2.d.022 The modified Tail Suspension Test (mTST): a new paradigm to categorize antidepressants. Effects of classical and atypical opiates

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The tail suspension test (TST), as originally described by Steru et al., 1985, is one of the most widely used pharmacological models for assessing antidepressant activity. Mice develop immobility when they are suspended by the tail from a horizontal ring-stand bar. The immobility behaviour is thought to reflect either a failure to persist in escape-directed behaviour after persistent stress or the development of passive behaviour that disengages the animal from active forms of coping with stressful stimuli. A broad spectrum of antidepressant drugs selectively reduces the development of behavioral immobility in the TST. However, the paradigm in its traditional form is unreliable at detecting the neurochemical profile of distinct antidepressant-like drugs. Therefore, the aim of this study is the investigation of specific behavioral components of active behaviors in the tail suspension test trying to distinguish

between neurochemically distinct antidepressant-like drugs, such as monoaminergic and opioid compounds.

The mTST in mice (CD1, 23–27 g) was performed as a model of antidepressant activity. Mice were individually suspended by the tail from a horizontal ring-stand bar. A time sampling technique was employed whereby the predominant behavior in each 5-s period of the 360-s test was recorded. Swinging behaviour was defined as when the animal (with the body straight) moved alternately from one side to the other. Pedalling behaviour was defined as when the animal moved its paws continuously without moving its body. Curling behaviour was defined as when the animal raised its head towards it hind paws. Immobility was assigned to when no additional activity was observed.

The compounds tested were: 5-HT/NA antidepressants: Imipramine (2.5–20 mg/kg, i.p.) and venlafaxine (2.5–20 mg/kg, i.p.); 5-HT antidepressants: Fluoxetine (10–40 mg/kg, i.p.) and citalopram (5–80 mg/kg, i.p.); NA antidepressant: Desipramine (2.5–20 mg/kg, i.p.): Opiates: Morphine (10–40 mg/kg, i.p.), codeine(10–40 mg/kg, i.p.), (–)-methadone (1.25–5 mg/kg, i.p.), levorphanol (0.03–10 mg/kg, i.p.) and pethidine (2.5–40 mg/kg, i.p.). Results were analyzed by a one-way ANOVA followed by Dunnett's test. $p < 0.05$ were considered to be significant.

Imipramine, venlafaxine, desipramine, fluoxetine and citalopram decreased the immobility time with respect to saline, but they did not modify the other parameters with respect to control. As regards opioid compounds, morphine, codeine, (–)-methadone, levorphanol and pethidine significantly decreased the immobility time. However all of them decreased the pedalling behaviour and increased the curling behaviour. No differences were observed in swinging behaviour for morphine and codeine. Methadone, levorphanol and pethidine showed a tendency to increase swinging behaviour.

Our results showed that opioid compounds produce stereotyped behavioural patterns, decreasing the pedalling behaviour and increasing the curling behaviour in the mTST. This suggests that this model could specifically differentiate between standard antidepressants and other compounds with antidepressant-like effects but with different mechanisms of actions, such as opiates.

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P.2.d.023 Different types of potassium channels underlie the antidepressant-like effect of adenosine in the mouse forced swimming test

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In the central nervous system, the activation of potassium channels leads to hyperpolarization of cell membranes, which results in a decrease in cell excitability and neurotransmitters release. It has been reported that nitric oxide (NO) can activate different types of potassium channels. A role for potassium channels in the modulation of mood has been suggested by preclinical studies [1,2]. The inhibitors of different types of potassium channels produce an antidepressant-like effect in the mouse forced swimming test (FST), by a mechanism dependent on the inhibition of NO-cGMP synthesis [2]. We have recently shown that the administration of adenosine elicits an antidepressant-like effect in the mouse FST also through an inhibition of NO-cGMP synthesis [3]. Thus, in this work we investigated the involvement of different types of potassium channels in the antidepressant-like effect of adenosine in the FST. Swiss mice (30–40 g, n = 6–8), maintained at 22–27ºC with free access to water and food, under a 12:12 h light: dark cycle were used. The potassium channel inhibitors or vehicle were administered by intracerebroventricular (i.c.v.) route 15 min before the administration of adenosine, which was administered by intraperitoneal (i.p.) route 20 min before the tests. In order to assess the behavior of mice in the FST, animals were individually forced to swim in an open cylindrical container (diameter 10 cm, height 25 cm), containing 19 cm of water at 25ºC and the immobility time was scored during 6 min. The ambulatory behavior was assessed in an open-field test. The apparatus consisted of a box (40 × 60 × 50 cm) with the floor divided into 12 equal squares. The number of squares crossed with all paws (crossing) was counted in a 6-min session. Comparisons between experimental and control groups were performed by two-way ANOVA followed by Newman-Keuls test when appropriate. A value of $P < 0.05$ was considered to be significant. Treatment of mice with tetraethylammonium (TEA, a non-specific inhibitor of potassium channels, 0.025 ng/site), glibenclamide (an ATP-sensitive potassium channel inhibitor, 0.5 μg/site) or charybdotoxin (a large- and intermediate- conductance calcium-activated potassium channel inhibitor, 0.025 ng/site), all at doses that do not produce any effect in the FST, was able to potentiate ($P < 0.05$) the action of a subeffective doses of adenosine (1 mg/kg). The administration of adenosine and potassium channels inhibitors, alone or in combination, did not produce any effect in the open-field test ($P > 0.05$). Moreover, the reduction in the immobility time ($P < 0.05$) elicited by adenosine (10 mg/kg, i.p.) or fluoxetine (a preferential serotonin reuptake inhibitor, 32 mg/kg, i.p.) in the FST was prevented by the pretreatment of mice with cromakalim (a potassium channel opener, 10 μg/site, i.c.v.). Together these results indicate that the inhibition of different types of potassium channels may underlie the antidepressant-like effect of adenosine in the FST.

Financial support: CNPq, CAPES (Brazil)

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P.2.d.024 5-HT1A receptor antagonism reverses and prevents fluoxetine-induced sexual dysfunction in rats: clinical implications

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Introduction: Selective serotonin reuptake inhibitors (SSRIs) represent one of the most commonly prescribed classes of antidepressants. Despite the advances to the treatment of depression since the introduction of the SSRIs, there are still unmet clinical