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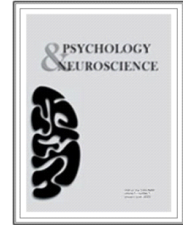
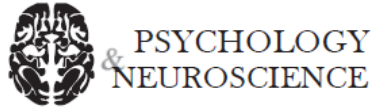
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**Antidepressant- and anxiogenic-like effects of acute 5-HT<sub>2C</sub> receptor activation in rats exposed to the forced swim test and elevated plus maze**

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Running head: Depression, anxiety, and 5-HT<sub>2C</sub> receptors

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## Abstract

This study investigated the behavioral effects in the forced swim test (FST) and the elevated plus-maze (EPM) of acute administration of WAY 161503 ([4aR]-8,9-dichloro-2,3,4,4a-tetrahydro-1*H*-pyrazino[1,2-*a*]quinoxalin-5[6*H*]-one), a selective 5-HT<sub>2C</sub> receptor agonist with putative antidepressant-like properties. Fifteen minutes after intraperitoneal (i.p.) injections of either WAY 161503 (1, 3 and 10 mg/kg) or saline, naive male Wistar rats were exposed to the EPM for 5 min to assess classical and ethological anxiety-like measures. Immediately after EPM exposure, each animal was exposed to the FST, and the latency to the first episode of immobility was recorded (trial session). Twenty-four hours later, the rats were reexposed to a second EPM-FST exposure sequence (test session for FST) under the effect of the same pharmacological treatment. The two lowest WAY 161503 doses selectively reduced open-arm exploration and increased risk-assessment without affecting locomotor activity. This selective anxiogenic-like effect was observed in both the first and second EPM exposures. The highest WAY 161503 dose produced robust locomotor impairment. In the FST, the same WAY 161503 doses significantly increased the latency to the first immobility in the test session, a behavioral profile that suggests an antidepressant-like action. These results further support the involvement of 5-HT<sub>2C</sub> receptors in the mediation of anxiety and suggest an intricate relationship between anxiogenic- and antidepressant-like actions. **Keywords:** anxiety, depression, serotonin, 5-HT<sub>2C</sub> receptor agonist, WAY 161503, animal models.

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## Introduction

The serotonin (5-hydroxytryptamine, 5-HT)<sub>2C</sub> receptor subtype appears to provide an interesting pharmacological target for screening new antidepressant agents. However, this possibility is based on contradictory findings showing the ability of both 5-HT<sub>2C</sub> agonists and antagonists to attenuate depression-related behaviors in animal models of depression. For example, acute and chronic 5-HT<sub>2C</sub> receptor activation by 5-HT<sub>2C</sub> agonists with different degrees of selectivity for the 5-HT<sub>2C</sub> receptor (e.g., WAY 161503, RO 60-0175, and RO 60-0332) are reported to decrease immobility in the rodent forced swim test (FST), an antidepressant-like effect comparable to selective serotonin reuptake inhibitors (Martin et al., 1998; Cryan, & Lucki, 2000; Rosenzweig-Lipson et al., 2007). 5-HT<sub>2C</sub> receptor blockade by nonselective, preferential, and selective 5-HT<sub>2C</sub> antagonists also appear to exhibit comparable antidepressant-like effects (Millan, 2005; Dekeyne et al., 2008). The reasons for these discrepancies remain unclear.

Interestingly, a different line of evidence suggests a critical role for the 5-HT<sub>2C</sub> receptor in the mediation of anxiety. For example, 5-HT<sub>2C</sub> receptor activation is relatively well documented to enhance anxiety-like parameters in humans (Charney, Woods, Goodman, & Heninger, 1987; Lowy, & Meltzer 1988; Bourin, Baker, & Bradwejn, 1998) and animal models (Kennett, Whitton, Shah, & Curzon, 1989; Rodgers et al., 1992; Grewal, Shepherd, Bill, Fletcher, & Dourich, 1997; Mora, Ferreira Neto, & Graeff, 1997; Olivier et al., 1998; Setem, Pinheiro, Motta, Morato, & Cruz, 1999; Bagdy, Graf, Anheuer, Modos, & Kantor, 2001; Zangrossi, Vianna, Zanoveli, Bueno, Nogueira, & Graeff, 2001; Jones, Duxon, & King, 2002; Bull, Huston, & Fone, 2003). 5-HT<sub>2C</sub> antagonists block these behavioral effects or induce anxiolytic-like actions themselves (for reviews, see Bourin, & Dhonnchadha, 2005; Filip, & Bader, 2009).

Despite these two different lines of evidence indicating a major role for 5-HT<sub>2C</sub> receptors in depression and anxiety, little attention has been given to experimental procedures in which the same animal is successively exposed to models of anxiety and depression after the administration of 5-HT<sub>2C</sub>-acting compounds. The present study evaluated the behavioral effects of pharmacological 5-HT<sub>2C</sub> receptor activation by injecting the selective 5-HT<sub>2C</sub> agonist WAY 161503 in rats successively exposed to the elevated plus maze (EPM) and FST, two of the most commonly used animal models of anxiety and depression, respectively.

## **Methods**

### *Subjects*

A total of 32 naive male Wistar rats (3 months old, 180-230 g bodyweight) from the animal colony of the University of Brasilia were housed in groups of four in polycarbonate cages (30 × 30 × 50 cm) with free access to food and water. The room temperature was controlled (25 ± 1°C) under a 12 h/12 h light/dark cycle (lights on 07:00-19:00). The maintenance, procedures, and minimal use of experimental animals followed the guidelines of the Brazilian Society of Neuroscience and Behavior under the recommendations of the Guide for the Care and Use of Laboratory Animals in Research (in accordance with the United States National Institutes of Health).

### *Drug*

WAY 161503 ([4aR]-8,9-dichloro-2,3,4,4a-tetrahydro-1H-pyrazino[1,2-a]quinoxalin-5[6H]-one; Tocris, Ballwin, MO, USA) was dissolved in sterile saline (0.9% NaCl) and injected intraperitoneally (i.p.) in a volume of 1.0 ml/kg.

### *Apparatus*

The EPM protocol followed the specifications described elsewhere (Cruz et al., 1994). It consisted of two open arms ( $50 \times 10$  cm) and two perpendicular closed arms ( $50 \times 10 \times 40$  cm) connected and delimited by a central area ( $10 \times 10$  cm). The maze was elevated 50 cm from the floor, and a rim of Plexiglas (1 cm high) surrounded the perimeter of the open arms to minimize falling from the arms. Each rat was placed in the central area facing a closed arm and allowed to freely explore the maze for 5 min. Before the next rat was introduced, the maze was cleaned with a solution of 20% ethanol and dried.

The rat FST apparatus was based on the specifications described by Porsolt, LePichnon and Jalfre (1977) and Porsolt, Bertin and Jalfre (1978) with some adaptations. Briefly, it consisted of a transparent cylinder (46 cm tall x 20 cm diameter) filled with water ( $26 \pm 2^\circ\text{C}$ ) to a depth of 30 cm inside which the rats were placed and forced to swim without the opportunity for escape. They remained inside water until develop immobility, which was defined as the cessation of limb movements except those necessary to keep the animal afloat.

Rats were tested in the FST with two exposures to the water tank spaced 24 h apart (trial session and test session, respectively). After swimming, each animal was gently dried with a towel and a hair blow dryer. The water in the tank was changed between rats.

Illumination (45 lux) was provided by a light bulb suspended above the apparatus. The EPM and FST sessions were videotaped for behavioral scoring at a later time by a blinded and highly experienced observer.

### *Procedure*

Animals were handled daily for 5 min for 7 consecutive days. Following this habituation trial, they were randomly assigned to four groups and injected with either saline-vehicle or WAY 161503 at doses of 1, 3, and 10 mg/kg. Fifteen minutes after the injections, each animal was exposed to the EPM for 5 min. The percentage of open-arm entries ( $100 \times \text{open-arm entries}/\text{total arm entries}$ ) and the absolute number of closed-arm entries were calculated as indices of anxiety and locomotor activity, respectively. Behaviors related to risk assessment were additionally recorded on the basis of previous results from our laboratory showing that this measure is sensitive to serotonergic manipulations (Setem et al., 1999).

Immediately after EPM exposure, animals were transferred to the FST apparatus and forced to swim in the water. The latency to the first episode of immobility was recorded. Animals were then removed from the apparatus and returned to their home cage. On the next day, they were subjected to a second EPM-FST exposure sequence 15 min after receiving the same pharmacological treatment. Reduced latency to the first episode of immobility in the test session compared with this same measure in the trial session indicated depressive-like behavior in the FST (Contreras, Martinez-Mota, & Saavedra, 1998; Contreras, Rodriguez-Landa, Gutierrez-Garcia, & Bernal-Morales, 2001; Mineur, Picciotto, & Sanacora, 2007).

#### *Statistical analysis*

The EPM and FST results were analyzed by two-way analysis of variance (ANOVA) followed by Dunnett's *post hoc* test when appropriate. Values of  $p < .05$  were considered statistically significant.

## **Results**



Fig. 1 shows the behavioral effects of WAY 161503 in the first and second EPM exposures. ANOVA indicated significant effects of treatment on the percentage of open-arm entries ( $F [3, 48] = 12.74; p < .05$ ), time spent engaging in risk assessment behaviors ( $F [3, 48] = 16.32; p < .05$ ), and closed-arm entries ( $F [3, 48] = 9.42; p < .05$ ), but no effect of EPM exposure.

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INSERT FIGURE 1 ABOUT HERE  
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Post hoc comparisons revealed that WAY 161503 significantly reduced open-arm exploration at doses of 3 and 10 mg/kg ( $ps < .05$ ) and increased risk-assessment at doses of 1 and 3 mg/kg ( $ps < .05$ ) compared with saline-vehicle-treated animals. At the dose of 10 mg/kg, this behavioral profile was accompanied by a significant reduction in the absolute number of closed-arm entries ( $p < .05$ ).

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FIGURE 2 ABOUT HERE  
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Fig. 2 shows the effect of WAY 161503 on the latency to the first episode of immobility during the FST test session. ANOVA indicated a significant effect of treatment ( $F [3, 48] = 9.67, p < .05$ ). Compared with animals injected with saline-vehicle, WAY 161503 significantly increased the latency to the first episode of immobility at doses of 1 and 3 mg/kg and decreased this measure at 10 mg/kg ( $ps < .05$ ).

## Discussion

The role of 5-HT receptors in the mediation of emotional states has been widely investigated. Our results showed that 5-HT<sub>2C</sub> receptor activation by the selective 5-HT<sub>2C</sub> agonist WAY 161503 induced behavior consistent with anxiogenic- and antidepressant-like effects in the EPM and FST, respectively.

The anxiogenic-like action in the EPM was detected by decreased open-arm exploration at the dose of 3.0 mg/kg and increased risk-assessment behaviors from the closed arms at the doses of 1.0 and 3.0 mg/kg. This enhanced anxiety seemed to be selective considering that these WAY 161503 doses did not affect the absolute number of closed arm entries at these doses, a reliable locomotor index in the rat EPM (Cruz et al., 1994). At the highest dose (10.0 mg/kg), however, the WAY 161503-induced changes in open arm exploration and risk-assessment were accompanied by a robust hypolocomotion as indicated by reduction in the absolute number of closed-arm entries. As a whole these results further corroborate previously reported studies showing selective, preferential and non-selective 5-HT<sub>2C</sub> agonists to exhibit anxiogenic-like properties and locomotor impairments (Kennett et al. 1989; Rodgers et al. 1992; Grewal et al. 1997; Mora et al. 1997; Olivier et al. 1998; Setem et al. 1999; Bagdy et al. 2001; Zangrossi et al. 2001; Jones et al. 2002; Bull et al. 2003, Alves et al., 2004).

Repeated EPM exposures are known to reduce or abolish the anxiolytic-like effects of benzodiazepines, a phenomenon known as “one-trial tolerance” or acute tolerance in this test (File, 1990; File, & Zangrossi, 1993; File, 1993; File, Zangrossi, Viana, & Graeff, 1993; File, Gonzalez, & Gallant, 1999; Frussa-Filho, & Ribeiro, 2002; Vargas, Da Cunha, & Andreatini, 2006; Albrechet-Souza, Borelli, & Brandão, 2008). Our present results with the 5-HT<sub>2C</sub> agonist WAY 161503 showed that both the first and second EPM exposures were similarly able to detect anxiogenic-like effects. This result markedly contrasts with the one-trial tolerance phenomenon but corroborates previous

studies in which one-trial tolerance in the EPM was evident after administration of anxiolytic but not anxiogenic drugs (File, 1993). A recent study reported by Wehrmeister, Izidio, Pereira, Izidio, & Ramos (2010) also found an absence of one-trial tolerance in rats exposed to a modified form of the EPM.

In the FST, WAY 161503 dose-dependently increased the latency to the first episode of immobility during the test session, a behavioral profile consistent with an antidepressant-like action. This was evident at the 1 and 3 mg/kg doses. At the highest dose (10 mg/kg), the behavioral effects appeared to be attributable to general hypolocomotion, reflected by a reduction in closed-arm entries observed at this dose in the EPM. Similar antidepressant-like effects of acute and chronic administration with 5-HT<sub>2C</sub> agonists have been described in rodents exposed to animal models of depression, including the FST (Lucki et al., 1989; Martin et al., 1998; Cryan, & Lucki, 2000; Rosenzweig-Lipson et al., 2007). In some of these studies, inhibitory effects on general locomotion were also described at higher doses (Lucki et al., 1989).

In contrast to the above FST findings and our present results, subchronic pharmacological blockade of 5-HT<sub>2C</sub> receptors by preferential and selective 5-HT<sub>2C</sub> antagonists exhibited comparable antidepressant-like effects in the FST (Millan, 2005; Dekeyne et al., 2008). The reasons for these discrepancies remain unclear but might involve methodological issues, including acute, subchronic, and chronic forms of drug administration, the selectivity of the drugs for the 5-HT<sub>2C</sub> receptor subtype, and variations in the FST procedures. Further controlling and testing the behavioral effects of these variables are necessary.

In conclusion, our results showed that 5-HT<sub>2C</sub> receptor activation by the selective 5-HT<sub>2C</sub> agonist WAY 161503 enhanced anxiety-like behavior in the EPM but exerted a clear antidepressant-like effect in the FST, which might be associated with the

therapeutic potential of WAY 161503 in the pharmacological treatment of depression. Such a pattern of results in these two widely used animal models might contribute to a better understanding of clinical findings, in which antidepressants have been shown to induce anxiety.

ACCEPTED

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**Figure Legends**

**Figure 1.** Behavioral effects of WAY-161503 in the first and second EPM exposures. Bars indicate the mean  $\pm$  SEM ( $n = 8$ ). \* $p < .05$ , # $p < .05$ , significant difference compared with group treated with saline-vehicle.

**Figure 2.** Behavioral effects of WAY-161503 in the FST test session. Bars indicate the mean  $\pm$  SEM ( $n = 8$ ). \* $p < .05$ , significant difference compared with group treated with saline-vehicle.

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FIGURE 1

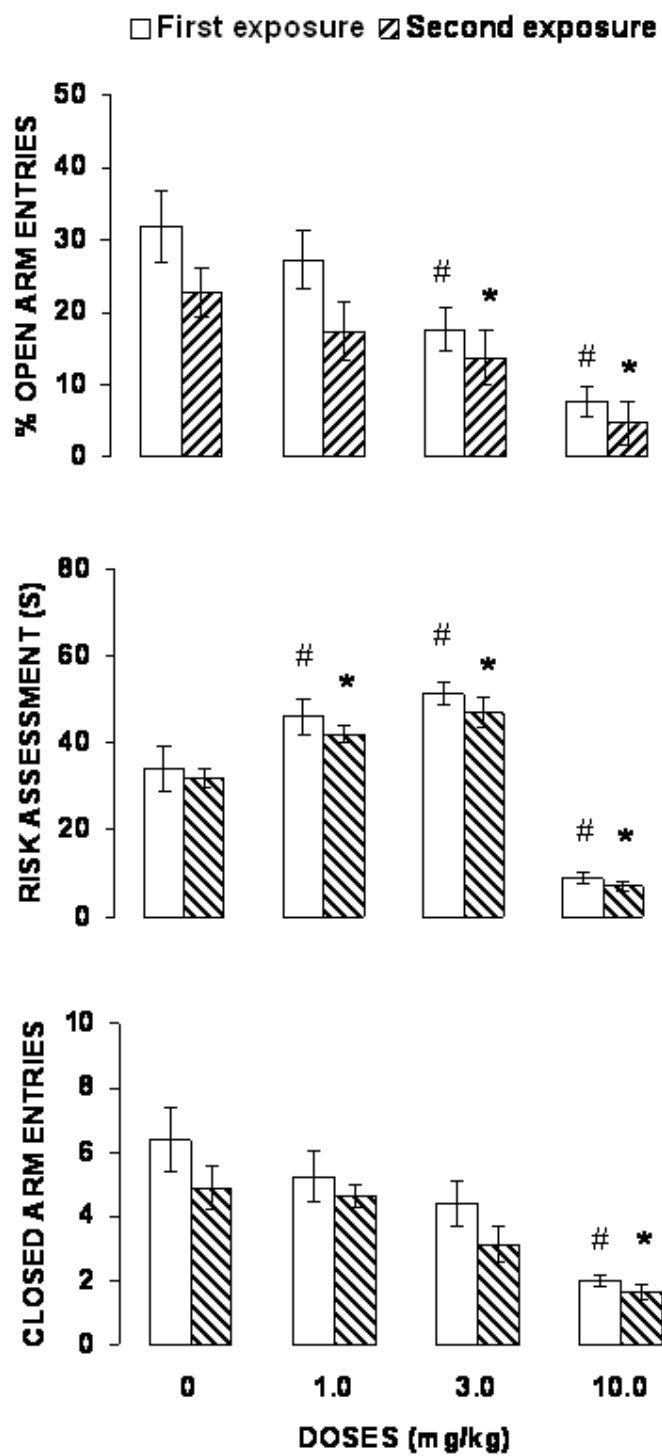
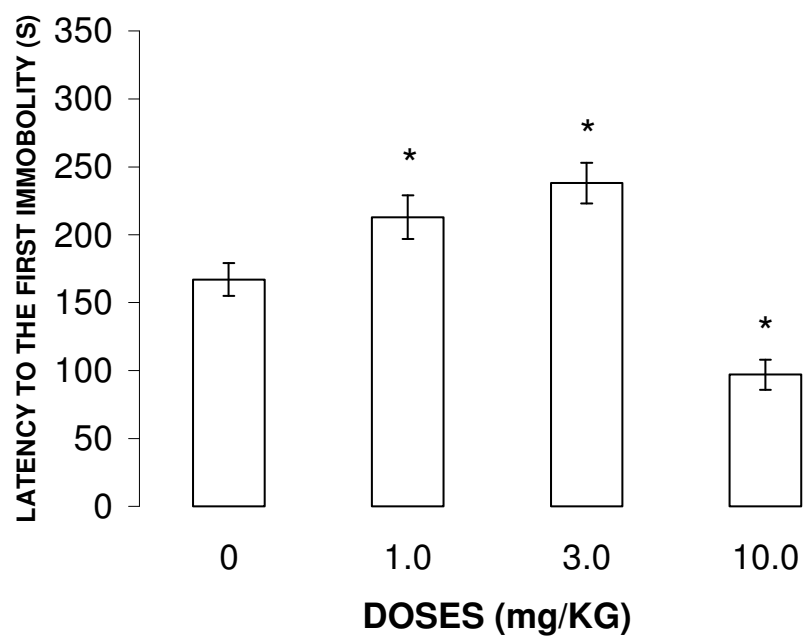


FIGURE 2



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