

## Psychology & Neuroscience



This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License. Fonte: <https://www.scielo.br/j/pn/a/dhsJ6nKndw849Fz4nbpKs3M/?lang=en#>. Acesso em: 10 set. 2021.

### REFERÊNCIA

GOMES, Flavia *et al.* 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. **Psychology & Neuroscience**, v. 3, n. 2, p. 245-249, 2010. DOI: <https://doi.org/10.3922/j.psns.2010.2.014>. Disponível em: <https://www.scielo.br/j/pn/a/dhsJ6nKndw849Fz4nbpKs3M/?lang=en#>. Acesso em: 10 set. 2021.



# 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

Flavia Gomes<sup>1</sup>, Marília Greidinger<sup>1</sup>, Marcelo Salviano<sup>1</sup>, Kalliu Carvalho Couto<sup>2</sup>, Graziela Ferreira Scaperlli<sup>2</sup>, Sérgio Henrique de Sousa Alves<sup>2</sup> and Antonio Pedro de Mello Cruz<sup>1</sup>

1- Universidade de Brasília, Brasília, DF, Brazil

2- Instituto de Ensino Superior de Brasília, DF, Brazil

## 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.

Received 22 October 2010; received in revised form 12 December 2010; accepted 12 December 2010. Available on line 28 December 2010

## 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 et al.,

---

Flavia Gomes, Marília Greidinger, Graziela Scaperlli, Marcelo Salviano and Antonio Pedro Mello Cruz, Departamento de Processos Psicológicos Básicos, Instituto de Psicologia, Universidade de Brasília, Brasília, DF, Brazil. Kalliu Carvalho Couto, Graziela Ferreira Scaperlli and Sérgio Henrique de Sousa Alves, Departamento de Psicologia, Instituto de Ensino Superior de Brasília, Campus Universitário Asa Sul, Brasília-DF. Correspondence regarding this article should be directed to: Antonio Pedro de Mello Cruz, Instituto de Psicologia, Universidade de Brasília, Campus Darcy Ribeiro, Asa Norte, Brasília, DF, 70.910-900, Brazil. E-mail: apmcruz@unb.br

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.

## Method

### 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-1*H*-pyrazino[1,2-*a*]quinoxalin-5[6*H*]-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 × 10 cm) and two perpendicular closed arms (50 × 10 × 40 cm) connected and delimited by a central area (10 × 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 × 20 cm diameter) filled with water (26 ± 2°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 × open-arm entries/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

Figure 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.

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 ( $p < .05$ ).

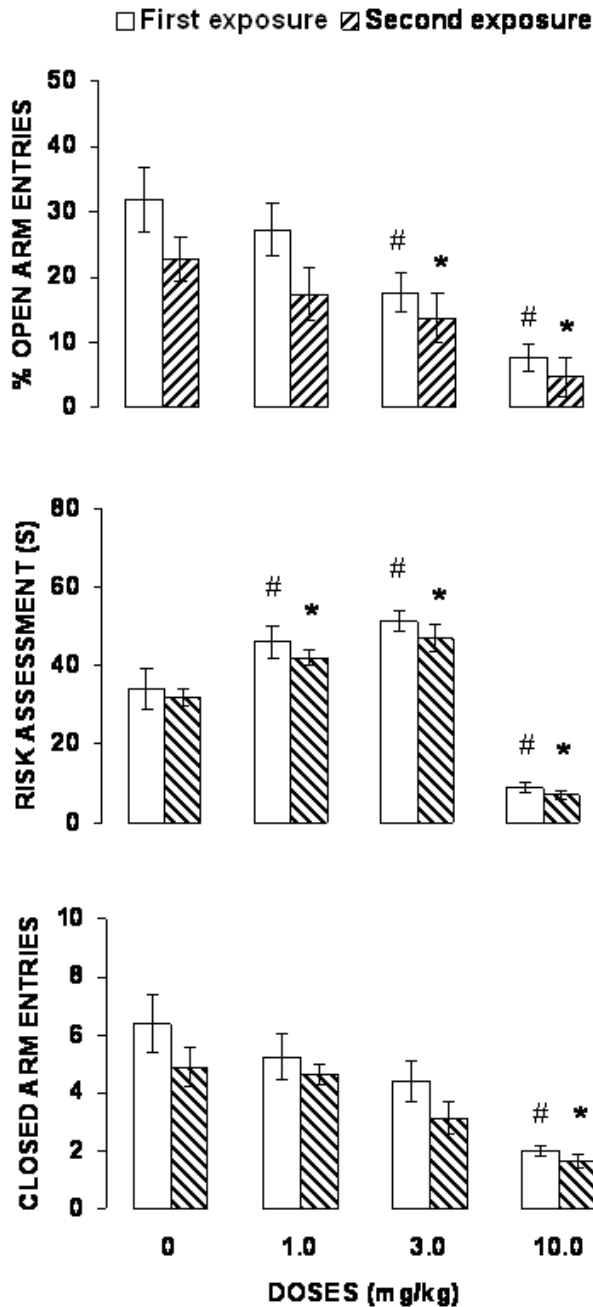


Figure 1. Behavioral effects of WAY-161503 in the first and second EPM exposures. Bars indicate the mean  $\pm$  SEM ( $n = 8$ ). \* $p < .05$ , # $p < .05$ , significant difference compared with group treated with saline-vehicle.

Figure 2 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 ( $ps < .05$ ).

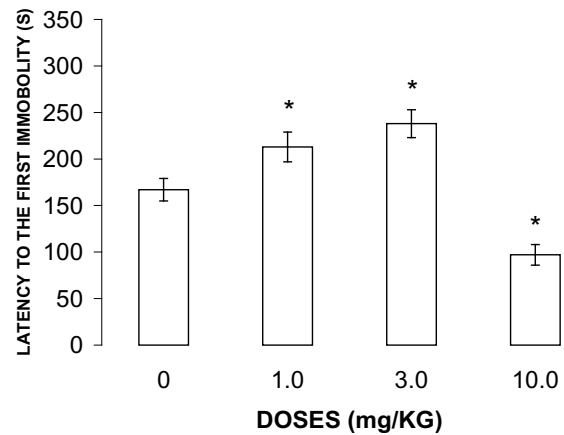


Figure 2. Behavioral effects of WAY-161503 in the FST test session. Bars indicate the mean  $\pm$  SEM ( $n = 8$ ). \* $p < .05$ , significant difference compared with group treated with saline-vehicle.

### 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, Ward, & Frazer, 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.

## References

- Albrechet-Souza, L., Borelli, K.G., & Brandão, M.L. (2008). Activity of the medial prefrontal cortex and amygdala underlies one-trial tolerance of rats in the elevated plus-maze. *Journal of Neuroscience Methods*, *169*, 109-118.
- Alves, S.H., Pinheiro, G., Motta, V., Landeira-Fernandez, J., & Cruz, A.P.M. (2004). Anxiogenic effects in the rat elevated plus-maze of 5-HT<sub>2C</sub> agonists into ventral but not dorsal hippocampus. *Behavioural Pharmacology*, *15* (1), 37-43.
- Bagdy, G., Graf, M., Anheuer, Z.E., Modos, E.A., & Kantor, S. (2001). Anxiety-like effects induced by acute fluoxetine, sertraline or m-CPP treatment are reversed by pretreatment with the 5-HT<sub>2C</sub> receptor antagonist SB-242084 but not the 5-HT<sub>1A</sub> receptor antagonist WAY-100635. *International Journal of Neuropsychopharmacology*, *4*, 399-408.
- Bourin, M., Baker, G.B., & Bradwejn, J. (1998). Neurobiology of panic disorder. *Journal of Psychosomatic Research*, *44*, 163-180.
- Bourin, M., & Dhonchadha, B.A.N. (2005). 5-HT<sub>2</sub> receptors and anxiety. *Drug Development Research*, *65*, 133-140.
- Bull, E.J., Huston, P.H., & Fone, K.C. (2003). Reduced social interaction following 3,4-methylenedioxymethamphetamine is not associated with enhanced 5-HT<sub>2C</sub> receptor responsivity. *Neuropharmacology*, *44*, 439-448.
- Charney, D.S., Woods, S.W., Goodman, W.R., & Heninger, G.R. (1987). Serotonin function in anxiety: II. Effects of the serotonin agonist mCPP on panic disorder patients and healthy subjects. *Psychopharmacology*, *92*, 14-21.
- Contreras, C.M., Martinez-Mota, L., & Saavedra, M. (1998). Desipramine restricts estral cycle oscillations in swimming. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *22*, 1121-1128.
- Contreras, C.M., Rodriguez-Landa, J.F., Gutierrez-Garcia, A.G., & Bernal-Morales, B. (2001). The lowest effective dose of fluoxetine in the forced swim test significantly affects the firing rate of lateral septal nucleus neurones in the rat. *Journal of Psychopharmacology*, *15*, 231-236.
- Cruz A.P.M., Frei, F., & Graeff, F.G. (1994). Ethopharmacological analysis of rat behavior on the elevated plus-maze. *Pharmacology, Biochemistry and Behavior* *49*, 171-179.
- Cryan, J.F., & Lucki, I. (2000). Antidepressant-like behavioral effects mediated by 5-hydroxytryptamine<sub>2C</sub> receptors. *Journal of Pharmacology and Experimental Therapeutics*, *295*, 1120-1126.
- Dekeyne, A., Mannoury La Cour, C., Gobert, A., Brocco, M., Lejeune, F., Serres, F.,...Millan, M.J. (2008). S32006, a novel 5-HT<sub>2C</sub> receptor antagonist displaying broad-based antidepressant and anxiolytic properties in rodent models. *Psychopharmacology*, *199*, 549-568.
- File, S.E. (1990). One-trial tolerance to the anxiolytic effects of chlordiazepoxide in the plus-maze. *Psychopharmacology*, *100*, 281-282.
- File, S.E. (1993). The interplay of learning and anxiety in the elevated plus-maze. *Behavioral Brain Research*, *58*, 199-202.
- File, S.E., & Zangrossi, H., Jr. (1993). “One-trial tolerance” to the anxiolytic actions of benzodiazepines in the elevated plus-maze, or the development of a phobic state? *Psychopharmacology*, *110*, 240-244.
- File, S.E., Zangrossi, H., Jr., Viana, M., & Graeff, F.G. (1993). Trial 2 in the elevated plus-maze: a different form of fear? *Psychopharmacology*, *111*, 491-494.
- File, S.E., Gonzalez, L.E., & Gallant, R. (1999). Role of the dorsomedial hypothalamus in mediating the response to benzodiazepines on trial 2 in the elevated plus-maze test of anxiety. *Neuropsychopharmacology*, *21*, 312-320.
- Filip, M., & Bader, M. (2009). Overview on 5-HT receptors and their role in physiology and pathology of the central nervous system. *Pharmacological Reports*, *61*, 761-777.
- Frussa-Filho, R., & Ribeiro, R.A. (2002). One-trial tolerance to the effects of chlordiazepoxide in the elevated plus-maze is not due to acquisition of a phobic avoidance of open arms during initial exposure. *Life Sciences*, *71*, 519-525.
- Grewal, S.S., Shepherd, J.K., Bill, D.J., Fletcher, A., & Dourich, C.T. (1997). Behavioural and pharmacological characterisation of the canopy stretched attend posture test as a model of anxiety in mice and rats. *Psychopharmacology*, *133*, 29-38.
- Jones, N., Duxon, M.S., & King, S.M. (2002). 5-HT<sub>2C</sub> receptor mediation of unconditioned escape behaviour in the unstable

- elevated exposed plus maze. *Psychopharmacology*, 164, 214-220.
- Kennett, G.A., Whitton, P., Shah, K., & Curzon, G. (1989). Anxiogenic-like effects of mCPP and TFMPP in animal models are opposed by 5-HT<sub>1C</sub> receptor antagonists. *European Journal of Pharmacology*, 164, 445-454.
- Lowy, M.T., & Meltzer, H.Y. (1988) Stimulation of serum cortisol and prolactin secretion in humans by MK-212, a centrally active serotonin agonist. *Biological Psychiatry*, 23, 818-828.
- Lucki, I., Ward H.R., & Frazer, A. (1989) Effect of 1-(m-chlorophenyl)-piperazine and 1-(m-trifluoromethylphenyl)-piperazine on locomotor activity. *Journal of Pharmacology and Experimental Therapeutics* 249, 155-164.
- Martin, J.R., Bös, M., Jenck, F., Moreau, J.L., Mutel, V., Sleight, A.J.,...van Delft, A.M.L. (1998). 5-HT<sub>2C</sub> receptor agonists: pharmacological characteristics and therapeutic potential. *Journal of Pharmacology and Experimental Therapeutics*, 286, 913-924.
- Millan, M.J. (2005). Serotonin 5-HT<sub>2C</sub> receptors as target for the treatment of depressive and anxious states: focus on novel therapeutic strategies. *Thérapie*, 60, 441-460.
- Mineur, Y.S., Picciotto, M.R., & Sanacora, G. (2007). Antidepressant-like effects of ceftriaxone in male C57BL/6J mice. *Biological Psychiatry*, 61, 250-252.
- Mora, P.O., Ferreira Neto, C., & Graeff, F.G. (1997). Role of 5-HT<sub>2A</sub> and 5-HT<sub>2C</sub> receptor subtypes in two types of fear generated by the elevated T-maze. *Pharmacology Biochemistry and Behavior*, 58, 1051-1057.
- Olivier, B., Molewijk, H.E., van der Heyden, J.A., van Oorschot, R., Ronken, E., Mos, J., & Miczek, K.A. (1998). Ultrasonic vocalizations in rat pups: effects of serotonergic ligands. *Neuroscience and Biobehavioral Reviews*, 23, 215-227.
- Porsolt, R., Le Pichon, M., & Jalfre, M. (1977). Depression: a new animal model sensitive to antidepressant treatments. *Nature*, 266, 730-732.
- Porsolt, R.D., Bertin, A., & Jalfre, M. (1978). "Behavioural despair" in rats and mice: strain differences and the effects of imipramine. *European Journal of Pharmacology*, 51, 291-294.
- Rodgers, R.J., Cole, J.C., Cobain, M.R., Daly, P., Doran, P.J., Eells, J.R., & Wallis, P. (1992). Anxiogenic-like effects of fluprazine and eltoprazine in the mouse elevated plus-maze: profile comparisons with 8-OH-DPAT, CGS 12066B, TFMPP and mCPP. *Behavioural Pharmacology*, 3, 621-634.
- Rosenzweig-Lipson, S., Sabb, A., Stack, G., Mitchell, P., Lucki, I., Malberg, J.E.,... Marquis, K.L. (2007). Antidepressant-like effects of the novel, selective, 5-HT<sub>2C</sub> receptor agonist WAY-163909 in rodents. *Psychopharmacology*, 192, 159-170.
- Setem, J., Pinheiro, A.P., Motta, V.A., Morato, S., & Cruz, A.P.M. (1999). Ethopharmacological analysis of 5-HT ligands on the rat elevated plus-maze. *Pharmacology Biochemistry and Behavior*, 62, 515-521.
- Vargas, K.M., Da Cunha, C., & Andreatini, R. (2006). Amphetamine and pentylentetrazole given post-trial 1 enhance one-trial tolerance to the anxiolytic effect of diazepam in the elevated plus-maze in mice. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 30, 1394-1402.
- Wehrmeister, T.D., Izidio, G.S., Pereira, E., Izidio, G., & Ramos, A. (2010). Absence of repeated-trial tolerance to the anxiolytic-like effects of chordiazepoxide in the rat triple test. *Pharmacology Biochemistry and Behavior*, 97, 301-309.
- Zangrossi, H., Jr., Vianna, M.B., Zanoveli, J., Bueno, C., Nogueira, R.L., & Graeff, F.G. (2001). Serotonergic regulation of inhibitory avoidance and one-way escape in the rat elevated T-maze. *Neuroscience and Biobehavioral Reviews*, 25, 637-645.