SERTRALINE INFLUENCE ON MORPHINE-INDUCED CONDITIONED PLACE PREFERENCE IN RATS

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SERTRALINE INFLUENCE ON MORPHINE-INDUCED CONDITIONED PLACE PREFERENCE IN RATS (Abstract): Serotonin reuptake inhibitors are an important pharmacological arsenal for treating major depression, a severe disease with poorly understood pathogenic mechanisms. Also, little is known about the action of antidepressants on reward system, the function of which is severely affected in this disorder. **Aim:** To assess the influence of sertraline on brain reward system by conditioned place preference technique in rats. **Results:** Both 3 and 5 mg/kg doses of sertraline determined a significant rewarding effect, whereas only the 5 mg/kg dose increased the morphine-induced rewarding effect (in the morphine-only group time spent in the conditioning chamber increased by 184.92±21.43% post-conditioning vs. pre-conditioning, whereas the increase was 195.56±18.3% in the group treated with morphine and sertraline 5mg/kg, p<0.05). **Conclusions:** The stimulant effect of sertraline on brain reward function might be involved in its therapeutic efficacy. **Keywords:** REWARDS SYSTEM, MORPHINE, SERTRALINE, CONDITIONED PLACE PREFERENCE.

Major depression (MD) is a disease which produces lots of disturbances in brain functioning. MD mechanisms are still insufficiently known. Antidepressant medication is one of the most frequently used in psychiatric practice. This medication has multiple action mechanisms. Most patients diagnosed with major-depression are nowadays treated with tricyclic antidepressants or with serotonin and/or norepinephrine reuptake inhibitors. Sertraline is one of the most often used serotonin-reuptake inhibitors in patients with major depression and bipolar disorder (1, 2, 3). There are also other important therapeutic uses for sertraline, including social phobia (4), panic disorder (5), or posttraumatic depression.

Brain reward system is essential for human and animal behaviour. Disturbances in its regulation are involved in the pathogenic mechanisms of several psychiatric diseases. One of the most important problems is the way in which different classes of antidepressant medication influence the brain reward system. The data on sertraline actions on reward system or any of its structural components are very scarce (in both humans and animals) (6). The aim of the present study was to investigate the effects of sertraline on reward system and its influence on morphine-induced conditioned place preference in rats.

Conditioned place preference (CPP) is an experimental protocol used to evaluate reward (drug or natural reward) in laboratory animals. The methods explores the associations between the rewarding effect of the addictive substance and other stimuli.
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(usually from the external environment) arbitrarily chosen.

MATERIAL AND METHODS

The present experiments were performed on adult male Wistar rats (180-270 g) hosted in individual cages; water and food were provided ad libitum, except for the behaviour testing periods. Animals were exposed to a 12/12-hour light-dark cycle; testing was performed during the light period. The conditioning apparatus (Panlab, Barcelona) consists of three chambers: two main chambers, distinguished by different wall and floor patterns, situated to the edges of the apparatus (one with black the other with white walls), and one smaller intermediary chamber. Communication between chambers may be either open or closed (by inter-changeable guillotine-like separations, suitable for a 180º movement). Illumination conditions were standardized by placing bulbs above each chamber. Prior to pre-conditioning, animals are subject to habituation sessions (2 sessions of 30 minutes daily, 2 days and one day before pre-conditioning). To induce morphine CPP we used the method described by Tzschentke (7).

1. Pre-conditioning (day 1) - natural animal preference towards one of the main chambers was determined. The rat spent 15 minutes in the apparatus (open communication between chambers). Time spent in each chamber was measured; the main chamber where it spent more time was referred to as preferred chamber, and the other as non-preferred. 2. Conditioning (days 2 – 9). Communication between chambers was closed. Days 2, 4, 6 and 8: the rat was restricted for 40 minutes to the preferred chamber, immediately after morphine (3 mg/kg, subcutaneously) administration. Days 3, 5, 7 and 9: alternatively, the rat was restricted for 40 minutes to the non-preferred chamber, immediately after the administration of 1 mL/kg saline solution. 3. Post-conditioning (day 10) - preference to main chambers was again measured for 15 minutes (open communication between chambers). Pre-conditioning, conditioning and post-conditioning stages took place in standard illumination conditions, during the same period of the day, in the absence of other stimuli that might have an influence on behavior (8). Pre-conditioning was initially applied to 80 rats. Animals showing a high preference towards a certain chamber (those spending more than 60% of the pre-conditioning time in any of the main chambers, or more time in the intermediary chamber than in any of the main ones) were excluded from further testing. Thus, 12 such animals (15% of the initial test group) were excluded. Of the remaining 68 animals, by applying homogeneity criteria 60 rats divided into 6 groups of 10 rats were selected for further tests.

According to the treatment received on experiment days 2, 4, 6 and 8 during the conditioning phase, the groups received: SS: saline solution (NaCl 0.9%), 1 mL/kg; Morph: morphine, 3 mg/kg; Sertr 3: sertraline, 3 mg/kg; Sertr 5: sertraline, 5 mg/kg; Morph + Sertr 3: morphine, 3 mg/kg + sertraline, 3 mg/kg; Morph + Sertr 5: morphine, 3 mg/kg, + sertraline 5 mg/kg; injected solutions were prepared so that each animal received 1 mL solution/kg at every administration. Doses were adjusted to animal weight changes during the experiment. On days 2, 4, 6 and 8 of the experiment, the rats received the previously described treatment, and then were placed in the non-preferred chamber. Morphine was administered subcutaneously, immediately before placing the animal in the non-preferred chamber; sertraline was administered intraperitoneally 2 hours before mor-
phine. On experiment days 3, 5, 7 and 9 all animals received saline solution, 1 mL/kg, and were placed immediately in the preferred chamber. Saline solution was administered intraperitoneally. Interpretation: a significant increase in time spent in the non-preferred (conditioning) chamber (preconditioning vs. post-conditioning) indicates that CPP was induced (change in preference). In such a case, it is believed that this is due to the fact that the animal associates reward (pleasant, euphoric effect of morphine administration) with the morphine-associated chamber.

The obtained results were statistically interpreted (p-value, t-test: paired – to compare post-conditioning vs. pre-conditioning time in each group; independent – to compare variance between groups in which CPP had been induced).

**RESULTS**

As expected, morphine determined a significant increase of time spent in the conditioning chamber (form 218.9±24.73 seconds – preconditioning, to 466.3±73.46 seconds, post-conditioning, p<0.001), indicating that a conditioned place preference was obtained. However, a significant conditioning effect was obtained with both sertraline doses (3 and 5 mg/kg), the effect of the 5 mg/kg sertraline dose being significantly higher compared to the 3 mg/kg dose (tab. I).

**TABLE I**

| Time spent in the conditioning chamber (pre-conditioning vs. post-conditioning) |
|---------------------------------|---------------------------------|---------------------------------|
|                                 | Time spent in the conditioning chamber (pre-conditioning) (seconds) | Time spent in the conditioning chamber (post-conditioning) (seconds) | Statistical significance (preconditioning vs. post-conditioning) |
| Morphine                        | Average                         | 218.9                           | 466.3                           | p<0.001 |
|                                 | Standard deviation              | 24.73                           | 73.43                           |         |
| Sertraline 3mg/kg               | Average                         | 217.5                           | 254.8                           | p<0.05  |
|                                 | Standard deviation              | 23.42                           | 41.01                           |         |
| Sertraline 5mg/kg               | Average                         | 238.7                           | 286.9                           | p<0.01  |
|                                 | Standard deviation              | 40.01                           | 36.71                           |         |

*Fig. 1. Variation of time spent in the conditioning chamber (% post-conditioning vs. pre-conditioning)*
The conditioning effect of sertraline slightly, but significantly potentiates the conditioning effect of morphine, but only if higher sertraline doses are used (fig. 1).

**DISCUSSION**

Addictive substances, as well as natural rewards (water, food, copulatory opportunity) may induce CPP. Bardo and Bevins, (9) enumerated the substances able to induce CPP. Morphine is one of the main addictive substances with rewarding effects proven by this paradigm. Brain reward system represents a system with important involvement in human and animal behavior. This system normal function is also impaired in major depression.

There are very few data regarding sertraline effects on brain reward system in both humans and animals, as well as its effects on different structures belonging to this system. Sertraline is an antidepressant, serotonin reuptake inhibitor, used in the treatment of major depression. This drug has the advantage of relatively few heart side effects (1, 2). Sertraline reduces anxiety and panic, having long-term effect. On the other hand, it has been shown that selective serotonin reuptake inhibitors (SSRI) have important anxiogenic effect. For example, fluoxetine (2.5-10 mg/kg, i.p.) and sertraline (15 mg/kg, i.p.) induce anxiety-like effects (decrease in time of total social interaction and increase in self-grooming compared to vehicle) under low-light, familiar arena test conditions. All these effects were reversed by pretreatment with the highly selective 5-HT2C receptor antagonist. SSRIs also produce anxiogenic effects in animals tested by the elevated plus-maze test (10, 11). We believe that sertraline effect on reward system is also due to receptor-mediated action. Our results are in agreement with other authors, showing that sertraline (2.5-10 mg/kg) induces CPP (12).

**CONCLUSIONS**

Sertraline, both 3 and 5mg/kg, induced a significant place conditioning. Also, sertraline 5 mg/kg significantly potentiated the rewarding effect of morphine, evaluated by conditioned place preference. We believe that the action of sertraline of stimulating brain reward function might be, at least partially, involved in its antidepressant action and explains its therapeutic efficacy.

**REFERENCES**

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**NEWS**

**LAWSONIA INERMIS-MEDIATED SYNTHESIS OF SILVER NANOPARTICLES**

*Lawsonia inermis* mediated synthesis of silver nanoparticles (Ag-NPs) has been studied by a group of researchers led by Gupta, in order to demonstrate its efficacy against *Candida albicans*, *Microsporum canis*, *Propionibacterium acne* and *Trichophyton mentagrophytes*. In this study, a two-step mechanism for bioreduction has been proposed, as well as the formation of an intermediate complex leading to the synthesis of nanoparticles and an antimicrobial gel for *M. canis* and *T. mentagrophytes*. The synthesis of Ag-NPs was done using the leaf extract of *L. inermis* in the presence of 1 mM AgNO3 and the compounds were further characterized by Ultraviolet-Visible spectrophotometer and Fourier transform infrared spectroscopy. The size of Ag-NPs was determined by transmission electron microscopy, nanoparticle tracking and analysis system. The antimicrobial activity was determined using disc diffusion method. The study concluded that Ag-NPs, due to their biogenic nature, may represent a better candidate drug and an answer to the drug-resistant microorganisms. (Gupta A, Bonde SR, Gaikwad S et al. Lawsonia inermis-mediated synthesis of silver nanoparticles: activity against human pathogenic fungi and bacteria with special reference to formulation of an antimicrobial nanogel. *IET Nanobiotechnol*. 2014;8(3):172-8. doi: 10.1049/iet-nbt.2013.001.

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