MINI-REVIEW

RECORDS OF PHARMACEUTICAL AND BIOMEDICAL SCIENCES

Effects of Serotonergic Agonists and Antagonists on the Competitive Behavior of Rats

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Abstract

When animals are housed in a group, they form social hierarchy, which may have a great influence on the cognitive abilities and health of the individuals of this group. The rank order of this social hierarchy may have its consequences on the individual survival, reproduction, and general health. Social hierarchy is formed based on the agonistic interactions among members of the group. Several methods of assessment of rank order in a specific group of animals have been developed in different behavioral laboratories; these included modified food competition test, sucrose solution competition test, water competition test, and tube test. It has been proposed that the aggressive behavior of animals is modulated by serotonin (5-HT) activity in the brains of the animals. Increased aggressive behavior was reported to be linked to decreased 5-HT level in the brain, and vice versa, submission was induced in animals by increased 5-HT activity in the brain. Administration of 5-HT agonists, e.g., fluoxetine, which inhibits the reuptake of serotonin from the synaptic area to the nerve terminal and therefore elevates synaptic serotonin level, could decrease aggression; whereas administration of ondansetron, which is a 5-HT receptor antagonist, could increase aggression in animals. The aim of the current review is to discuss the basis of social hierarchy, the role of central 5-HT, and the behavioral effects of 5-HT agonists and antagonists.

Keywords: Social hierarchy; serotonin, 5-HT agonists; 5-HT antagonists; aggression.

1. Introduction

Humans and other social species' life when living in groups is greatly affected by their rank in a specific social hierarchy **(Zhou et al., 2018)**. The aggressive interaction among the individuals of a group of animals may determine the rank order of each animal in its social group **(Olivier & Van Oorschot, 2005)**. These agonistic interactions between animals is derived by the limited resources for food, water, territory or sexually receptive female **(Zhou et al., 2018)**. Animals with higher rank in their groups may have first access to the aforementioned limited resources. Indeed, once rank order is established it may decrease fighting between animals and save energy **(Sapolsky, 2004)**. Several researchers have presented different animal models to evaluate the agonistic and competitive behavior of animals. Social hierarchy and rank order of animals could be determined in these animal models, including modified food competition test, sucrose solution competition test, water competition test, and tube test **(Timmer et al., 2011; Lozano-Montes et al., 2019; Costa et**

al., 2021).

It was important to investigate the central neural mechanisms that determine the rank order of animals and their social hierarchy. Serotonin (5-HT) is a major determinant factor of the aggressive behavior of animals **(Alekseyenko & Kravitz, 2014)**. Many authors reported that increased activity of brain 5-HT is accompanied by an inhibitory state of the brain **(Daw et al., 2002)**, which may result in decreased aggression of that animal **(Davidson et al., 2000; Veenema, 2009)**. In the contrary, decreased serotonergic activity in the brain is accompanied by an increased aggression of the animal **(Miczek et al., 1994; Márquez et al., 2013)**.

Many studies have been conducted to investigate the effects of different drugs on the aggressive behavior of animals. Reduced aggression was observed in animals treated with 5-HT agonists. This depressive effect on aggressive behavior has been observed after treatment with either direct 5-HT receptor agonists or indirectly acting agonists that increase synaptic level of 5-HT by inhibiting its reuptake, e.g., fluoxetine **(Olivier et al., 1987)**. In contrast, 5-HT3 receptor antagonists, e.g., Ondansetron, have been reported to decrease central 5-HT brain activity and increase aggression **(Engleman et al., 2008)**. The objectives of the current review are to review the basis of social hierarchy and rank order of animals, and to discuss the inverse relationship between central 5-HT neurobiological activity and aggressive behavior of animals. Further, the review aimed to explore the effects of 5-HT agonists and antagonists, on aggressive and competitive behavior of animals.

2. Social Hierarchy

Social hierarchy has been assessed in animals by measuring the agonistic behavior of these animals. Several models have been proposed by several researchers, they all based on evaluation of the competition outcomes for limited resources of food, water, or sexually receptive females **(Zhou et al., 2018)**.

Access to the scarce resources, e.g., food, water or others, may determine the rank position of the animal in its social hierarchy; the animal that gets this access is referred to as dominant animal or "winner", whereas the other animal is referred to as the subordinate animal or "loser". Social hierarchy is accompanied by priority access to various limited resources and decreased agonistic interactions to save energy **(LeClair et al., 2021)**. Dominance-subordination social interactions determine the basis of social hierarchy in mammals **(Fernald, 2014)**. Dominance-subordination relationship among different individuals in a group may have major consequences on the individual's mental and physical status **(Zhou et al., 2018)**.

Among the factors that may determine the social status are external and internal factors; the external factors are not inherited rather they come from outside, such as environment, opponent state, past experience of winning or defeat. Internal factors are inherited, such as body weight, courage, and stress **(Zhou et al., 2018)**. Several methods of assessment of animal hierarchy in the laboratory have been developed; these included food competition test, sucrose solution competition test, water competition test, and tube test **(Costa et al., 2021)**.

3. The Role of the Central Neurotransmitter Serotonin

Serotonin is widely distributed in the animals' CNS. It is synthesized in raphe nuclei from tryptophan amino acid. The highest concentrations of 5-HT are found in the limbic system in the brain **(Siegel & Crockett, 2013)**. 5-HT regulates many body functions such as aggressive behavior, sleep, pain, and sexual activity; further, it takes part in several diseases such as anxiety, headache, major depression, and addiction **(Roczniak et al., 2015)**. It is well established that high serotonin brain levels inhibit behavioral activation and aggression and vice versa, low serotonin levels are accompanied by increased aggression **(Alekseyenko & Kravitz, 2014)**.

4. Effects of 5-HT Pharmacological Agents on Behavior

The concept of modulatory role of 5-HT on aggressive behavior has been supported by a large body of research evidence in animals and human; decreased serotonergic function is associated with increased aggression, whereas pharmacological intervention that enhances serotonergic function reduces aggression **(Fuller, 1996)**. Brain lesions in the raphe nucleus that deplete 5-HT or by neurotoxins are reported to induce aggressive behavior in animals **(Eriksson & Jumbleb, 1990)**. These effects of 5-HT depletion are reversed by the

treatment with a precursor of 5-HT that enhances its synthesis. Many pharmacological studies have documented that administration of 5-HT receptor agonists could reduce the aggressive behavior in animals **(Ferris et al., 1999; Fish et al., 1999)**. Conversely, 5-HT receptor knock-out increased aggression in mice **(Saudou et al., 1994)**. Further, drugs that enhance the serotonergic function by direct activation 5-HT receptors or indirectly by inhibiting 5-HT reuptake to increase its availability at the synaptic area, e.g., fluoxetine, could decrease aggression in the treated animals **(Olivier et al., 1987)**.

5. Central Effects of 5-HT3 Receptors Antagonists

Blockers of 5-HT3 receptors are used in the treatment of nausea and vomiting induced by administration of chemotherapeutic agents. Several selective 5-HT3 blockers, e.g., Ondansetron, Itasetron, Alosetron, and Tropisetron, that are readily absorbed and cross the blood-brain barrier, are clinically useful antiemetic agents **(Hesketh, 2008)**. In addition to the anti-emetic effect of ondansetron, cognition and behavioral sensitization have been assessed in rats **(Davidson et al., 2002)**. Ondansetron administration could improve cognitive performance in rats **(Diez-Ariza et al., 2003)**.

6. Role of Central 5-HT in Regulating Food Intake

Researchers reported an inhibitory effect of serotonin on sucrose intake, which is mediated by 5-HT receptors **(Hayes & Covasa, 2005)**. Similarly, **Savastano et al. (2005)** showed the involvement of 5-HT3 receptors in the inhibitory effect of serotonin on food intake. Thus, the aforementioned observations proved the involvement of 5-HT receptors in the regulation of feeding behavior, which may affect the competitive behavior of animals to food. However, it was stated that this effect of serotonin is observed in food-deprived animals and not in fed mice **(Li et al., 2015)**.

A negative relationship between food intake and central 5-HTactivity has been observed **(Lam et al., 2010; Cui et al., 2012)**. Inhibited food intake was noted with increased activity of central 5-HT; whereas decreased activity of central 5-HT increased hyperphagia **(Fetissov et al., 2000; Lam et al., 2010)**. An inhibitory effect on feeding has been demonstrated after the administration of selective-serotonin reuptake inhibitors, e.g., fluoxetine, and serotonin releasers, e.g., fenfluramine **(Simansky, l996)**. In a previous study, similar results of serotonergic agonists were recorded on feeding behavior; authors suggested an enhanced satiation that decreased eating rate **(McGuirk et al., l992)**. Many studies have documented a modulatory effect of 5-HT3 receptors on feeding behavior. It has been proposed that many neurons related to feeding, e.g., peptide-mediated signaling, are affected by activation of 5-HT3 receptors **(Cui et al., 20l2, Wu et al., 2012)**. For instance, ondansetron, which is a selective 5-HT3 receptor antagonist, could decrease satiety induced by cholecystokinin (CCK) **(Daughters et al., 2001; Janssen et al., 2011)**.

7. Conclusion

The animals' brain serotonin levels are inversely related to the aggressive behavior of animals. 5-HT agonists, such as fluoxetine have a depressive effect on the aggressive and competitive behavior of animals; while 5-HT antagonists, such as ondansetron, decrease the brain serotonin activity and produce an enhanced aggressive and competitive behavior. It is recommended to conduct clinical research to explore the benefits of 5-HT agonists in treating impulsive aggression in violent patients. It is also recommended to investigate the beneficial effects of 5-HT agonists, eg. fluoxetine, in the treatment of dangerous aggressive dogs.

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