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Effect of Sulpiride on the Ontogenesis of Psychomotor Functions in Male Rats

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Abstract

Background: Scientific research has increasingly focused on studying the effects of substances on brain function. However, these studies often evaluate overall effects without identifying the specific brain regions involved in behavior control. **Objective:** This study aimed to determine the effects of sulpiride, an antipsychotic drug, on the behavior of male rats and to identify the brain areas affected by the neuroleptic (sulpiride). **Methods:** We used sixteen (16) female rats and eight (8) male rats for breeding. Vaginal smears were performed each morning to determine the first days of gestation. After identifying the first day of gestation using vaginal smear analyses, eight (8) pregnant female rats were assigned to the control group, while the other eight (8) pregnant rats received sulpiride treatment from the 11th day of gestation until the 10th postnatal day. On the 10th postnatal day, behavioral tests were performed on male rats from the control and treatment groups. Observations were made for 45 days. **Results:** The study revealed that sulpiride, a neuroleptic agent, influenced several brain regions, causing either activation or inhibition. The administration of sulpiride decreased the hind paws lifting reflex, wire-grasping time, and leap execution latency in male rats. In contrast, sulpiride increased crawling-wire latency and locomotor activity in male rats. **Conclusion:** Our study shows that sulpiride is a neuroleptic capable of acting on several brain areas responsible for behavior. It acts on brain areas causing either a decrease or an increase in central nervous system activity. These results provide valuable information on the specific brain regions affected by sulpiride, contributing to a better understanding of its overall impact on brain function.

Keywords

Hind Paws Lifting Reflex, Crawling-Wire, Locomotor Activity

1. Introduction

Antipsychotics are molecular substances that act on the activity of the central nervous system by modulating the action of neurotransmitters that regulate neuron function. These antipsychotics, also known as neuroleptics, are sometimes used in the symptomatic treatment or prevention of certain psychiatric disorders such as schizophrenia, behavioral disorders, and other acute or chronic psychoses. These substances are regularly used today due to the increase in diseases related to central nervous system disorders. Some recent reports even indicate an increase in the use of certain antipsychotics during pregnancy [1] [2]. Antipsychotics in general aim to reduce or relieve the patient's suffering and improve emotional, relational, and social functioning. In addition, these substances also reduce anxiety and promote the individual's ability to follow appropriate therapy.

Neuroleptics are divided into two main groups according to their beneficial effects: first-generation neuroleptics (typical neuroleptics), which are older, and second-generation neuroleptics (atypical neuroleptics), which are slightly newer and regularly used today because of their advantages.

Atypical neuroleptics differ from typical neuroleptics in their ability to inhibit certain behaviors, their side effect profile, their mechanism of action, and the fact that combining them with other drugs can sometimes be beneficial [3]. Neuroleptics act on dopamine receptors by influencing the neurotransmitter dopamine. It is important to note that dopamine is an essential brain neurotransmitter involved in the regulation of motor, emotional, and cognitive functions. Atypical neuroleptics are known to act on D2 and D3 receptors, while typical neuroleptics act mainly on the D2 receptor and have a less pronounced effect on the D3 receptor [4]. The main mechanism of action of neuroleptics is the blocking of D2 receptors, which leads to a reduction in dopaminergic hyperactivity in the mesolimbic pathway. This hyperactivity is thought to be the cause of positive symptoms. For example, an atypical neuroleptic will increase dopaminergic activity in the mesocortical pathway while reducing it in the mesolimbic pathway. In contrast, typical neuroleptics reduce this activity in both pathways. This difference in action is of great importance in the treatment of psychoses, particularly schizophrenia [5].

Although these antipsychotics generally play an important role in the treatment of psychiatric disorders, they can also cause adverse effects, including immediate side effects during treatment. In addition, other possible disturbances may occur as a result of these treatments, such as delays in motor development in young children [6]. The use of antipsychotics is common in the treatment of psychiatric disorders. However, some studies have shown delayed development in cognitive, socio-emotional, and behavioral areas in some individuals undergoing antipsychotic treatment [7].

Currently, second-generation neuroleptics (atypical neuroleptics) are increasingly preferred due to their reduced side effect profile in patients. Indeed, cumulative data suggest that these second-generation neuroleptics have a low risk of increasing major malformations [8] [9]. In addition, these second-generation neu-

roleptics (antipsychotics) are preferred over first-generation neuroleptics because of their better safety profile, particularly their effectiveness on targeted symptoms and their tolerability [10]. Initially, these drugs were intended to treat all symptomatic dimensions of schizophrenia, but subsequently, the evaluation of the effects of these second-generation neuroleptics has expanded to include their ability to reduce or treat negative, cognitive, and affective symptoms via modulation of dopamine transmission [11]. In addition, other clear and indisputable evidence has established that second-generation antipsychotics are beneficial and much more tolerable during treatment. Comparative studies between these two types of neuroleptics have shown better results in favor of second-generation neuroleptics [12]. Among these benefits are mood stabilization and antidepressant effects. However, first-generation neuroleptics (neuroleptics) are being used less and less due to their short- and long-term side effects. Evidence shows abnormalities in rats exposed prenatally to typical antipsychotics, particularly haloperidol [13]-[15]. These abnormalities are attributed to alterations in the development of the dopaminergic system in different regions of the brain [16]-[18].

While it is true that these antipsychotics play an important role in the treatment of psychiatric disorders, these substances sometimes have negative effects that cause disturbances in certain areas of the brain. This is demonstrated first by the presence of immediate side effects during treatment with these drugs. In addition to these side effects, other possible disturbances may occur as a result of these treatments, such as neurological or mental disorders at school [19]. Studies have also shown that certain antipsychotics cause delayed cognitive, socio-emotional, and behavioral development [20].

Due to the pharmacological activities of neuroleptics on various receptors, including dopaminergic, cholinergic, and adrenergic receptors, neuroleptics also induce various side effects, both central and peripheral. These side effects can be psychological or cognitive in nature. These substances mainly affect the extrapyramidal, neuroendocrine, and metabolic systems, as well as the autonomic nervous system [21]. Toxic, hepatic, hematological, and other manifestations have been associated with their use, as well as malignant syndrome, which can be fatal.

Neuroleptics are substances that have an influence (positive or negative effects) on a number of nuclei and structures in the central nervous system. The limbic system is the part of the CNS that contains a number of nuclei and structures whose anatomy and function are often influenced by neuroleptics.

The cerebral cortex is the part of the central nervous system composed mainly of cell bodies and certain glial cells. In the brain, the cortex is located on the periphery, *i.e.*, around the white matter. It is formed by a stack of layers of nerve cells. Structural brain imaging studies of patients with schizophrenia treated with antipsychotics have shown the impact of neuroleptics on the cerebral cortex. In fact, individuals treated with antipsychotics experienced a reduction in cerebral cortex volume specifically in the frontal and temporal lobes. These structural neu-

roimaging studies indicate that treatment with typical and atypical antipsychotics can affect the regional volume of the cerebral cortex. Typical antipsychotics caused an increase in the volume of the cerebral cortex of the basal ganglia, while atypical antipsychotics reversed this effect after the change [22]. In addition, the hypothalamus is a structure of the central nervous system located on the ventral side of the brain. This part of the brain consists of several substructures called nuclei. These nuclei are anatomically independent groups of neurons that perform various functions. One of the most important functions of the hypothalamus is to link the nervous system and the endocrine system via an endocrine gland: the pituitary gland [23].

The use of antipsychotics (neuroleptics) sometimes causes disturbances in certain areas of the brain, exposing the individual to several side effects. Among the many effects of antipsychotic drugs, one of the main side effects is significant weight gain caused by disturbances in the hypothalamus. The hypothalamus is therefore considered an important target for neuroleptics and contains certain neural circuits responsible for regulating food intake [24]. Hypothalamic dysfunction is therefore observed during treatment, causing overweight in users of neuroleptic drugs.

As part of our study, we exposed pregnant female rats to sulpiride (a second-generation neuroleptic) in order to assess its impact on the ontogenesis of certain psychomotor functions in male pups. To do this, we conducted behavioral tests from the 10th to the 45th postnatal day, comparing the results of male control pups with those of male pups exposed to perinatal treatment. These tests were performed in order to identify the areas of the brain targeted by sulpiride and their stimulatory or inhibitory effects on the development of psychomotor functions in male rats.

2. Materials and Methods

2.1. Animals

Animals were used to conduct the experiments. Male and female rats were raised under optimal temperature conditions. At 3 months of age, these rats were bred with a body weight of 190 to 200 g for females and 200 to 250 g for males. They were kept in standard laboratory conditions at an ambient temperature of 30˚C ± 2˚C. To facilitate breeding, three (3) females for each (1) male were housed in each polypropylene cage (27 × 37 × 18 cm) with a floor covered with dried grass. The animals were fed a pellet diet and tap water.

Every morning, we performed vaginal smears to determine the first days of gestation in the rats using the vaginal smear method. As soon as the presence of sperm was detected, that day was considered the first day of gestation, and the pregnant rat was immediately isolated in a new cage. After determining the first days of gestation of the sixteen (16) rats using the vaginal smear method, eight (8) pregnant rats were used as controls and the other eight (8) were treated with sulpiride. From the 11th day of gestation, eight (8) rats were treated with sulpiride,

meaning that these eight (8) pregnant rats consumed only water dosed with sulpiride from the 11th day of gestation until the 10th day postnatal.

For the dosage, we measured out 4.5 g of sulpiride in 3 liters of hydrogen peroxide. This gave us 3 liters of sulpiride water. This sulpiride water was poured into graduated feeding bottles and given to the eight pregnant female rats from the 11th day of gestation. We divided the staff into two large groups. The first group was responsible for cleaning the animals and equipment and feeding them. The second group was responsible for conducting the experiments.

After birth, the pups were left undisturbed until they were 10 days old. Sex identification took place on the 10th postnatal day. Tests were performed at 10, 15, 20, 25, 30, and 45 days of age. The same pups were evaluated from the 10th to the 45th postnatal day. Similarly, the body weight of the pups was measured from the 10th to the 45th postnatal day. All animals had free access to laboratory food and plain water.

2.2. Behavioral Tests

Neural development was assessed using a series of behavioral tests (previously described in Bâ [25]) that examine the development of psychomotor functions in rat pups. Five (5) neurodevelopmental abilities were tested in the offspring from postnatal days 10 to 45: postural recovery reflex, suspension times, locomotor activity, wire-walking latencies, and jump execution latencies. Behavioral tests were performed using wire pull apparatus and hole board apparatus.

2.2.1. Traction Test

The traction device consists of a metal wire connecting the two vertical bars and suspended approximately 36 cm above the ground. The device was used to measure the postural recovery reflex, suspension times, ground jump execution latencies, and movement execution latencies along the wire.

- *Hind paws lifting reflex*

The animal was suspended and remained clinging to the metal wire with its two front legs in the middle of the wire. The time taken for the animal to regain its balance by placing its hind legs on the wire was measured.

- *Wire-grasping time*

Suspension times were recorded during periods when the animal clung solely to the wire with its front limbs until it let go and fell to the ground due to fatigue.

- *Crawling execution latencies*

The latency time for movement along the wire is the choice made by the animal to travel the long, stressful distance in order to avoid the shock of falling directly from the wire.

leap execution latencies

The jump latency is the choice made by the animal to fall directly from the wire, which is the short route accompanied by shock, avoiding the long route accompanied by stress.

2.2.2. Hole Board Test

- Locomotor activity

The space on the hole board was crossed by two perpendicular light beams, allowing the animal's movement to be quantified each time their trajectories were interrupted. The number of beams crossed was recorded during a test under five different rainfall conditions by an automatic device. A single 5-minute test was performed at each age.

3. Statistical Analyses

Two-way ANOVA was used to assess the effects of age × treatment (2 factors) on neurobehavioral measures in developing offspring. Scheffé's post hoc F test was used to compare the means of neurobehavioral measures between control male rats and treated male rats.

4. Results

Two-factor analyses of variance (ANOVA) were used to evaluate each behavioral variable and test for [age x treatment] differences by performing multiple comparisons of means using Scheffé's F-test [25].

4.1. Ontogeny of Reflex Motor Functions in Male Rats

- Hind paws lifting reflex

Two-way ANOVA used to analyze the hind paws lifting reflex (time required to bring the hind legs back to maintain balance) of control male rats and treated male rats shows a very significant reduction in the hind paws lifting reflex according to age (10th to 45th day) [$F(3, 72) = 177.804$, $p < 0.0001$]. There is a strong interaction between age and treatment [age × treatment: $F(3, 72) = 6.555$, $p < 0.0005$].

Post hoc comparison of means ($p \leq 0.05$) using Scheffé's F test shows a very rapid reduction in the postural recovery reflex in male rats treated with sulpiride compared to control rats [$F(1, 72) = 260.805$, $p < 0.0001$]. Sulpiride reduced the time of the hind paws lifting reflex of the hind legs of male rats treated with sulpiride (Figure 1).

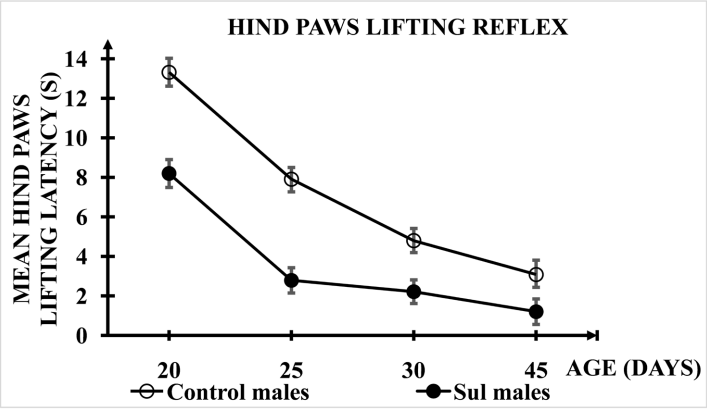

Figure 1. Development of the hind paws lifting reflex in male rats.

-The mean latency of the hind paws lifting reflex is shown as a function of age.

-A decrease hind paws lifting times in male rats compared to control male rats

N = 10 rats control; N = 10 rats treated

- Wire-gaping times

The wire-grasping time is the time it takes for the rat, hanging from the wire by its front paws, to fall after becoming exhausted.

A two-way ANOVA used to analyze the wire-grasping time of control male rats and treated male rats indicates an exponential increase in wire-grasping time with age (10th to 45th day) [$F(3, 72) = 1917.380$, $p < 0.0001$]. There is an interaction between age and treatment [age x treatment: $F(3, 72) = 159.934$, $p < 0.0001$].

Post hoc comparison of means ($p \leq 0.05$) using Scheffé's F test shows a significantly reduced Wire-grasping time in male rats treated with sulpiride compared to male control rats [$F(1, 72) = 483.045$, $p < 0.0001$]. Sulpiride significantly reduced wire-grasping time in treated male rats (Figure 2).

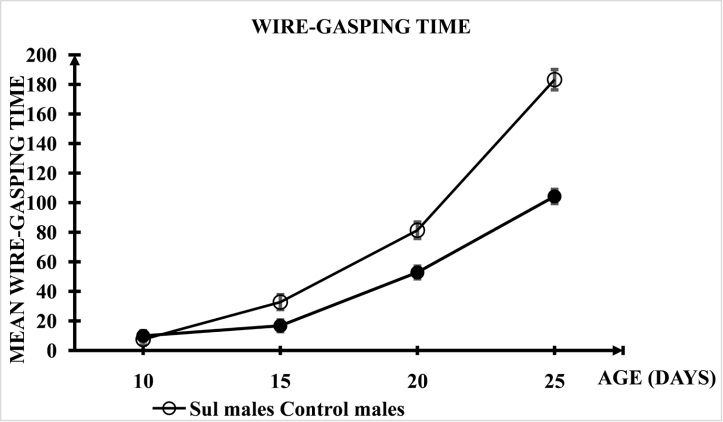

Figure 2. Development of wire-gaping times in control and treated male.

The mean wire-gaping times is presented as a function of age.

A decrease mean wire-gaping times in male rats compared to control male rats

N = 10 rats control; N= 10 rats treated

4.2. Ontogeny of Reflex Motor Functions in Male Rats

- Crawling along the wire

The crawling execution latencies is the choice of the long route taken by the animal to avoid impact by falling directly from the wire.

Two-way ANOVA used to analyze crawling execution latencies indicates a significant reduction in crawling execution latencies in control male rats and treated male rats according to age (10th to 45th postnatal day) [$F(3, 72) = 206.770$, $p < 0.0001$]. There is a strong interaction between age and treatment [age x treatment: $F(3, 72) = 12.233$, $p < 0.0001$].

Post hoc comparison of means ($p \leq 0.05$) using Scheffé's F test shows very high crawling execution latencies sulpiride-treated male rats compared to control male rats [$F(1, 72) = 116.610$, $p < 0.0001$]. Sulpiride caused an increase in crawling

execution latencies in male rats treated with sulpiride (Figure 3).

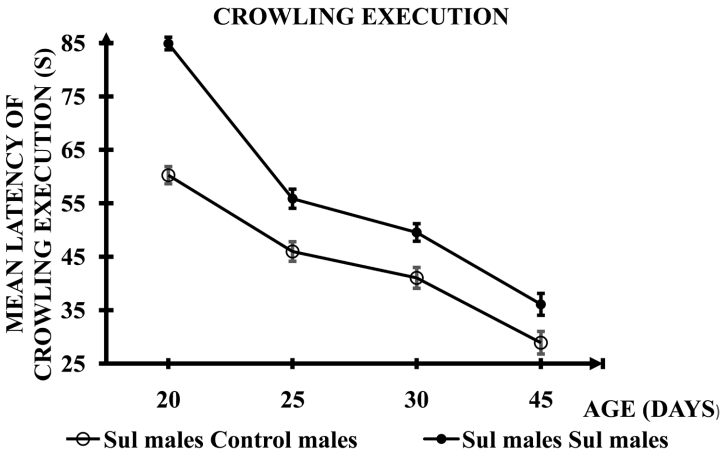

Figure 3. Development of latency of movement along the wire in male rats.

-The mean latency of crawling execution is presented as a function of age.

-An increase crawling execution latencies in male rats compared to control male rats

N = 10 rats males; N = 10 rats treated

- leap execution latency

The leap execution latency is the choice of the long route taken by the animal to avoid impact by falling directly from the wire.

Two-way ANOVA used to analyze leap execution latencies indicates a significant reduction in leap execution latencies in control male rats and treated male rats according to age (10th to 45th postnatal day) [$F(3, 72) = 206.770$, $p < 0.0001$]. There is a strong interaction between age and treatment [age x treatment: $F(3, 72) = 12.233$, $p < 0.0001$].

Post hoc comparison of means ($p \leq 0.05$) using Scheffé's F test shows very high leap execution latencies in sulpiride-treated male rats compared to control male rats [$F(1, 72) = 116.610$, $p < 0.0001$]. Sulpiride caused an increase in movement execution latencies in male rats treated with sulpiride (Figure 4).

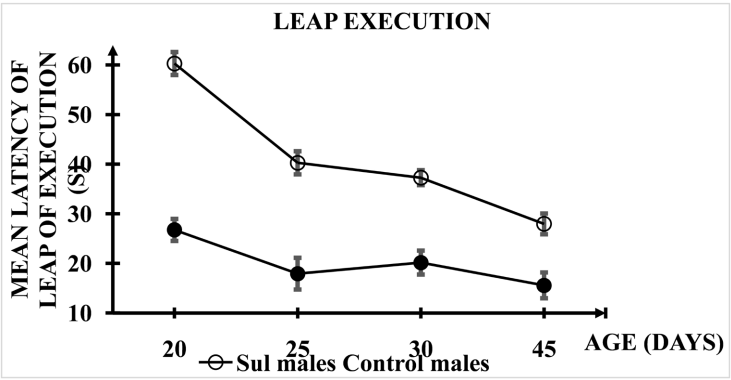

Figure 4. Development of leap execution latency in male rats.

- The mean latency of leap execution is presented as a function of age.

- A decrease mean latency of leap execution in male rats compared to control male rats

N = 10 rats males; N = 10 rats treated

4.3. Ontogeny of Automatic Motor Function in Male and Female Rats

-Locomotor activity

Locomotor activity is the number of times a rat crosses a horizontal line during its movement in 5 minutes.

Two-way ANOVA used to analyze locomotor activity indicates a significant increase in locomotor activity in male control rats and male treated rats according to age (10th to 45th day) [$F(5, 131) = 65.588$, $p < 0.0001$]. There is a clear interaction between age and treatment [age x treatment [$F(5, 108) = 4.295$, $p < 0.001$].

Post hoc comparison of mean latencies ($p \leq 0.05$) using Scheffé's F test shows significantly higher locomotor activity in male rats treated with sulpiride compared to male control rats [$F(1, 108) = 74.258$, $p < 0.0001$). Sulpiride caused an increase in locomotor activity in male rats treated with sulpiride (Figure 5).

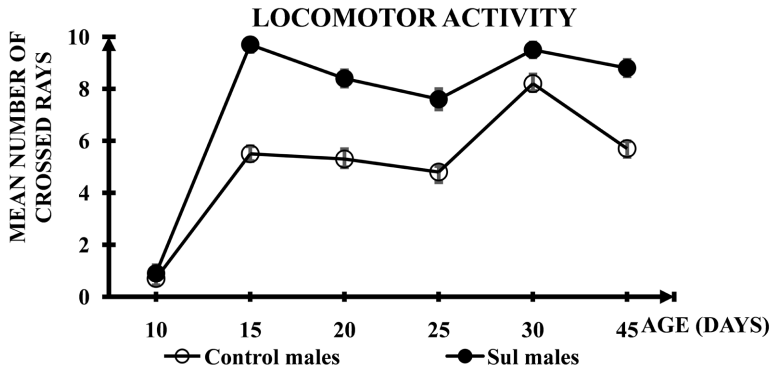

Figure 5. Development of locomotor activity in male rats.

Locomotor activity, is presented as a function of age.

- An increase locomotor activity in male rats compared to control male rats

N = 10 rats males; N = 10 rats treated

5. Discussion

Our results demonstrate that exposure to sulpiride during the critical period of brain development has an impact on the ontogenetic development of centrally regulated motor behavior in offspring.

The hind paws lifting reflex, which is a proprioceptive reflex whose reflex centers are located in the subcortical regions (cerebellum) [26], involves subcortical structures such as the striatum and pallidum in the execution and regulation of this reflex, reaching functional maturity on the 20th postnatal day [27]. In our experiment, we observed that male rats treated with sulpiride exhibited a very

early postural recovery reflex compared to male control rats ($p < 0.0001$). This suggests that sulpiride may impact the functions of the striatum and pallidum involved in the execution and regulation of this reflex in treated male rats. Our results are consistent with other studies [28] demonstrating alterations in the striatum associated with other neuroleptics such as risperidone and tiazin, which induce fetal neurotoxicity and degeneration during prenatal treatment. These substances caused abnormal functioning of the striatum, leading to a reduction in the hind paws lifting reflex. In addition, some authors have obtained similar results with a reduction in the postural reflex. In contrast, these authors used a combination of two substances (haloperidol + morphine) and also obtained inhibition of postural reflexes in rats [29]. Morphine is a substance that causes a state of immobility in which all reflexes used for stable static support (standing, straightening up, clinging, and supporting oneself) are inhibited. However, adding morphine to haloperidol causes a reduction in postural reflexes in rats. This suggests that the combination of haloperidol and morphine has the same effect on the striatum as sulpiride.

The wire-gaping times is the time it takes for the rat to remain hanging from the wire until it falls. This suspension time is mainly influenced by the increasing development of supraspinal structures on gamma (γ) motor neurons with age [30]. The activation of gamma (γ) motor neurons by supraspinal structures is mainly transmitted by impulses from the reticulospinal and vestibulospinal tracts. The continuous contraction of these muscles during suspension requires the intervention of γ fibers, which adjust muscle tension and tone by acting on the intrafusal fibers [31]. Muscle contractions are activities controlled by the cerebellum, a brain structure that plays an important role in brain function. Located under the brain, at the back of the skull, in the occipital region, the cerebellum is the nerve center that communicates with the entire nervous system. It processes information received from the spinal cord and brain to provide chronological and temporal-spatial organization to motor movement programs. The cerebellum not only coordinates motor functions, but also plays a role in modulating cognitive and affective processes [32]. The cerebellum regulates, coordinates, and synchronizes the muscular activities involved in voluntary movements such as walking or running. It also controls the tonic muscular activities involved in posture and balance during movement or less dynamic activities such as standing or squatting. Suspension times work in conjunction with muscle contractions. In our study, suspension times were extremely short in male rats treated with sulpiride. This exaggerated reduction in suspension times could be due to a weakening of the influence of supraspinal structures on γ motor neurons, thereby reducing the pulling force of the muscles during suspension. Sulpiride could therefore weaken these supraspinal structures, leading to a reduction in suspension duration in treated male rats. Authors such as Cogan *et al.* (1983) [33] and Cohen *et al.* (1985) [34] obtained similar results, but they exposed pregnant rats to alcohol (ethanol), which is different from the sulpiride we used. The pups from these treatments showed a decrease in

suspension time as well as slow muscle development.

Crawling execution latencies and leap execution latencies reflect decision-making processes in response to a given situation. These decisions and fear are regulated by the cerebral cortex and hippocampus, which continue to develop after the 20th postnatal day [35].

Behavioral tests conducted during the experiments indicate that execution latencies along the wire are delayed in small males treated with sulpiride compared to small male controls ($p < 0.0001$). This delay in decision-making indicates a slowing of prefrontal cortex or hippocampus function in pups treated with sulpiride during gestation. Indeed, sulpiride may also disrupt myelination of frontal lobe axons in treated pups, which would slow the transmission of nerve impulses responsible for the delay in decision-making. These results are consistent with those of Majdecki *et al.* (1986) [36], who exposed pregnant rats to ethanol and obtained similar results. In addition, this delay in decision-making could also be due to reduced neuronal differentiation and a lack of organization in the cerebral cortex [37]. The hippocampus is also a brain structure that regularly intervenes in decision-making. This crucial brain structure begins its development in mid-embryogenesis and continues into the postnatal stages, preceding the formation of the neocortex [38] [39]. During perinatal exposure, sulpiride may influence the development of the hippocampus by acting on the neurotransmitters dopamine and serotonin, which affect the hippocampus. This destabilizing action of sulpiride may also be responsible for the delay in decision-making in rat pups treated with sulpiride (second-generation antipsychotics). Our findings are supported by emerging evidence suggesting that antipsychotics affect dopamine and serotonin, which play a key role in hippocampal development in addition to their role in neurotransmission [40]-[42]. It is well established that the therapeutic effects of antipsychotics are based primarily on their action on dopamine and serotonin [43].

For leap execution latencies, our results show a significant difference between control male raccoons and treated raccoons ($p < 0.0001$). This decision-making function, accompanied by shock, is early and largely unfavorable to treated male raccoons, demonstrating a considerable effect of sulpiride on the brain areas responsible for decision-making. Studies show that the ventromedial prefrontal cortex is one of the brain structures involved in decision-making through interactions with the ventral striatum and amygdala [44]. Our results show very early decision-making in treated raccoons, suggesting that sulpiride may have impacted the interaction between these brain structures, promoting an imbalance in functioning. This abnormal functioning of the interaction between the cortex and the striatum appears to be the cause of early decision-making in sulpiride-treated rat pups. Similar results have been obtained by other authors [45] using sulpiride, who have shown a decrease in memory.

Locomotor activity was measured based on the movement of the rats from one compartment to another on the hole board tray for 5 minutes. The study of loco-

motor activity development reflects the maturation of the spinal circuit, as stride length and gait coordination are controlled by spinal automatism [46]. Locomotor activity is controlled by the cerebellum and nucleus accumbens, which are involved in several aspects of locomotor activity regulation through D3 dopaminergic receptors [47]. Indeed, these studies clearly show that stimulation of D3 receptors in the cerebellum and nucleus accumbens had effects on locomotor activity in rats. Our results show very pronounced hyperactivity in male rats treated with sulpiride compared to controls ($P < 0.0001$). This hyperactivity in treated pups could be explained by a dysfunction of the spinal circuit influenced by sulpiride during treatment. This abnormality could be the cause of this hypersensitization of the spinal circuit, leading to exaggerated mobility in male pups treated with sulpiride. Similar results were obtained by Stefan (1976) [48], who used a unilateral injection of 2 ml of sodium glutamate and observed hyperactivity in the pups. This exaggerated mobility in male pups treated with sulpiride could also be explained by an imbalance in the cerebellum, which is the brain structure that controls locomotor activity. Our results are supported by the work of Barik and Beaurepaire (1996) [49], who not only demonstrated that D3 dopaminergic receptors play a functional role in regulating locomotor activity, but also showed that amisulpride modifies locomotor activity in a dose-dependent manner. At low doses, amisulpride modifies locomotor activity by further stimulating it, causing intense mobility in the animal. In addition, other authors agree with our results, having also observed very high locomotor activity in rats, with the difference that these authors used another second-generation neuroleptic that is increasingly used in children to manage the symptoms of attention and behavioral disorders. These authors administered risperidone to rats to observe locomotor activity. These treated rats had increased locomotor activity compared to controls [50], which is consistent with our results.

6. Conclusion

Our study has contributed to understanding the effects of antipsychotics on animal behavior by providing physiological data. Furthermore, our results show that sulpiride (a neuroleptic) acts on certain regions of the brain, inducing either an increase or a decrease in brain function. The areas of the brain targeted by neuroleptics could be the subject of future studies.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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