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Research Paper

Paternal Aggression in Early-life Impairs the Spatial Memory and Passive Avoidance Learning in Adulthood of Male Rats: The Possible Role of *DRD2*

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ABSTRACT

Introduction: Negative early-life experiences (e.g. having an aggressive father) can leave long-lastingimpacts on the behavior. However, it is not clear if they influence learning and memory.

Methods: In this study, we investigated the influences that the presence of an aggressive father had on the level of passive avoidance learning and spatial memory. We also studied the changes in the dopamine receptor D2 (*DRD2*) and peroxisome proliferator-activated receptor gamma coactivator 1-α (*PGC-1α*) gene expression in the hippocampus. Then, we evaluated if a *DRD2* antagonist (sulpiride, 0.125, 0.25, or 0.5 µg/rat) could modulate these changes.

Results: We found that the subjects exposed to early-life stress made by aggressive fathers had impaired passive avoidance learning and spatial memory compared to subjects with normal fathers. Treatment with sulpiride improved passive avoidance learning and spatial memory in rats with aggressive fathers. The rats with aggressive fathers also had higher expression of the *DRD2* gene in their hippocampus than those with normal fathers, while the *PGC-1α* gene expression was not different among groups. Treatment with sulpiride (0.125, 0.25, or 0.5 µg/rat) reduced the *DRD2* gene expression in those with aggressive fathers to the normal level compared to those with normal fathers.

Conclusion: These data suggest that having and living in a shared place with an aggressive father, even without any physical contact, can detrimentally affect passive avoidance learning and spatial memory which is accompanied by the increased expression of the *DRD2* gene. Also, sulpiride as a dopaminergic antagonist could reverse this process.

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Highlights

- Having and living with an aggressive father reduced learning and memory in offspring.
- Having and living with an aggressive father during early life increased *DRD2* gene expression.
- Sulpiride improved learning and memory and also normalized *DRD2* gene expression.
- A combination of genetic and environmental factors may modulate learning and memory.

Plain Language Summary

In this study, we looked at how having an aggressive father, can affect behavior in the long term. We wanted to find out if this factor influences learning and memory. To do this, we investigated how the presence of an aggressive father affected passive avoidance learning and spatial memory in subjects. We also examined specific genes in the brain, called *DRD2* and *PGC-1α*, which are known to be involved in learning and memory. Specifically, we wanted to see if the expression of these genes in the hippocampus (a region of the brain important for memory) was affected by having and presence of an aggressive father. To understand the role of the *DRD2* gene further, we used a drug called sulpiride, which blocks the action of *DRD2*. We administered sulpiride to the subjects with aggressive fathers to see if it could reverse any negative effects on learning and memory. What we found was that subjects that had aggressive fathers had impaired passive avoidance learning and spatial memory compared to those with normal fathers. However, when we treated the subjects with sulpiride, their learning and memory improved. Additionally, we observed that rats with aggressive fathers had higher levels of the *DRD2* gene in their hippocampus, while the *PGC-1α* gene expression was not different among the groups. The administration of sulpiride reduced the expression of the *DRD2* gene in rats with aggressive fathers, bringing it back to normal levels similar to those with normal fathers. These findings suggest that having and living in the same environment as an aggressive father, even without direct physical contact, can negatively impact passive avoidance learning and spatial memory. This effect seems to be associated with increased expression of the *DRD2* gene. However, using sulpiride as a dopaminergic antagonist can reverse this process and improve learning and memory in these subjects.

1. Introduction

Learning and memory are two crucial physiological abilities by which animals can percept and restore information. These processes help animals recall the information in the moment of need and adjust the efficacy of their behaviors. Spatial memory has immense importance in the lives of animals as well as humans. For example, it helps animals to remember the place of food and improve the outcome of foraging (Boyer & Walsh, 2010), associate positive and negative valences with various environments (Herry & Johansen, 2014; Kummer et al., 2011), and avoid potential predators.

Various internal and external factors can influence learning and memory capacity in animals. The early-life experience might be the most important modulator of the future brain's ability among external factors. For example, experiencing a higher level of maternal care in the early-life period, as a positive environmental signal, improves spatial learning and memory (Liu et al., 2000). Not only the behavior of mothers, but also fathers' behaviors toward their offspring, like aggressive behavior, can have a deep impact on their behavioral development, like their adulthood aggression (Frazier et al., 2006), depression, and anxiety (Khalifeh et al., 2020). However, the impact of being in a stressful condition with an aggressive father on the memory of offspring in adulthood is not very clear yet.

The literature suggests that dopamine receptor D2 (*DRD2*) plays an important role in spatial memory (Bezu et al., 2017; Raut et al., 2014). The activity of *DRD2* can also modulate the performance of mice in the passive avoidance task (Ichihara et al., 1992). Peroxisome proliferator-activated receptor gamma coactivator 1-α (*PGC-1α*) is a key regulator of mitochondrial biogenesis (Valero, 2014), and also can be a modulator factor of learning and memory (Ashabi et al., 2012; Azimi et al., 2018). Therefore, alterations in the level of *DRD2* and *PGC-1α* can modulate learning and memory. Early-

life stress leaves long-lasting epigenetic marks, which switch off or on multiple genes (Silberman et al., 2016). This can be a ground for various behavioral impairments. The presence of an aggressive father can be an early-life stressor. It raises whether the early-life presence of an aggressive father can modulate later learning and memory by changing the expression of *DRD2* and genes. Moreover, sulpiride has antidopaminergic properties and can antagonize *DRD2* (Caley & Weber, 1995). It can modulate learning in rodents (Rinaldi et al., 2007). Using these features, sulpiride can help us to better understand the role of *DRD2* in the scenario of having an aggressive father.

This study aimed to investigate whether the having and early-life presence of an aggressive father can impact the passive avoidance learning and spatial memory of the male offspring in adulthood. We also questioned whether changes in *DRD2* and *PGC-1α* gene expression might have a role in this process. Then, we investigated the effects of sulpiride treatment with three different doses in modulating the impact of aggressive fathers on learning and memory.

2. Materials and Methods

Animals

Adult Wistar rats were purchased from the Pasteur Institute (Tehran, Iran). They were kept in standard cages with temperature (22±2˚C) and humidity-controlled environment in 12:12 h light/dark cycles (light on at 7:00 AM) and were given unlimited access to water and standard rat chow ad libitum.

Aggression training

Male albino Wistar rats were used as the resident rats based on the previously described method with some modifications (Hattori et al., 2015; Kinn Rød et al., 2014) (Figure 1). Each male rat was housed with an adult female rat for two weeks. Before each session of testing the level of aggressiveness, the female rat was removed from the cage and an intruder male rat was placed into the cage. The behavior of the resident male rat was recorded for 5 minutes. Then, the intruder was removed, and the female was returned to the cage. The subjects that attacked the intruder within the first 60 s of the session for three consecutive sessions and had higher attack latency in a shorter period were usually considered aggressive (Miczek, 1979; Razzoli et al., 2011; Wood et al., 2015). Testing the level of aggressiveness was conducted for at least six sessions at four-day intervals. All the processes were performed during the light phase of the day. Resident rats with shorter attack latencies and more attack bites within a short period were considered aggressive rats.

Mating

Both aggressive and non-aggressive male rats were used for mating. Each male rat was mated with a naïve non-aggressive female rat in a standard cage for 3 or 4 days and then removed.

Study design

After the birth of offspring, the biological fathers were returned to the home cage for three weeks, but they were separated from females and offspring with a net, still having the olfactory, visual, and auditory connections. Although physical contact was not possible, paternal olfactory, visual, and auditory threats made a stressful atmosphere for offspring. Behavioral and molecular investigations were performed when the offspring were eight-week-old. In this study, male offspring of aggressive fathers were randomly divided into four treatment groups (n=10/group) and the same division was done for male offspring of non-aggressive fathers (n=10/group). In each aggressive and non-aggressive set, the first group was just treated with saline (aggressive control group and non-aggressive control group). The next aggressive or non-aggressive groups received either 0.125, 0.25, or 0.5 µg/rat ICV sulpiride treatment (Nasehi et al., 2013; Zarrindast et al., 2012). After that, the groups underwent behavioral experiments, namely passive avoidance task and Y-maze test. Then, the molecular studies were performed.

Drug preparation and surgery procedure

To prepare the drug solution, sulpiride (0.125, 0.25, or 0.5 µg/rat) was dissolved in 0.9% physiological serum just before the injection. A combination of ketamine hydrochloride and xylazine was used for anesthetizing the offspring. Then, rats were prepared for surgery by the stereotaxic device (Stoelting, USA). The guide cannula was inserted into the left ventricle (coordinates, 1.5 mm lateral to the midline, −0.8 mm posterior to the bregma, and −4.6 mm ventral to the skull surface). The injection (5 µL/rat) was done using Hamilton's syringe, and the drug or saline was injected slowly for 180 seconds.

Behavioral investigations

Passive avoidance task

The shuttle box was used to evaluate passive avoidance learning and memory (Brandewiede et al., 2014; Khakpour-Taleghani et al., 2008) with some modifications. The apparatus was made of polyvinyl chloride and consisted of two compartments separated by a removable gate; the dark compartment had a floor of electrically conductive rods and the light compartment. Electric shocks were delivered to the rods with an adjustable stimulator. For the first step, rats were habituated and trained in the apparatus. For the training, the observer put the rat in the light compartment and opened the gate ten seconds later. After the passage of the four paws of the rat from the gate, the observer closed the gate, and the rat was delivered an electrically shocked (50 Hz, 1 mA intensity, 1.5 sec) in the dark compartment. If the rat did not enter the dark compartment after 120 seconds, it was considered a trained rat and ready for the main test.

Twenty-four hours after the training, a passive avoidance memory retrieval test was carried out in all rats over which shock was not delivered (Pakdel & Rashidy-Pour, 2007). Similar to the training session, rats were put in the light compartment of the apparatus one by one. After opening the gate, the latency to enter the dark compartment for the first time and the time that rats spent in the dark compartment were recorded for ten minutes by the observer.

Y-maze test

Similar to the previously described methodology (Kraeuter et al., 2019) with some modifications, rats were tested in a Y-maze made of Plexiglass. It had three arms with a 120° angle between each arm. Rats were transferred to the test room 20 minutes before the beginning of trials. Then, they were placed in an arm of Y-maze which had a barrier. The barrier was removed 5 seconds after the rats entered into Y-maze, and all the movements of rats in different arms were recorded for eight minutes. An arm entry was considered when all four paws of a rat passed the entrance of the arm. Based on the literature (Ansari Dezfouli et al., 2019; Kraeuter et al., 2019), the successful consecutive entries as the index of the behavioral test showing learning memory were calculated as "successful consecutive entries=(entries into three different arms consecutively/[number of total arm entries–2])×100."

Molecular analysis

After the behavioral tests, the rats were sacrificed, and the hippocampus was extracted for molecular studies.

mRNA extraction and cDNA synthesis

We extracted total RNA from the hippocampus tissue using YTzol Pure RNA (Yektatajhiz azma, Tehran, Iran). The quality of RNA was investigated by an ND-2000 spectrophotometer (Thermo Fisher Scientific, Wilmington, DE, USA). Synthesis of cDNAs was done by PrimeScript 1st Strand cDNA Synthesis Kit (Pars Tous, Tehran, Iran).

Real-time PCR

Real Time-PCR (RT-PCR) was performed using the Real Q-PCR Master Mix Kit (Ampliqon, Herlev, Denmark) on an ABI system (step one). The samples were used to amplify *PGC-1α* gene (forward primer, 5′-ATGAATGCAGCGGTCTTAGC-3′; reverse primer, 5′-AACAATGGCAGGGTTTGTTC-3′; annealing temperature 55°C) and *DRD2* gene (forward primer, 5′-CTGGTCGCCTCTTGTGC-3′; reverse primer, 5′-CGCATGACTCGTTCAGATCC-3′; annealing temperature 59°C). For the control sample, distilled water was used. The β-acting gene (forward primer, 5′-TCTATCCTGGCCTCACTGTC-3′; reverse primer, 5′-AACGCAGCTCAGTAACAGTCC-3′) was used as the housekeeping gene.

Statistical analysis

Data were expressed as Mean±SEM and were analyzed using two-way analysis of variance (ANOVA) followed by Tukey-test using Graph Pad Prism software, version 5. The $P<0.05$ was considered significant.

3. Results

Rats with aggressive fathers showed reduced passive avoidance learning and memory, and sulpiride injection improved the Outcome

Data indicated that for the time spent in the dark compartment, there was a significant treatment effect ($P<0.001$), group effect (aggressive vs. normal father) ($P<0.001$), and treatment×group interaction ($P<0.001$). The rats in the control group with aggressive fathers spent more time in the dark compartment of the passive avoidance task compared to the controls with normal fathers ($P<0.001$) (Figure 2A). Sulpiride injection in rats with aggressive fathers (all three doses: 0.125, 0.25, 0.5 µg/rat) caused a significant decrease in the spent time in the dark part compared to the aggressive group ($P<0.001$). In addition,

sulpiride injection had no significant effect on the time that rats with normal fathers spent in the dark part compared to the control group. This measure was also different between rats with aggressive and normal fathers after injection of sulpiride (0.125 µg/rat) (P<0.001).

For the step-through latency, there was also a significant treatment effect (P<0.001), aggressive father effect (P<0.001), and treatment×aggressive father interaction (P<0.001). Control rats with aggressive fathers had shorter step-through latency than the controls with normal fathers (P<0.001) (Figure 2B). Sulpiride injection in all three different doses (0.125, 0.25, 0.5 µg/rat) caused a significant increase in the step-through latency in rats with the aggressive fathers compared to the group with aggressive fathers (P<0.001) but did not have a significant effect on rats with normal fathers compared to the controls with normal fathers. The step-through latency in rats with normal fathers treated with 0.25 µg/rat or 0.125 µg/rat sulpiride was higher than those treated with aggressive fathers (P<0.001).

Rats with aggressive fathers showed reduced spatial memory, but sulpiride injection improved their memory

The Y-maze test was used to evaluate spatial memory in rats of different groups. The results showed that for spontaneous alteration, there was a significant treatment effect (P<0.001), group effect (aggressive vs. normal father) (P<0.001), and treatment×group interaction (P<0.001). The control rats with aggressive fathers had less spontaneous alternation number than the controls with normal fathers (P<0.001) (Figure 3A). Sulpiride in all three different doses (0.125, 0.25, 0.5 µg/rat) increased the number of spontaneous alternations significantly in treated rats with aggressive fathers compared to the controls with aggressive fathers (P<0.001). In contrast, sulpiride injection in male rats with normal fathers made no significant change in spontaneous alternation compared to the controls with normal fathers.

We observed similar results for the total number of entries in Y-maze arms (Figure 3B). For this parameter, there was a significant treatment effect (P<0.001), the aggressive father effect (P<0.001), and treatment×aggressive father interaction (P<0.001). The control rats with aggressive fathers had significantly less number of entries than those with normal fathers (P<0.001), but sulpiride injection in all three doses (0.125, 0.25, and 0.5 µg/rat) caused a significant increase (P<0.001). Also, sulpiride injection in male rats with normal fathers made no significant change in the total number of entries in treated rats with normal fathers compared to the controls with normal fathers.

Rats with aggressive fathers had a higher level of *DRD2* gene expression in the hippocampus, and sulpiride injection reversed this effect

Results from RT-PCR showed that there was a significant treatment effect (P<0.001), the aggressive father effect (P<0.001), and treatment×aggressive father interaction (P<0.001) on the level of *DRD2* gene expression in the hippocampus. The *DRD2* gene expression of the controls with aggressive fathers was significantly higher compared to the controls with normal fathers (P<0.001) (Figure 4). Sulpiride injection (0.125, 0.25, 0.5 µg/rat) in treated rats with aggressive fathers significantly decreased the level of *DRD2* mRNAs compared to the controls with aggressive fathers (P<0.001). Sulpiride injection in rats with normal fathers made no significant change in the *DRD2* gene expression level compared to the controls with normal fathers.

Rats with aggressive fathers did not have different *PGC-1α* gene expression in the hippocampus, and sulpiride injection also did not cause any change

We observed no significant treatment effect, the aggressive father effect, or treatment×aggressive father interaction. *PGC-1α* gene expression was not different between controls with aggressive fathers and controls with normal fathers (Figure 5). Also, sulpiride treatment with either dosage did not change the level of *PGC-1α* gene expression compared to the control rats with either aggressive or normal fathers.

4. Discussion

In this study, we aimed to investigate the consequences of paternal aggressiveness on their offspring's learning and memory. We found that even though there was no physical contact with an aggressive father, offspring exposure to this environment along with having aggressive father made a challenging atmosphere in which baby rats' passive avoidance learning and spatial memory were impaired. Moreover, the rats in this environment had significantly higher *DRD2* gene expression in the hippocampus compared to the normal rats, while the *PGC-1α* gene expression did not significantly differ. The rats with aggressive fathers that were treated with different dosages of sulpiride (0.125, 0.25, or 0.5 µg/rat) showed significantly improved passive avoidance learning and spatial memory compared to the controls. The treatment also normalized the expression of the *DRD2*

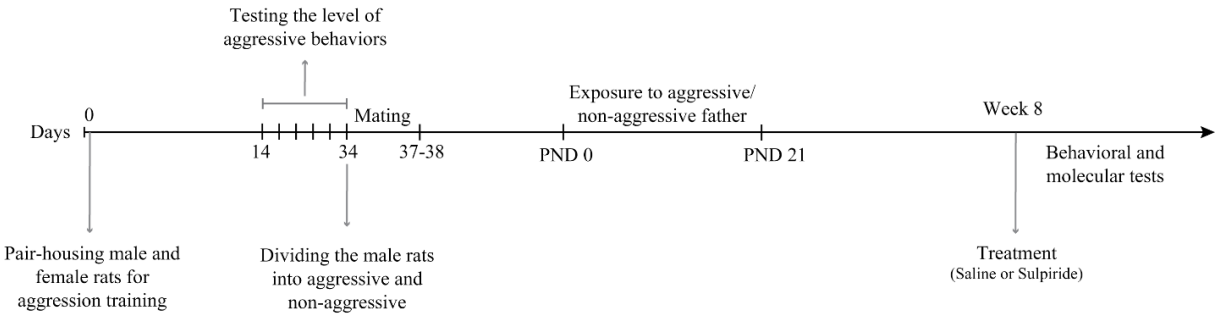

Figure 1. The timeline that the procedures were conducted

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gene in offspring with aggressive fathers to the level of the control group.

Ample human evidence showed that children's exposure to domestic violence leads to long-term psychiatric and behavioral detriments (Cicchetti, 2016; Marshall et al., 2019; Vachon et al., 2015). Indeed, domestic violence and exposure to this environment are believed to be a precursor to a wide range of phycological disorders for children (Margolin & Vickerman, 2007). Majali et al. found that children as witnesses or victims of parental aggression can show psychological and emotional disturbances in their adulthoods (Al Majali & Alsrehan, 2019). Socio-psychological disability, stress, anxiety, and less self-esteem have been reported in these children (Al Majali & Alsrehan, 2019; Øverlien, 2010; Rehan et al., 2019). Chronic stress is one of the most common consequences of parental aggressiveness which detrimentally affects children's physical and mental health (Moffitt, 2013). Chronic stress as a result of domestic violence can lead to psychological alterations in some regions of the brain such as the cerebral cortex, limbic system, corpus callosum, cerebellum, and hypothalamus (Tsavoussis et al., 2014). Smith and Pollak also found that early life stress can have a permanent and pervasive impact on the hippocampus, amygdala, prefrontal network, and dopaminergic circuits (Smith & Pollak, 2020). Negative emotions activate amygdala-dependent memory formation and change associative memory performance (Okada et al., 2011).

In a study by Nguyen et al., it has been revealed that the environment in which children live strongly affects their emotions, behaviors, and memories. Negative emotions and unpleasant behaviors in children resulting from aggressive parents in early postnatal life lead to impaired hippocampal-dependent memory, aggression, anxiety, and fear-memory formation in adulthood (Nguyen et al., 2015). This underlines the long-lasting impact of early-life paternal behavior on offspring.

In this study, rats experiencing a traumatic and anxious environment with aggressive fathers had shorter step-through latencies and spent more time in the dark compartment of the passive avoidance test. Our results showed that the passive avoidance learning and memory of these rats were reduced compared to rats in normal situations. In addition, in the Y-maze test, control rats under pressure with an aggressive father had less successful spontaneous alternations and fewer entries than the control group living in a healthy environment, which means they have reduced spatial memory compared to rats with normal conditions. Therefore, these findings support the negative effects of early-life paternal aggression on passive avoidance learning and spatial memory of offspring in adulthood. This might be due to the early-life stress induced by paternal aggression and the related memory impairments. For example, early-life stress induced by other sources like maternal separation can also impair learning and memory (Maghami et al., 2018), which supports stress as the possible bridge between paternal aggression and impaired learning and memory.

Moreover, the genetics and epigenetic effects make offspring susceptible to environment stressors which needs further investigation to uncover their effect size

DRD2, as a member of the dopaminergic receptors family, affects spatial and long-term memory in rats (Rocchetti et al., 2015). Different studies have shown different associations between this receptor and negative emotions such as depression (Chiesa et al., 2014), anxiety (Wang et al., 2014), and fear (Huertas et al., 2010). The role of this gene in learning and memory has also been demonstrated (Rocchetti et al., 2015; Zhu et al., 2010). It is also involved in parental care (Curry et al., 2013; Zhu et al., 2010). In 2013, Yi Zhang et al., found that maternal separation- which also is an early-life stressor-results in changes in the *DRD2* gene expression in the nucleus accumbens, which leads to behavioral problems and spatial memory impairment in adulthood (Zhang et al., 2013). We found that rats that experienced tension in their early life with aggressive fathers had

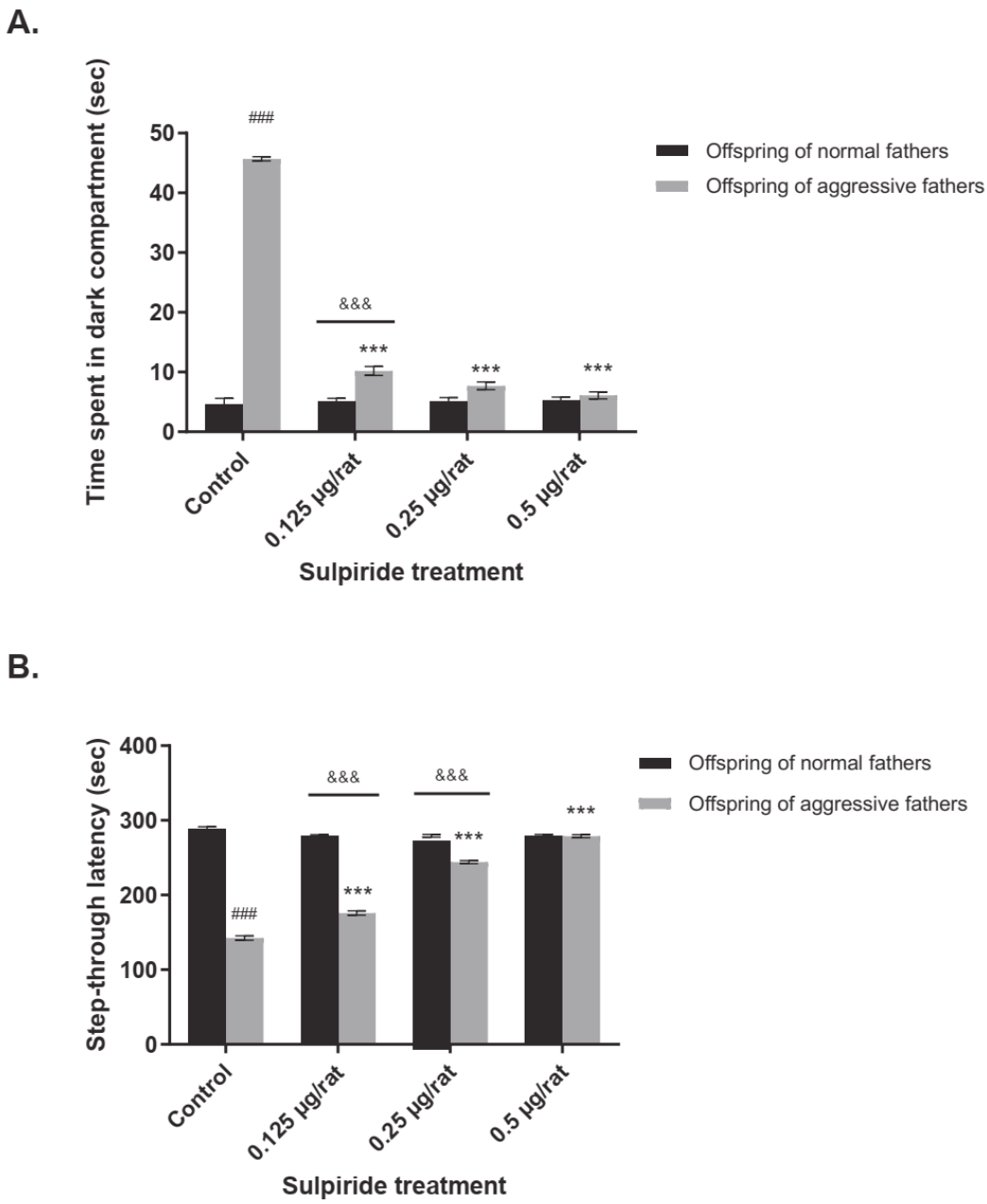

Figure 2. Passive avoidance learning and memory using passive avoidance task

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A) The time spent in the dark compartment in different groups of rats, B) The time of first entrance to the dark compartment of the task in different groups of rats. Each bar shows the Mean±SEM. (n=10/group). ###P<0.001 vs. controls with normal fathers, ***P<0.001 vs. controls with aggressive fathers, &&&P<0.001. Comparison between those with aggressive and nonaggressive fathers in the same treatment group.

a higher level of *DRD2* gene expression compared to the rats in normal situations. This result is similar to other studies which demonstrated an association between memory impairment and increased expression of the *DRD2* gene (Noohi et al., 2014; Persson et al., 2015). We also found that i.c.v sulpiride injection in either three different doses can improve the passive avoidance and spatial memory in rats with aggressive fathers.

Moreover, stress can increase the *DRD2* gene expression in memory-related brain regions like the prefrontal cortex (Tomas-Roig & Havemann-Reinecke, 2019). In specific, perinatal stress can increase *DRD2* gene expression in the hippocampus of rats (Berger et al., 2002). This is similar to our findings that paternal aggression in early life (as a stressor) increases *DRD2* expression in the hippocampus. In terms of the roles that this receptor plays

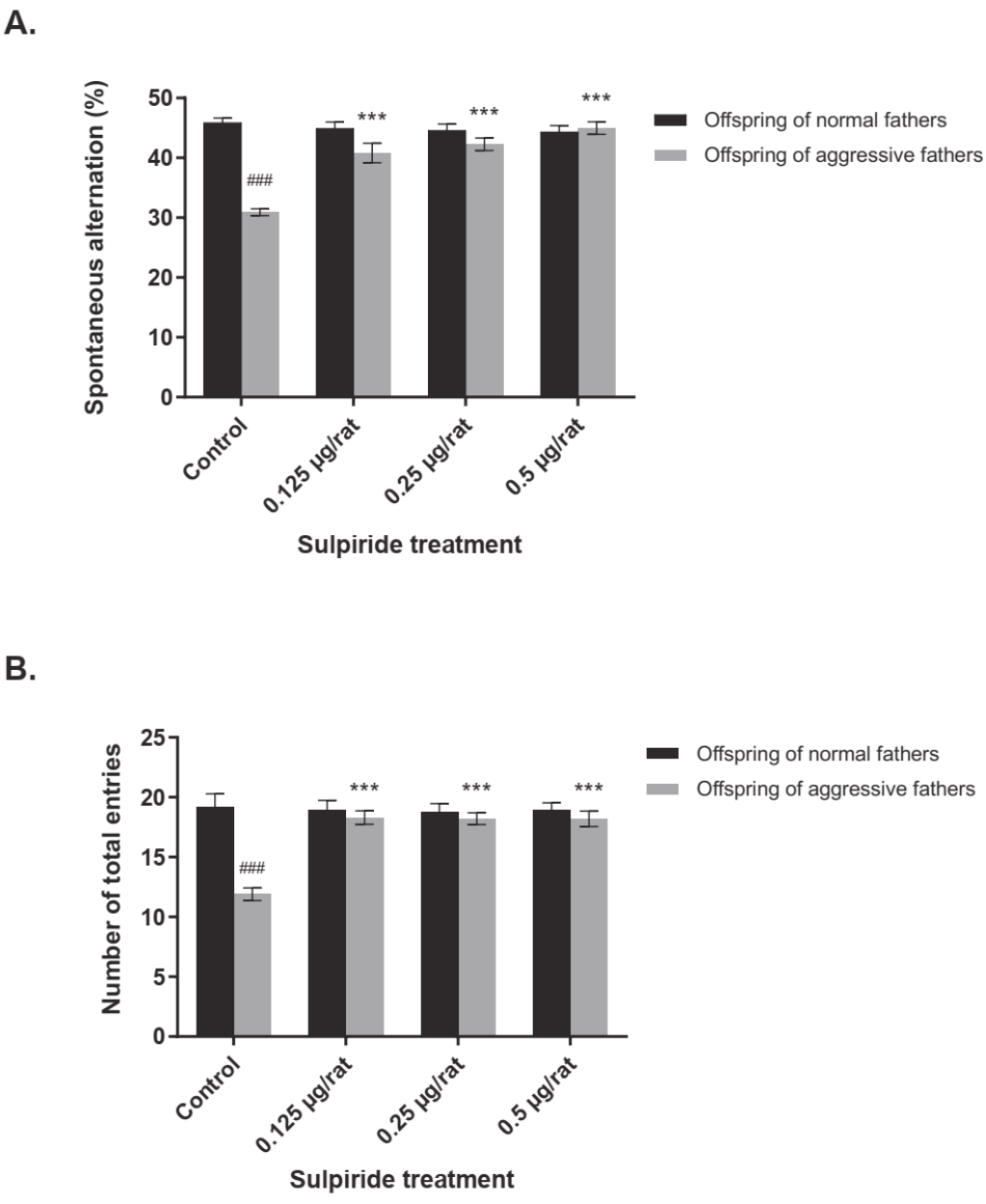

Figure 3. Spatial memory using Y-maze

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A) The number of spontaneous alternations in the Y-maze test in different groups of rats, B) The total number of movements in arms in the Y-maze test in different groups of rats. Each bar shows the Mean±SEM. (n=10/group). ###P<0.001 vs. controls with normal fathers, ***P<0.001 vs. controls with aggressive fathers.

in memory, the literature suggests that when the level of hippocampal *DRD2* is in the physiologic range, its activation may improve and its deactivation may impair learning and memory (Wilkerson & Levin, 1999). However, hyperactivation of *DRD2* in the hippocampus during adolescence impairs spine development, neural circuits, and spatial memory. Interestingly, *DRD2* blockers prevented the negative impacts of *DRD2* hyperactivation on spine development and spatial memory (Jia et al., 2013). This evidence might explain our findings. The early-life experience of an aggressive father may act as a stressor and, therefore, increase the *DRD2* gene expression level in the hippocampus. This increased level may cause hyperactivation of *DRD2* receptors and impairs spatial memory by interfering with the spine development of the neurons. As we observed, the memory impairment was reversed by using sulpiride, as a *DRD2* blocker.

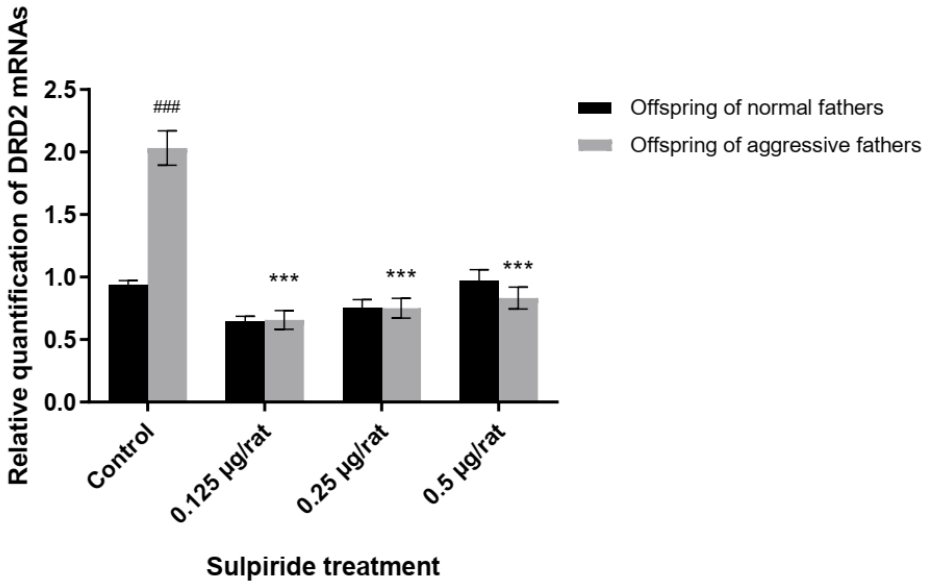

Figure 4. The level of *DRD2* gene expression in the hippocampus of different groups of rats

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Each point shows the Mean±SEM. (n=4/group). ###P<0.001 vs. controls with normal fathers, ***P<0.001 vs. controls with aggressive fathers.

On the other side, sulpiride, as an antagonist of *DRD2* in the central nervous system, is used for the treatment of psychiatric diseases (Caley & Weber, 1995; Ciszowski et al., 2010). In line with our results, Floresco et al. found that sulpiride can be a promising candidate for the treatment of various psychological disorders, enhancement of memory and improvement of attention, working memory, and behavioral flexibility (Floresco & Jentsch, 2011). Similarly, Passetti et al. showed that medial prefrontal cortex impairment is relevant to neuropsychological dysfunction. On the other hand, modulating the dopaminergic pathway in basal ganglia can alleviate any neuropsychological deficit (Passetti et al., 2003). In 2005, Mehta et al. reported that sulpiride can improve working memory and facilitate the responses to visual learning tasks (Mehta et al., 2005). The half-life of sulpiride is 24 hours in the case of systemic injection, but we followed the literature and used i.c.v injection to increase its lifetime and provide better availability of the drug in the brain (Mizuchi et al., 1983).

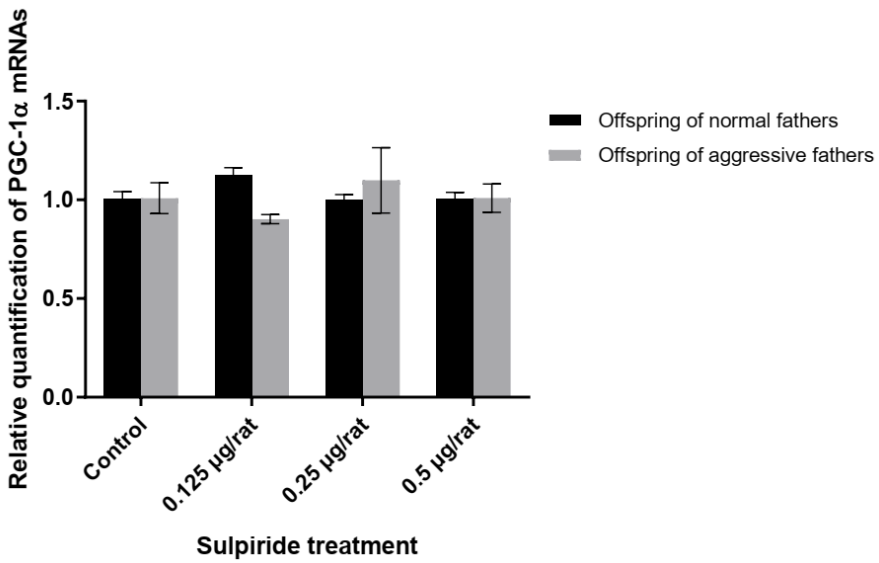

Figure 5. The level of *PGC-1a* gene expression in the hippocampus of different groups of rats

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Each point shows the Mean±SEM (n=4/group).

PGC-1α is a key regulator of mitochondrial biogenesis (Valero, 2014), and also can be a modulator factor of learning and memory (Ashabi et al., 2012; Azimi et al., 2018). It is shown that acute stress in adulthood can change learning and memory by modulating the level of *PGC-1α* (Sardari et al., 2015). However, our observation showed that the *PGC-1α* gene expression in the rats with aggressive fathers was not significantly different from those with normal fathers. It suggests that, in contrast to acute stress in adulthood, the early-life stress of having an aggressive father does not change the *PGC-1α* gene expression in the hippocampus. The sulpiride treatment did not change this expression. Moreover, the injection of sulpiride with different doses in rats with normal fathers had no significant effect on their passive avoidance and spatial memory as well as their *DRD2* and *PGC-1α* gene expression profile.

The results of our study showed that having and living in a shared place with an aggressive father, even without any physical contact, can detrimentally affect passive avoidance learning and spatial memory which is accompanied by the increased expression of the *DRD2* gene. However, sulpiride as a dopaminergic antagonist could reverse this process.

Ethical Considerations

Compliance with ethical guidelines

All investigations and procedures were approved by the Research Ethics Committee of the Neuroscience Research Center, Shahid Beheshti University of Medical Sciences (Code: IR.SBMU.PHNS.REC.1397.055). During the entire process, the highest effort was made to minimize the suffering of subjects.

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Authors' contributions

All authors equally contributed to preparing this article.

Conflict of interest

The authors declared no conflict of interest.

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