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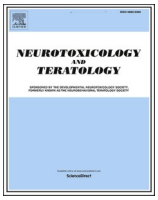

Full Length Article

Long-lasting behavioral effects of quinpirole exposure on zebrafish

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ABSTRACT

The human brain matures into a complex structure, and to reach its complete development, connections must occur along exact paths. If at any stage, the processes are altered, interrupted, or inhibited, the consequences can be permanent. Dopaminergic signaling participates in the control of physiological functions and behavioral processes, and alterations in this signaling pathway are related to the pathogenesis of several neurological disorders. For this reason, the use of pharmacological agents able to interact with the dopaminergic signaling may elucidate the biological bases of such disorders. We investigated the long-lasting behavioral effects on adult zebrafish after quinpirole (a dopamine D2/D3 receptor agonist) exposure during early life stages of development (24 h exposure at 5 days post-fertilization, dpf) to better understand the mechanisms underlying neurological disorders related to the dopaminergic system. Quinpirole exposure at the early life stages of zebrafish led to late behavioral alterations. When evaluated at 120 dpf, zebrafish presented increased anxiety-like behaviors. At the open tank test, fish remained longer at the bottom of the tank, indicating anxiety-like behavior. Furthermore, quinpirole-treated fish exhibited increased absolute turn angle, likely an indication of elevated erratic movements and a sign of increased fear or anxiety. Quinpirole-treated fish also showed altered swimming patterns, characterized by stereotypic swimming. During the open tank test, exposed zebrafish swims from corner to corner in a repetitive manner at the bottom of the tank. Moreover, quinpirole exposure led to memory impairment compared to control fish. However, quinpirole administration had no effects on social and aggressive behavior. These findings demonstrate that dopaminergic signaling altered by quinpirole administration in the early life stages of development led to late alterations in behavioral parameters of adult zebrafish.

1. Introduction

During prenatal life, the human brain turns into a complex organ, controlling movements, behaviors, cognitive processes, and routine activities (Bjørling-Poulsen et al., 2008; Julvez and Grandjean, 2009). To reach its complete development, connections must occur precisely. All processes involved in brain development must occur rigidly, in precise time and sequence, so that each stage of development occurs correctly. If these processes are altered, inhibited, or interrupted at any of these stages, the consequences can be permanent (Bjørling-Poulsen et al., 2008; Rice and Barone Jr., 2000). Furthermore, changes in pathways during neurotransmitter systems development may underlie pathophysiological processes of neurological disorders (Banerjee et al., 2014; Cai et al., 2021; Valenzuela et al., 2011).

The dopaminergic system is involved in many central nervous system functions such as movement, executive functions, reward, motivation, learning, and memory (Beaulieu and Gainetdinov, 2011; Björklund and Dunnett, 2007; Goldman-Rakic, 1998; Jones and Miller, 2008). By acting through its receptors, dopamine can control movement and several other behavioral functions (Beaulieu and Gainetdinov, 2011). Dopamine receptors are a class of G protein-coupled receptors that act as mediating dopamine actions in the central and peripheral nervous systems. Both pre- and postsynaptic dopamine receptors are present in the nervous system of vertebrates and are grouped into two families: D1-like receptors (D1 and D5), which increase cyclic AMP levels following stimulation; and D2-like receptors (D2, D3, and D4), which decrease

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cyclic AMP levels or lead to a decrease in intracellular calcium following stimulation (Beaulieu and Gainetdinov, 2011).

Dopaminergic signaling is implicated in several neurological, psychiatric, and neurodegenerative disorders in humans (Armstrong and Okun, 2020; Burns et al., 2019; Chadehumbe and Brown, 2019; D'Amelio et al., 2018; Howes et al., 2015; Klein et al., 2019). More specifically, dopamine receptors are involved in a set of symptoms characteristic of schizophrenia, attention deficit hyperactivity disorder, Huntington's chorea, Parkinson's disease and Alzheimer's disease, Tourette syndrome, tardive dyskinesia, and substance abuse (Brown et al., 2012; Kostrzewa, 1995; Kostrzewa et al., 2014; Kostrzewa et al., 2016a; Kostrzewa et al., 2016b; Kostrzewa and Brus, 2016; Maple et al., 2015). Moreover, dopamine receptors are considered as targets for the treatment of such disorders. Due to the overwhelming importance of dopamine receptors in neuropathological processes, studies in animal models were carried out to understand the association between them and their role in animal behaviors, intending to provide a common thread with human neurological disorders (Hoffman, 2011; Kostrzewa et al., 2016c; Martel and Gatti, 2020; Medin et al., 2013; Mishra et al., 2018; Nabinger et al., 2021; Pan et al., 2019; Vaz et al., 2018).

In this sense, quinpirole, a selective agonist of dopamine D2/D3 receptors has been used to understand mechanisms underlying human neurological disorders, such as schizophrenia, anxiety, and obsessive-compulsive disorder (Archer and Kostrzewa, 2016; Bortolato and Pittenger, 2017; Brown et al., 2012; Camilla d'Angelo et al., 2014; Stuchlik et al., 2016; Szechtman et al., 2017). In animal models, quinpirole administration leads to several behavioral alterations and is correlated to these neurological disorders. Some of the endophenotypes include alterations in locomotor activity, elevated erratic and repetitive movements, induction of stereotypical responses, and alterations in cognitive processes (Abounoori et al., 2020; Bortolato and Pittenger, 2017; Camilla d'Angelo et al., 2014; Eilam et al., 1989, 1991; Irons et al., 2013; Nabinger et al., 2021; Naderi et al., 2016a, 2016b). Furthermore, quinpirole exposure during development can sensitized dopamine receptors causing effects at late stages of development (Kostrzewa and Brus, 1991; Kostrzewa et al., 1993, 2011; Maple et al., 2015; Nowak et al., 2001).

Zebrafish (*Danio rerio*), a translationally relevant biomedical research organism, have become a significant species to study mechanisms implicated in brain function and dysfunction. Due to high genetic and physiological homology to mammals, ease of several experimental manipulations, and the sensitivity to various pharmacological agents, this species has contributed to our better understanding of neurosciences (Gerlai, 2012; Kalueff et al., 2014; Stewart et al., 2014). The main neurotransmitter systems are known to be involved in several neurological disorders as dopaminergic, serotonergic, glutamatergic, and GABAergic are functional and well-characterized in zebrafish (Stewart et al., 2015). Specifically, the development of the dopaminergic system begins around 15–18 h post-fertilization (hpf), and all neuronal cells and their projections are present by 4 days post-fertilization (dpf), (Boehmler et al., 2004, 2007; Li et al., 2007; Rink and Wullimann, 2001, 2002; Tay et al., 2011). The dopaminergic receptors homologous to the mammalian subtypes were identified, except for D5. Around 30 hpf, the expression of genes encoding dopamine receptor is detected, and the receptors are functional at 4 dpf (Boehmler et al., 2004, 2007; Li et al., 2007). Furthermore, behavioral endophenotypes linked to neurological disorders, such as stereotypy, impulsivity, anxiety-like behavior, decision-making, depression, and attention deficit have also been observed in this animal model (Kalueff et al., 2013). All these characteristics make zebrafish a promising animal model for the study of neurological disorders. Given that, we hypothesized that quinpirole exposure during the early life stages of zebrafish might lead to later alterations in behavioral patterns, as increase swim activity and anxiety-like behaviors. Thus, we investigate the late behavioral effects of quinpirole exposure during the early life stages of zebrafish to better understand the mechanisms underlying neurological disorders related to the dopaminergic system. We hope that our study sets a precedent and will lead to a better understanding of the mechanisms underlying human neurological disorders related to the dopaminergic system with the use of zebrafish.

2. Materials and methods

2.1. Animals

Zebrafish (*D. rerio*), wild-type AB strain from both genders were used. To obtain fertilized eggs, females and males (1:2) were placed in breeding tanks (beach style design - Tecniplast, Italy) separated by a transparent barrier overnight. Larvae were raised in Petri dishes (30 fertilized eggs per dish) and kept in maintenance water on a 14/10 h light/dark cycle following standards methods for the species (reverse osmosis-filtered water reconstituted to reach 400–600 μS of salinity, pH 6.5–7.5, temperature 27 °C ± 2 °C, ammonia <0.004 ppm, nitrate <50 mg/L, nitrite <1 mg/L, chloride 0 mg/L and hardness 80–300 mg/L) up to an age of 5 dpf. At 5 dpf, quinpirole hydrochloride (Sigma-Aldrich, St. Louis, MO, USA - Q102) exposure was conducted in Petri dishes (30 larvae per dish) at concentrations of 0 (control group), 5.5, 16.7, and 50 μM for 24 h (Fig. 1). Quinpirole exposure concentrations were chosen based on previous studies (Irons et al., 2013; Nabinger et al., 2021). After the exposure period, larvae were raised in maintenance water, following the conditions described above and respecting proportional density for each stage of development – at 7 dpf larvae were transferred to 3 L-tanks, with a density of one fish per 60 mL until 30 dpf, when the density changed to one fish per 200 mL until 120 dpf, when all experimental procedures were conducted. The number of exposed larvae was calculated considering the overall mortality of 30% of the embryos, so that the necessary sample size for the experiments could be reached at 120 dpf. The experiments have been conducted with fish coming from three different breeding, and the final sample consisted of 1/3 of each one. For feeding, animals received paramecium between 4 and 14 days dpf and subsequently received commercial flakes (TetraMin Tropical Flake Fish®) three times a day supplemented with brine shrimp (Westerfield, 2007). The hatching rate, general morphology, and mortality rate of the animals were monitored daily. Only fish without morphological changes were used for exposure and behavioral tasks, ensuring that the behavioral effects were not confounded. The study was approved by the Institutional Animal Care Committee from Pontifícia Universidade Católica do Rio Grande do Sul (CEUA-PUCRS, permit number 8181), following the National Council for the Control of Animal Experimentation (CONCEA) guidelines. This study was registered in the Sistema Nacional de Gestão do Patrimônio Genético e Conhecimento Tradicional Associado - SISGEN (Protocol No. A3B073D).

2.2. Open tank test

At 120 dpf, fish were evaluated for exploratory and locomotor activity ($n = 24$ per group). Fish were placed individually in experimental tanks (30 cm long × 15 cm high × 10 cm wide) with water. After 1 min of familiarization, the exploratory and locomotor behavior of the zebrafish were recorded for 5 min for subsequent analysis using software EthoVision XT (30 frames per second) (Gerlai et al., 2000; Nabinger et al., 2018). Total distance traveled, time mobile, and acceleration were analyzed, being considered as the main parameters for exploration and swim activity of a new environment. Absolute turn angle was also determined, which evaluates erratic movements. Last, we quantified the time spent in the bottom zone of the tank, which is considered an indicator of anxiety-like behavior.

2.3. Social interaction task

Social interaction was evaluated at 120 dpf after exposure to quinpirole during early life stages of development ($n = 20$ per group). Briefly,

Fig. 1. Experimental flowchart. Larvae from quinpirole groups were exposed to the respective concentrations (0, 5.5, 16.7, and 50 μM) at 5 dpf for 24 h. At the end of the 24-h exposure period, animals were kept in maintenance water until 120 dpf, when the behavioral tasks were performed.

fish was individually placed in an experimental tank (30 cm long × 15 cm high × 10 cm wide). The apparatus consisted of three tanks, on one side of the experimental tank, an empty fish tank was placed; on the other side, a tank holding 15 zebrafish was placed (stimulus tank). After 1-min familiarization, a 5-min session was video recorded for subsequent analysis with EthoVision XT (30 frames per second) (Gerlai et al., 2000). To quantify social interaction, the experimental tank was virtually divided into two halves, a "stimulus zone" closer to the "stimulus tank" and the other remaining half closer to the empty tank, the time spent at the stimulus zone was measured.

2.4. Aggression test

The mirror test was used to quantify aggressive behavior ($n = 24$ per group) (Gerlai et al., 2000; Rambo et al., 2017). Briefly, at 120 dpf fish were individually placed in an experimental tank (30 cm long × 15 cm high × 10 cm wide). To the back wall of the tank, a mirror (45 cm × 38 cm) was placed at an angle of 22.5°, on this configuration, the left vertical edge of the mirror touched the side of the tank, and the right edge was further away. Thus, when a test fish swam to the left side of the tank, their reflection appeared closer to them. A 5-min session following 1-min familiarization was video recorded for subsequent quantification of aggressive behavior with EthoVision XT (30 frames per second). The tank was virtually divided into four equal sections allowing counting the number of entries and time spent in each zone. Entry to the zone nearest to the mirror was assumed as a preference for proximity to the opponent. The amount of time spent, frequency of entries, and the circle swimming movement in each segment were measured for quantification of aggressive behavior.

2.5. Inhibitory avoidance task

To evaluate whether administration of quinpirole at early life stages of development could impair avoidance memory in adult zebrafish, we performed an inhibitory avoidance test (n = 24 per group) (Blank et al., 2009). The task consisted of two sessions, training and test with 24 h interval. In each session, fish were individually placed in an experimental tank with two compartments of equal size divided by guillotine door, one black (right side) and one white (left side) (18 cm long × 7 cm high × 9 cm wide). Throughout the training session, for 1 min of familiarization, fish were placed in the white compartment with the door closed. After, the guillotine door was lifted. When the fish swam into the black compartment, the guillotine door was closed, and an electric shock pulse (3 ± 0.2 V) was applied for five seconds. Zebrafish were then returned to their housing tank for 24 h until the test session. The test session followed the same procedure as the training session, except for the electric shock. During training and test sessions, a time limit of 3 min was established for the task (fish that did not cross to the black compartment during training session within this period of time were excluded from the task). The latency to enter the black compartment during the training and test sessions was quantified and the expected increase in the test session was used as an index of memory retention.

2.6. Statistical analysis

Data normality was analyzed by Kolmogorov-Smirnov. Data normally distributed were expressed as mean ± standard error of the mean (S.E.M) and further analyzed by one-way ANOVA followed by a post hoc Tukey's test. Nonparametric data were expressed as median ± interquartile range and analyzed by Kruskal-Wallis test followed by a post hoc Dunn's test. For the inhibitory avoidance task, training and test latencies within each group were compared by the Wilcoxon matched-pairs test. The latencies of multiple groups were compared by the Kruskal-Wallis and Mann-Whitney *U* tests. For all comparisons, the *p*-value <0.05 was considered as a significant difference.

3. Results

3.1. Open tank test

The swimming pattern of adult zebrafish was evaluated in an open tank test at 120 dpf after quinpirole exposure during development. Distance traveled, time mobile, and acceleration were considered as the main parameters for exploratory behavior and swimming activity and no alterations were observed in these parameters (ANOVA, Distance traveled: $F_{(3, 88)} = 2.145$, $p = 0.1003$; Kruskal-Wallis, Time mobile: $H = 6.021$, $p = 0.1106$; Acceleration: $H = 3.825$, $p = 0.2810$) (Fig. 2a, b, c).

To evaluate whether quinpirole exposure could cause anxiety, the time swimming at the bottom of the tank (Kruskal-Wallis, $H = 13.37$, $p = 0.0039$) and the swim absolute turn angle (ANOVA, $F_{(3, 88)} = 4.580$, $p = 0.005$) were evaluated. Fish exposed to 50 μM quinpirole ($p = 0.0025$) remained at the bottom of the tank longer than control fish, indicating an anxiety-like behavior (Fig. 2d). Furthermore, zebrafish exposed to 16.7 μM ($p = 0.0197$) presented increased absolute turn angle, likely an indication of elevated erratic movements, a sign of increased fear or anxiety (Fig. 2e).

Additionally, zebrafish exposed to quinpirole presented an altered swimming pattern with increased time of duration (Kruskal-Wallis, $H = 18.52$, $p = 0.0003$) and frequency (ANOVA, $F_{(3, 88)} = 4.065$, $p = 0.0094$) when compared to controls. Animals exposed to 5.5 ($p = 0.0098$), 16.7 ($p = 0.0154$), and 50 μM ($p = 0.0002$) presented a stereotypic swimming characterized by the pattern of rigid and repetitive behavior. The fish swam from corner to corner at the bottom of the tank repetitive times with high-velocity locomotion; the changes of direction during stereotypic swimming were made by rapid turning within a single behavioral bout. All fish exposed to quinpirole that performed this behavior presented the same pattern, with time and number of episodes of repetitions varying among the groups (Fig. 2f, g) (behavioral results are summarized and presented in Fig. 6).

3.2. Social behavior

There were no alterations in social behavior. Adult zebrafish exposed to quinpirole during development displayed the same preference for the stimulus area as control group when evaluated individually at the social interaction task (Kruskal-Wallis, Time in stimulus zone: $H = 0.8445$, $p = 0.8388$; Frequency in stimulus zone: $H = 0.2283$, $p = 0.9729$) (Fig. 3).

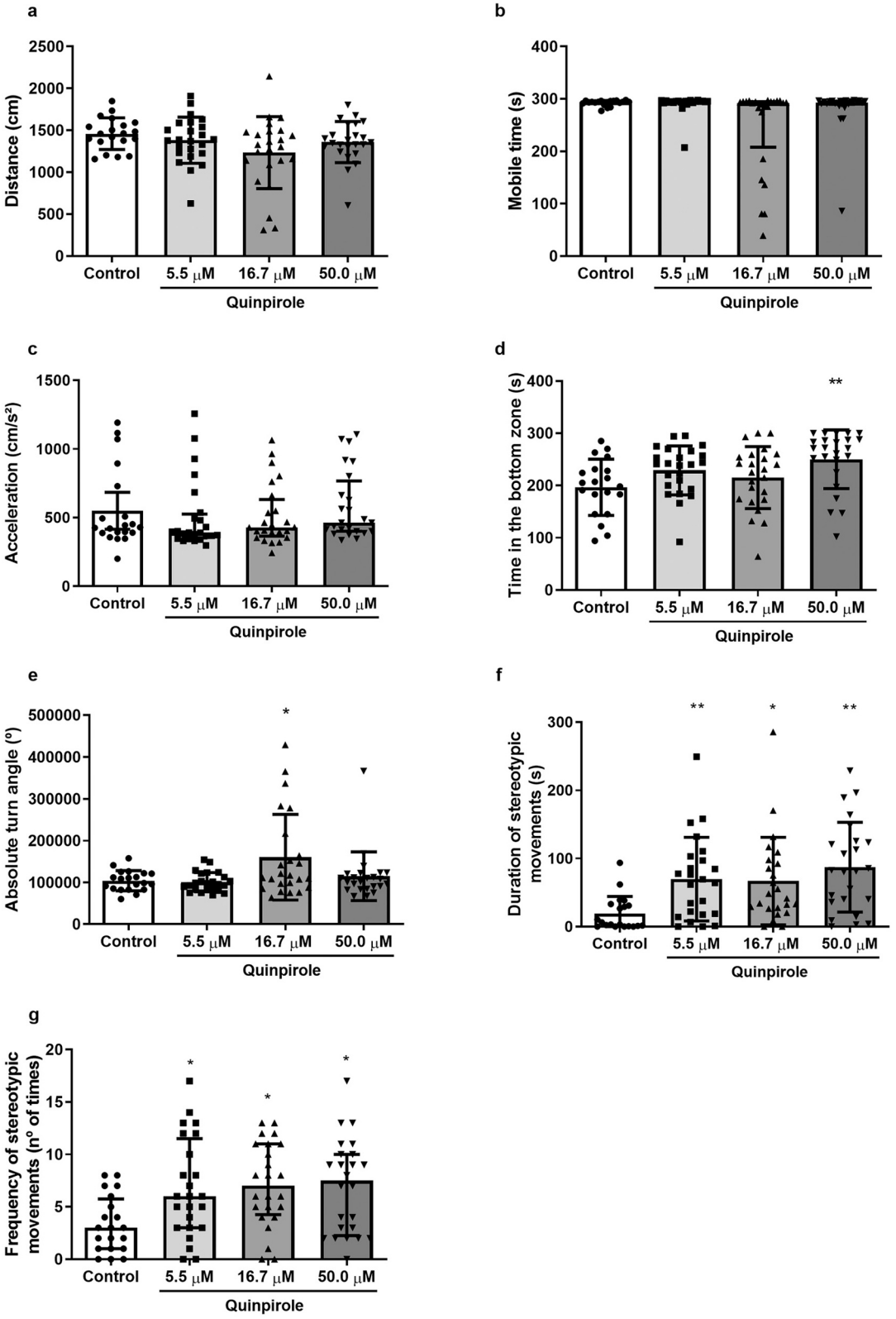


Fig. 2. Locomotor and exploratory activity of adult zebrafish evaluated in the open tank test. Sample sizes are $n = 20$ for control group and $n = 24$ for quinpirole groups. Distance (a), mobile time (b), acceleration (c), time in the bottom of the tank (d), absolute turn angle (e), duration (f), and frequency of stereotypic movements (g) were analyzed at 120 dpf after exposure to quinpirole during development. For nonparametric data, Kruskal-Wallis was used, followed by a post hoc Dunn's test. Data from graphs b, c, d, and f are presented as median ± interquartile (each dot represents the individual data). For data normally distributed, one-way ANOVA was used, followed by post-hoc Tukey's test. Data from graphs a, e, g are presented as media ± SD (each dot represents the individual data). Comparisons between control and the quinpirole groups are indicated by asterisk. * indicates significant difference at $p \leq 0.05$ and ** $p \leq 0.01$. Note that exposure to quinpirole led to anxiety-like behaviors and stereotypic movements at 120 dpf (time spent in the bottom zone (d), absolute turn angle (e), duration (f), and frequency of stereotypic movements (g). For detailed results of statistical analysis, see Results.

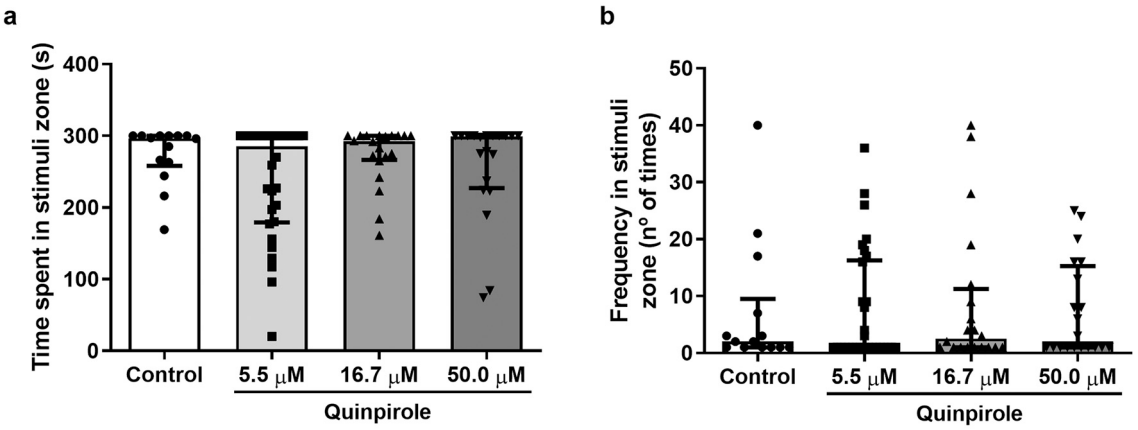


Fig. 3. Analysis of social behavior in adult zebrafish individually tested at the social interaction task. Median ± interquartile are shown (each dot represents the individual data). Sample sizes are $n = 14$ for control group and n = 20 for quinpirole groups. Time spent in the stimulus zone (a) and frequency in the stimulus zone (b) were analyzed at 120 dpf after exposure to quinpirole during development. Kruskal-Wallis was used, followed by a post hoc Dunn's test. Zebrafish exposed to quinpirole presented the same preference for the stimulus area as controls when evaluated individually at social interaction task. For detailed results of statistical analyses, see Results.

(See Fig. 6).

3.3. Aggression test

Exposure to quinpirole during the early life stages of zebrafish did not induce any alteration in aggressive behavior. Zebrafish exposed to quinpirole concentrations presented the same response to the mirror protocol than control fish when tested at 120 dpf (Kruskal-Wallis, Time in the zone nearest to the mirror: H = 6.028, $p = 0.1103$; Frequency in the zone nearest to the mirror: H = 3.600, $p = 0.3080$; Rotation: H = 6.829, $p = 0.0776$) (Fig. 4). (See Fig. 6).

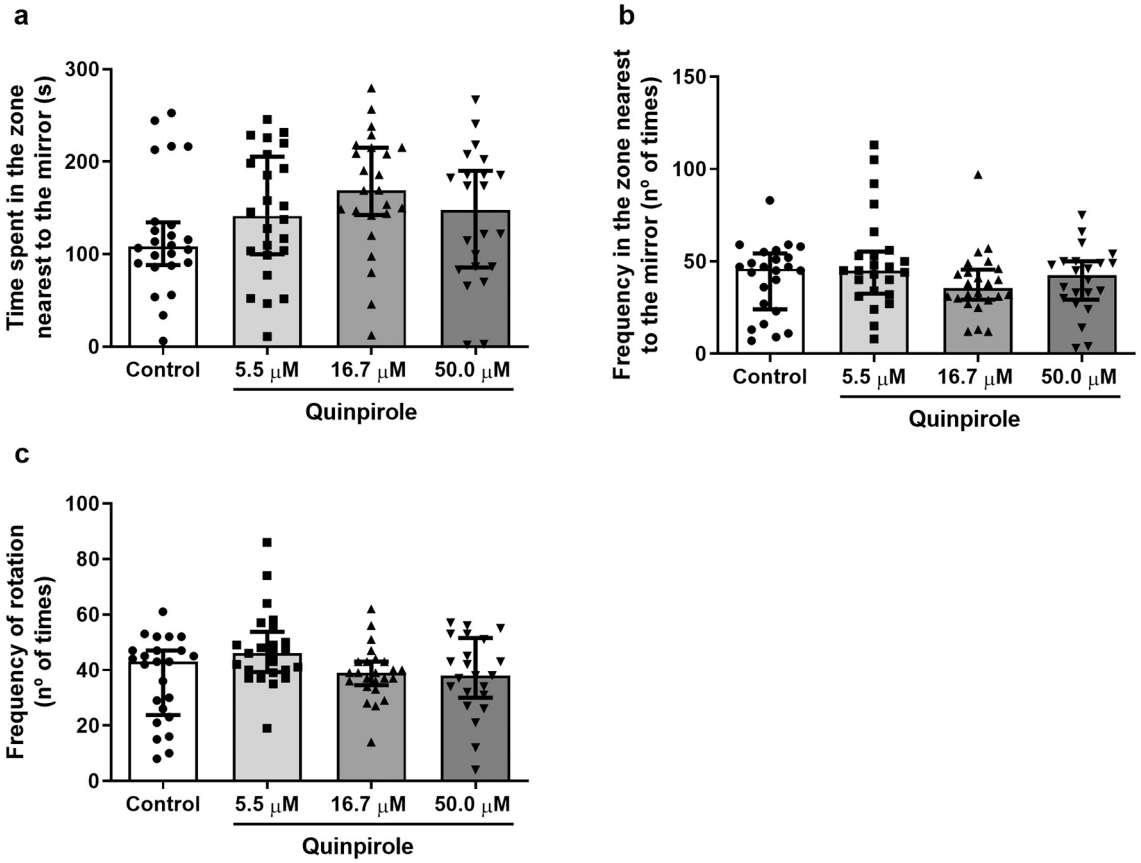


Fig. 4. Evaluation of aggressive behavior in adult zebrafish in the mirror-induced aggression task. Median ± interquartile are shown (each dot represents the individual data). Sample sizes are n = 24 for each group. Time spent in the zone nearest to the mirror (a), frequency in the zone nearest to the mirror (b) and frequency of rotations (c) were analyzed at 120 dpf after exposure to quinpirole during development. Kruskal-Wallis was used, followed by a post hoc Dunn's test. No alterations were observed on fish exposed to quinpirole on the parameters evaluated in the mirror-induced aggression task. For detailed results of statistical analyses, see Results.

3.4. Inhibitory avoidance task

Aversive memory was assessed by the inhibitory avoidance task. Zebrafish exposed to quinpirole at the early stages of development presented memory impairment. There were no differences in the latency to enter the dark compartment for training and test sessions for fish exposed to 50 μM, indicating an impairment of aversive memory, whereas there was a significant difference in the control group ($p < 0.0001$), 5.5 μM ($p = 0.045$), and 16.7 μM ($p = 0.0083$) groups (Fig. 5a). Comparing the groups only at the test session, there is a significant decreasing latency at fish injected with 16.7 (Mann-Whitney, W = 141.5; $p = 0.029$) and 50 μM (Mann-Whitney, W = 116.5; $p = 0.0061$) when compared to controls (Fig. 5b). (See Fig. 6.)

4. Discussion

In our study, we investigated the late effects of quinpirole exposure during the early life stages of zebrafish on behavioral parameters at 120 dpf. The exposure to quinpirole concentrations during development led to late anxiety-like behaviors, stereotypy, and impaired memory. At the open tank test, fish exposed during development remained longer at the bottom of the tank when tested at 120 dpf, indicating an anxiety-like behavior. Furthermore, quinpirole-treated fish exhibited increased absolute turn angle, likely an indication of elevated erratic movements, and a sign of increased fear or anxiety. Additionally, quinpirole-treated fish showed a stereotypic swimming pattern – with repetitive swimming at the bottom of the tank. Quinpirole exposure led to memory impairment compared to control fish when evaluated at avoidance task. However, quinpirole administration had no effects on social and aggressive behavior.

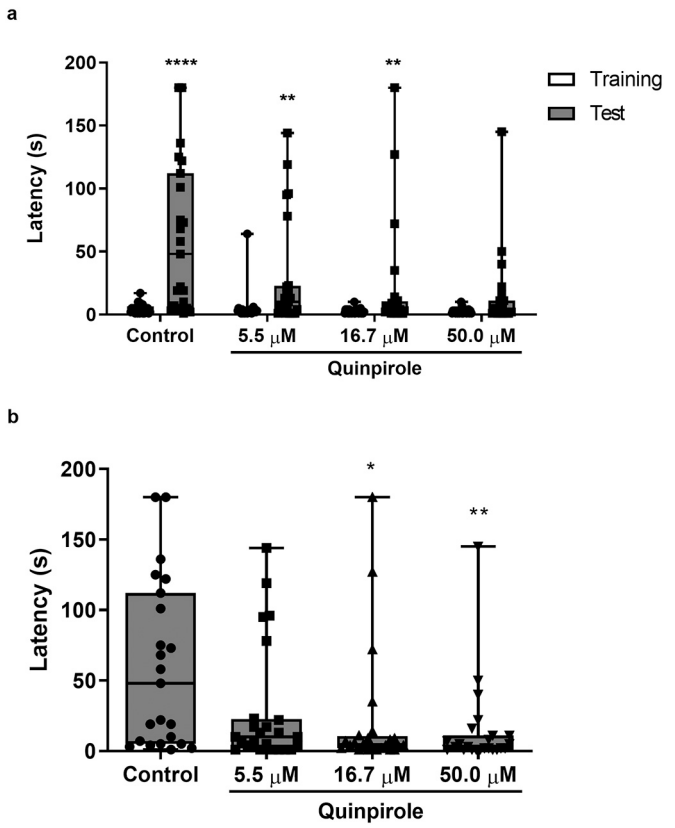
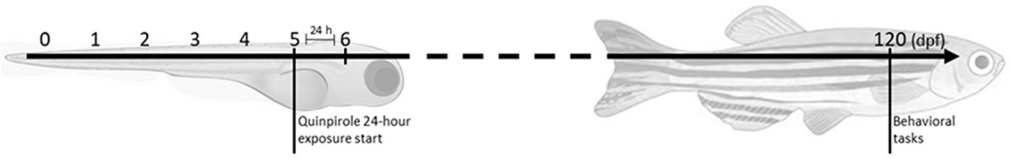


Fig. 5. Inhibitory avoidance task. Sample sizes are n = 24 for each group. Median ± interquartile are shown (each dot represents the individual data). Inhibitory avoidance training and test latencies within each group were compared by the Wilcoxon matched pairs test. Latencies differences between training and test session are indicated by asterisk. ** indicate significant difference at $p \leq 0.01$ and **** $p \leq 0.0001$ (a). Latencies between groups at training session were compared by Mann-Whitney test. Latencies differences at testing session between controls and quinpirole groups are indicated by hashtag. # indicate significant difference at $p \leq 0.05$ and ## $p \leq 0.01$ (b). Note that quinpirole administration caused memory impairment. Note that quinpirole induced memory impairment at 120 dpf in fish exposed to 50 μM quinpirole concentrations at the beginning of development. For detailed results of statistical analyses, see Results.

Neurodevelopment depends on both intrinsic and extrinsic factors that influence the general pattern of neural circuit formation and neurogenesis, which has a straight impact on behavior. Alterations in the dopaminergic signaling and brain morphology at the early stages of development and mutations in genes related to neurodevelopment are strongly associated with numerous neuropsychiatric disorders. Such evidence supports the premise of a neurodevelopmental cause of at least some forms of mental diseases (Souza and Tropepe, 2011; Souza et al., 2011). Zebrafish is considered an important biomedical model, largely used in different research fields, including studies of development, toxicology, genetics, drug screening, and neurobiology of diseases. A specific advantage is that neurotransmitter systems are evolutionarily conserved among zebrafish and other vertebrates, including humans (Wasel and Freeman, 2020). The dopaminergic system in zebrafish is well characterized and is completely developed at 4 dpf (Rink and Wullimann, 2002). Here we performed a pharmacological manipulation of dopamine D2 and D3 receptors during zebrafish development, focusing on the late changes that this exposure could cause in adulthood. In rodents, this exposure protocol has been used as a model for studying psychiatric disorders, and our study aimed to present zebrafish as a model for its study as well (Einat and Szechtman, 1993; Kostrzewa et al., 1993, 2016c; Kurylo and Tanguay, 2003; Maple et al., 2015; Vorhees et al., 2009). The choice of exposure at 5 dpf was given because at this stage the dopaminergic receptors are already functional and are sensitive to quinpirole exposure (Boehmler et al., 2004, 2007; Li et al., 2007). Additionally, it is known that several processes of dopaminergic signaling can be affected by feed status, the proportion of nutrients, and the amount of food intake (Baladi and France, 2009; Briguglio et al., 2018; Sevak et al., 2008). Recently, we demonstrated that nutritional status affects quinpirole exposure effects on zebrafish larvae. Zebrafish larvae that received food before quinpirole exposure presented endophenotypes linked to neuropsychiatric disorders, which were not seen in non-fed animals (Nabinger et al., 2021). For this reason, in the present study, the larvae started to be fed before quinpirole exposure (i.e., at 4 dpf), an attempt to enhance the quinpirole effects over dopamine receptors.

Dopaminergic neurons are classically known to control and modulate locomotion in vertebrates (Ryczko and Dubuc, 2017). As in mammals, dopamine also participates in the control and regulation of locomotion in zebrafish and, for instance, is essential for the initiation of movement (Ek et al., 2016; Irons et al., 2013; Lambert et al., 2012; Souza and Tropepe, 2011; Souza et al., 2011; Thirumalai and Cline, 2008). In our study, quinpirole exposure during development had no late effect over the main parameters considered for exploration and swim activity, as distance traveled, time mobile, and acceleration. However, quinpirole exposure leads to alterations in locomotor activity in zebrafish with controversial results. Larvae (around 5 and 7 dpf) exposed to similar quinpirole concentrations used here (5.5 to 30 μM) have been reported to either present increased and decreased locomotor activity (Boehmler et al., 2007; Irons et al., 2013; Lange et al., 2018; Nabinger et al., 2021; Souza and Tropepe, 2011; Souza et al., 2011). In adult zebrafish, other studies have shown no effects of quinpirole on locomotor activity after exposure to 1 mg/L of this agonist (Naderi et al., 2016a, 2016b).

Dopamine, just like in mammals, is also involved in several neurobehavioral functions and phenomena in zebrafish, including not just the locomotor activity, but also anxiety, aggression, social behavior, and learning and memory (Irons et al., 2013; Kacprzak et al., 2017; Liu et al., 2020; Naderi et al., 2016a, 2016b; Scerbina et al., 2012; Teles et al.,



		5.5 µM	16.7 µM	50 µM
Swimming activity	Distance	=	=	=
	Mobile time	=	=	=
	Acceleration	=	=	=
Anxiety-like behavior	Tigmotaxis	=	=	↑
	Erractic movements	=	↑	=
	Stereotypy	↑	↑	↑
Social interaction		=	=	=
Aggression		=	=	=
Aversive memory		=	↓	↓

Fig. 6. Summary of late behavioral effects of quinpirole exposure during development. The signs in the table indicate the results compared to the control group. = indicates that there is no statistically significant difference between fish treated with quinpirole and controls. ↑ indicates statistically significant increase and ↓ indicates statistically significant decrease comparing quinpirole groups to the control group.

2013). We found quinpirole exposure during development to cause late behavioral alterations such as elevated anxiety-like behavior and to induce stereotypic swimming movements and memory impairment. To the best of our knowledge, such late phenotypes have not been observed in zebrafish after quinpirole exposure during development. Yet, during the early life stages of development, a partial agonist of the D2 dopamine receptor was found to induce anxiety-like behavior in zebrafish larvae (Félix et al., 2017a, 2017b). However, the administration of partial agonists of D2 and D3 receptors in adult zebrafish has been shown to either have an anxiolytic and anxiogenic effect (Barcellos et al., 2020; De Campos et al., 2015; Ek et al., 2016; Johnson and Hamilton, 2017; Müller et al., 2020; Pittman and Hylton, 2015; Riehl et al., 2011). In addition to the effects related to anxiety, partial agonists of D2 receptors have also been found to reduce aggression and disrupt shoaling in zebrafish (Michelotti et al., 2018; Riehl et al., 2011; Zakhary et al., 2011).

Besides leading alteration on anxiety, quinpirole administration caused stereotypic behavior. The administration of this dopamine receptor agonist has been associated with perseveration, stereotypy, repetitive behaviors, and reduced behavioral variability, which are related to alterations observed in neuropsychiatric disorders (Depoortere et al., 1996; Hoffman, 2011; Kostrzewa and Brus, 2016; Mattingly et al., 1993; Nielsen et al., 2017; Sams-Dodd, 1998; Szechtman et al., 1994; Szechtman et al., 2017). Quinpirole exposure also triggered a repetitive travel pattern along routes limited to a specific area (Eilam et al., 1989, 1991). This is like what we observed here since zebrafish exposed to quinpirole during the development presented a stereotypic behavior, characterized by a repetitive movement, swimming from corner to corner at the bottom of the tank. For fish exposed to the lower quinpirole concentrations, this behavior occurred randomly during the test. However, for animals exposed to the highest concentration, the stereotypic behavior was always followed and preceded by episodes of immobility. Furthermore, ketamine, a partial agonist of the D2 dopamine receptor, has also been found to induce stereotypical behaviors and evoke circular swimming in zebrafish (Michelotti et al., 2018; Riehl et al., 2011; Zakhary et al., 2011).

The results regarding anxiety and stereotypic behavior observed here are in line with what was observed in these previous studies. However, as mentioned above, these studies used partial agonists of D2 and D3 dopamine receptors. Partial agonists also act via other receptors from different signaling systems, justifying some of the controversial findings of our study. Nevertheless, quinpirole administration has been used in rats and mice to model psychiatric disorders, such as obsessive-compulsive disorder and schizophrenia. After exposure, the animals presented anxiety-like behavior and elevated stereotypic and erratic movements as we observed here. Only a few studies have reported alterations in social and aggressive behavior (Hoffman, 2011; Kostrzewa et al., 2016c; Maple et al., 2017; Navarro and Maldonado, 1999; Nielsen et al., 2017; Sams-Dodd, 1998; Szechtman et al., 2017).

Even though not seeing alterations in aggressive and social behaviors, quinpirole exposure during development led to late effects on memory. The dopaminergic system is known to participate in learning and memory processes (Goldman-Rakic, 1998). Few studies evaluating memory after quinpirole exposure have been performed, and depending on the task, zebrafish presented memory impairment or facilitation when compared to controls. Using a plus-maze associative learning paradigm, an enhanced performance was observed in zebrafish exposed to quinpirole immediately before the training and the probe test, but not when exposed after it (Naderi et al., 2016a). The same authors, assessing cognitive performance using a complex maze, showed that quinpirole exposure before and after training significantly impacts learning and memory in zebrafish (Naderi et al., 2016b). As observed for zebrafish, the assessment of memory after quinpirole exposure in rodents also presents controversial results. For example, in a fear conditioning paradigm, the administration of quinpirole was found either to improve or to impair learning and memory processes in rodents (Farahmandfar et al., 2016; Lénárd et al., 2017; Nader and LeDoux, 1999a, 1999b). Here we performed an inhibitory avoidance task after quinpirole administration during development and we observed impaired learning/memory performance at fish exposed to the higher concentrations tested. To the best of our knowledge, this is the first demonstration of quinpirole leading to late effects in inhibitory avoidance learning/memory performance in zebrafish. As mentioned, the dopaminergic system participates in memory processes, and evidence indicates the involvement of dopamine receptors on consolidation and reconsolidation, acquisition, retrieval, and extinction phases of different kinds of learning and

memory (El-Ghundi et al., 2007; Puig et al., 2014). Specifically, earlier studies observed and identified a differential involvement of D2 receptor in the acquisition of different kinds of memory (Brown et al., 2000; Kurylo, 2004; Merritt and Bachtell, 2013; Ponnusamy et al., 2005; Yawata et al., 2012; Young et al., 2014), explaining the contradictory findings. Also, quinpirole may have a dose-dependent biphasic profile in zebrafish, a possibility already confirmed in mammals (Li et al., 2010). This biphasic dose-response is assumed to result from the dose-dependent activation of D2 versus D3 receptor - depending on the quinpirole concentration pre- or postsynaptic D2/D3 receptors can be activated (De Mei et al., 2009). It has been demonstrated that the activation of postsynaptic receptors led to recall of memory (Bracs et al., 1984; Ichihara et al., 1988; Naderi et al., 2016a); likely this could indicate that the impaired memory observed here results from presynaptic activation of D2 receptors. Additional studies are necessary to deepen the role of D2/D3 receptors in zebrafish memory.

The manipulation of dopaminergic receptors during development led to neurological alterations that reflected the altered behaviors observed here. However, the underlying mechanisms involved in the late behavioral effects of quinpirole exposure are still unknown. Yet, neurodevelopmental and psychiatric disorders are linked with abnormalities in several epigenetic mechanisms (Archer et al., 2010; Shorter and Miller, 2015). The behavioral effects showed in the present study fit into the behavioral spectrum observed in animal models used to study human neuropsychiatric conditions, including obsessive-compulsive disorders, schizophrenia, and anxiety (Archer and Kostrzewa, 2016; Bortolato and Pittenger, 2017; Brown et al., 2012; Camilla d'Angelo et al., 2014; Stuchlik et al., 2016; Szechtman et al., 2017). Zebrafish models to study such disorders, excepting anxiety, are lacking (Kalueff et al., 2013; Khan et al., 2017). In addition, the late effects of quinpirole exposure during the early life stages of the zebrafish observed here may indicate the use of this species and this agonist to better understand the disorders related to the dopaminergic system, especially those that occur due to changes during the development.

Thus, in summary, our study shows that quinpirole exposure during the early life stages of zebrafish led to late and persistent behavioral alterations in the adult phase. Quinpirole effects highly observable include anxiety-like behaviors, stereotypic behavior, and memory impairment, behavioral phenotypes corresponding to the ones observed in some human neurological disorders and in animal models used to study these disorders. The observed alterations demonstrate the participation of the dopaminergic neurotransmitter system in a variety of brain functions and behaviors and show that the zebrafish present similar psychopharmacological responses to mammalian model organisms. Thus, our study expands the possibility of using zebrafish, a simple vertebrate, for studying neuropsychiatric diseases, contributing to their better understanding.

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Declaration of Competing Interest

The authors declare that they have no competing interest.

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