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Zebrafish models: Gaining insight into purinergic signaling and neurological disorders

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ABSTRACT

Zebrafish (*Danio rerio*) has been considered a complementary model for biomedical studies, especially due to advantages such as external and rapid development, and genetic manipulation. There is growing interest in this model in neuroscience research since the species has morphological and physiological similarities to mammals and a complex behavioral repertoire. The purinergic signaling has been described in zebrafish, and purinoceptors and nucleotide- and nucleoside-metabolizing enzymes have already been identified in the central nervous system (CNS) of this species. The involvement of the purinergic system in several models of neurological disorders, such as Alzheimers disease, Parkinson's disease, epilepsy, schizophrenia, and autism has been investigated in zebrafish. This mini review presents several studies describing purinergic signaling in the zebrafish CNS and the action of this neurotransmitter system in models of neurological disorders using this species as a biological model. The use of pharmacological approaches at different stages of development may be a useful tool for preclinical assays and the testing of purinergic compounds as new alternatives for the treatment of neurological disorders.

1. Introduction

Zebrafish (*Danio rerio*) is a teleost from the Cyprinidae family that has been extensively used in biomedical research due to the similarity of this species to other vertebrates, since zebrafish genes show about 70% homology with human genes (Howe et al., 2013). The nervous system of this animal is well characterized, and several neurotransmitter systems are conserved between zebrafish and other species including humans (Cheng et al., 2014; Stewart et al., 2015). Genetic knowledge, together with the description of the central nervous system (CNS), general organization, and neural circuits similar to those observed in mammals, have meant the zebrafish has become a model for behavioral studies (Arenzana et al., 2005; Panula et al., 2006; Stewart et al., 2014). Moreover, the zebrafish has emerged as a good model for the study of CNS diseases through the establishment of pharmacological and genetic models of Alzheimer's disease, Parkinson's disease, epilepsy, anxiety, depression, stress, schizophrenia and autism (Maximino et al., 2011; Piato et al., 2011; Savio et al., 2012; Bortolotto et al., 2014, 2015; Seibt et al., 2015; Siebel et al., 2015; Zimmermann et al., 2017; Menezes et al., 2018).

Purinergic signaling has been identified in zebrafish (Norton et al., 2000; Kucenas et al., 2003, 2009; Rico et al., 2003; Appelbaum et al., 2007). This neurotransmitter system comprises P2 receptors activated by triphosphate and diphosphate nucleosides, and P1 receptors triggered by adenosine (Burnstock and Kennedy, 1985). The P2 receptors are divided into two different families: P2X and P2Y purinoceptors. P2X family receptors (P2X1–7) are ionotropic and are distributed in several cell types, including neurons and glial cells. The P2Y family receptors (P2Y1, P2Y2, P2Y4, P2Y6, P2Y11, P2Y12, P2Y13, and P2Y14) are metabotropic and present a wide distribution in tissues and systems such as vascular, nervous, and cardiac systems (Burnstock and Kennedy, 1985; Burnstock, 2012). ATP levels are regulated by ectonucleotidases, a group of enzymes constituted by nucleotide pyrophosphatase/phosphodiesterases (NPP), nucleoside triphosphate diphosphohydrolases (NTPDases), alkaline phosphatase and ecto-5′-nucleotidase. The ectonucleotidases promote the extracellular hydrolysis of ATP to adenosine, which acts on P1 metabotropic receptors (A_1, A_{2A}, A_{2B}, and A_3). Adenosine, through the action of adenosine deaminase (ADA), may be subsequently deaminated to inosine (Bonan, 2012; Zimmermann et al., 2016).

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The enzyme activities of NTPDases, ecto-5′-nucleotidase and ADA have been demonstrated in zebrafish brain membranes, along with the gene expression patterns of these enzymes (Rico et al., 2003; Senger et al., 2004; Rosemberg et al., 2007, 2008, 2010). In addition, molecular characterization of P2X receptors has demonstrated the presence of P2X1, P2X2, P2X3 (P2X3.1 and P2X3.2), P2X4 (P2X4.1 and P2X4.2), P2X5 (P2X5.1), P2X7, and P2X8 receptors in zebrafish (Norton et al., 2000; Kucenas et al., 2003, 2009; Appelbaum et al., 2007; Low et al., 2008). P2Y receptor expression has been reported in zebrafish thrombocytes and retina (Gregory and Jagadeeswaran, 2002; Battista et al., 2009; Battista and Faillace, 2012; Medrano et al., 2017). Studies have also identified A_1, A_{2A}, and A_{2B} adenosine receptors (A_1R, $A_{2A}R$, and $A_{2B}R$, respectively) in this teleost (Boehmler et al., 2009; Capiotti et al., 2011). Recently, a new member of the adenosine receptor family, named A_{2C}, was identified in zebrafish olfactory epithelium (Wakisaka et al., 2017). Therefore, this review will discuss the use of zebrafish as a biological model for understanding the role of purinergic signaling in neurological disorders.

2. Alzheimer's disease

Alzheimer's disease (AD) is the most common neurodegenerative disease, presenting progressive and irreversible cognitive, behavioral, and memory impairment (Selkoe, 2001). Adenosine receptors are considered possible pharmacological targets for AD treatment, since adenosine plays a neuromodulatory role, controlling neuronal excitability and regulating homeostasis (Chen et al., 2013; Dias et al., 2013; Woods et al., 2016; Cieślak and Wojtczak, 2018; Liu et al., 2019). Analyses performed in patients diagnosed with late AD demonstrate A_1R clusters in damaged neurons, containing neurofibrillary tangles and within dystrophic neurites (Angulo et al., 2003). Increased expression of $A_{2A}R$ was observed in postmortem frontal cortex analysis of patients in the early and advanced stages of AD (Albasanz et al., 2008). Moreover, adenosine receptors are involved in cognitive processes in humans and animal models in rodents and humans (Gomes et al., 2011; Sebastião et al., 2012). Caffeine (a nonselective antagonist of adenosine receptors) consumption is closely related to the low incidence of AD (Maia and de Mendonça, 2002; Ritchie et al., 2007). In zebrafish, an overexpression of genes encoding A_1R, $A_{2A1}R$, and $A_{2A2}R$ has been observed after exposure to caffeine, along with a reduction in the expression of $A_{2B}R$ and genes related to AD (*APP*, *Psen1*, *Psen2*, *ApoE* and *Sorl1*) (Capiotti et al., 2011; Abdelkader et al., 2015).

Using scopolamine, an antagonist of the muscarinic cholinergic receptor, Bortolotto et al. (2015) developed a memory-deficit model in adult zebrafish. It was found that scopolamine impaired memory processing in inhibitory avoidance tasks. This task evaluated zebrafish memory in two sessions, called training and test sessions. In the training session, the animal was placed on the white side of a two-compartment aquarium separated by a guillotine door and, after moving to the second compartment (dark), received a shock. In the test session, 24 h later, the animal was placed in the same context, but did not receive a shock. The latency (in seconds) of the animal moving into the dark compartment was evaluated and considered a measurement of aversive memory (Blank et al., 2009). Bortolotto et al. (2015) also evaluated the preventive role of adenosine signaling. Acute pretreatments with caffeine and selective $A_{2A}R$ (ZM241385) and A_1R (DPCPX, 8-cyclopentyl-1,3-dipropylxanthine) antagonists prevented memory deficits induced by scopolamine exposure. The use of nucleoside transporter or ADA inhibitors (dipyridamole and EHNA (erythro-9-(2-hydroxy-3-nonyl)-adenine), respectively) also prevented memory deficits induced by scopolamine (Bortolotto et al., 2015). These findings demonstrated that adenosine modulation reduced scopolamine-induced memory deficits through antagonism of adenosine receptors or inhibition of nucleoside transport.

Cannabidiol may be a potent drug against memory impairment and demonstrates therapeutic properties (Cheng et al., 2014; Watt and Karl, 2017). However, signaling through CB1 receptors has shown impaired capacity for memory acquisition (Pamplona et al., 2006; de Carvalho et al., 2014). A study using zebrafish assessed whether constant caffeine exposure throughout development (3 h post-fertilization (hpf) to 4 months post-fertilization) would cause changes in the memory acquisition (pre-training evaluation) and consolidation (post-training evaluation) of adult animals treated with cannabidiol in inhibitory avoidance tasks (Nazario et al., 2015). The effects of cannabidiol exposure per se promoted aversive memory impairment when the treatment was performed both prior to and post-training sessions. Caffeine-only exposure throughout development did not alter the memory acquisition and consolidation of adult animals. When cannabidiol treatment was performed prior to training session in animals exposed to caffeine, there was no significant difference in memory acquisition. However, when cannabidiol was administered post-training, in the memory consolidation phase, caffeine was able to prevent memory damage in zebrafish (Nazario et al., 2015). Therefore, these results suggest that the action of caffeine depends on the time of its administration, being effective in the consolidation of memory affected by cannabidiol exposure.

Evidence indicates adenosinergic signaling as a possible pharmacological target in the prevention of memory impairment (Cieślak and Wojtczak, 2018). Pharmacological and transgenic zebrafish models have been used to induce AD (Xi et al., 2011; Caramillo and Echevarria, 2017). The *APP* gene in zebrafish has two genes associated with humans: *APPa* and *APPb*. *APPa*-morpholino blockade in zebrafish has few effects on larvae, but *APPb* blockade causes defects in fish neuronal development, including changes in axonal and synapse formation (Song and Pimplikar, 2012; Abramsson et al., 2013). In addition, Paquet et al. (2009) produced fluorescently labeled TAU transgenic zebrafish with pathological characteristics, including TAU protein hyperphosphorylation, tangle formation and neuronal and behavioral dysfunctions (Paquet et al., 2009). Therefore, the modulation of adenosinergic signaling in the *APPa*-morpholino blockade or transgenic TAU zebrafish models may be an interesting approach to evaluate the effects of adenosine receptors on cognitive impairment, allowing the search for new therapeutic targets.

3. Parkinson's disease

Parkinson's disease (PD) is characterized by late onset and the progressive occurrence of three main symptoms: rigidity, tremor at rest and bradykinesia (Djaldetti et al., 2006). In addition, nonmotor clinical manifestations are also reported, such as cognitive impairment and dementia (Janvin et al., 2006). Adenosinergic signaling is associated with the pathophysiology of PD due to its interaction with the dopaminergic system and its effects on motor function (Canals et al., 2003; Morelli et al., 2010). D_2 dopamine receptors (D_2Rs) have a mutual influence with $A_{2A}Rs$, forming heterodimers. In this modulation, adenosine acts through the adenosine $A_{2A}R$, which antagonizes the dopamine D_2R, decreasing its affinity through the heterodimerization of these receptors (Fuxe et al., 2003; Casadó-Anguera et al., 2016; Ferré et al., 2016).

Pesticides and toxins, such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and 6-hydroxydopamine (6-OHDA), mimic in animals the symptoms caused by Parkinson's disease progression in humans (Duty and Jenner, 2011; Soliman et al., 2018). MPTP (20 mg/kg) or 6-OHDA (25 mg/kg) i.p. was found to reduce dopamine and noradrenaline levels in the brains of adult zebrafish 24 and 48 h after application. In addition, a reduction in the velocity and distance traveled by zebrafish in the novel tank task was observed after 1, 3 and 6 days of MPTP or 6-OHDA i.p. injection (Anichtchik et al., 2004). These findings reinforce the idea that this animal has a neurochemical and behavioral repertoire that mimics the typical symptoms of PD and can be used as an animal model for studies involving the prevention and treatment of this disease.

Paraquat has also been used to induce Parkinsonism in experimental animals since it is known that this toxin accelerates the development of PD (Tanner et al., 2011). In zebrafish, the administration of six i.p. injections (one every 3 days) of paraquat (10 and 20 mg/kg) was able to reduce over time the distance traveled in the two doses evaluated, as well as the absolute turn angle at the higher dose, which reflected impairment in the animal's motor coordination (Bortolotto et al., 2014). In addition, in both doses tested, paraquat-treated animals showed impairment in the acquisition and consolidation of memory in the Y-maze task. This pesticide increases dopamine and reduces DOPAC (3,4-Dihydroxyphenylacetic acid) levels, thereby suggesting that paraquat plays a role in the reduction of dopamine metabolism (Bortolotto et al., 2014).

The interaction between dopaminergic lesions caused by neurotoxins and adenosinergic pathways has been evaluated in zebrafish using MPTP and caffeine (Boehmler et al., 2009). Analysis at 5 days post-fertilization (dpf), after treatment (24 hpf to 5 dpf) with these drugs, showed that MPTP (40 μM) was able to inhibit expression of dopamine transporter (*dat*) gene in diencephalic or pretectal neurons of zebrafish larvae. When animals were treated with MPTP and caffeine (10 μM) together, *dat* expression was similar to the control group in diencephalic neurons. However, caffeine was not able to protect pretectal dopaminergic neurons against MPTP neurotoxicity. Caffeine-only treatment had no effect on *dat* expression. Together, these results show that, in zebrafish larvae, caffeine exerts a protective effect, inhibiting the action of MPTP in decreasing *dat* expression in diencephalic neurons. However, this adenosine antagonist was not effective in pretectal neurons, since A_1R and A_{2A}R transcripts were not identified in pretectal neurons (Boehmler et al., 2009).

These studies demonstrated that the model of Parkinsonism using neurotoxins is well established in zebrafish. In addition, the existence of orthologous genes associated with this pathology, such as *pink 1*, *dj-1*, *parkin* and *lrrk2*, was demonstrated in zebrafish, and transgenic and knockout models for PD have been used for studying neurochemical and behavioral aspects related to this disease (Anichtchik et al., 2008; Xi et al., 2011). Taken together, the genetic and neurotoxin models are important tools for characterizing PD symptoms in zebrafish. In addition, the modulation of the adenosinergic system as a tool to attenuate the symptoms or development of PD may be a way to improve the quality of life for PD patients.

4. Epilepsy

Epilepsy is a neurological disorder characterized by recurrent and unpredictable seizures due to an enduring imbalance between excitatory and inhibitory processes (Moshé et al., 2015). Adenine nucleosides and nucleotides are related to epilepsy and, through inhibition of ADA, they could be used in its treatment (Siebel et al., 2011; Stewart et al., 2012). It has been suggested that ATP influences epileptogenesis, and this nucleotide might be catabolized into adenosine, which is considered an endogenous anticonvulsant since it exhibits inhibitory effects on neuronal activity (Boison, 2016). The anticonvulsant properties of adenosine are mediated by A_1R activation, endogenously modulating the release of the presynaptic neurotransmitter and stabilizing the membrane potential (Fredholm et al., 2005; Fedele et al., 2006). As well as adenosine, it has been proposed that AMP activates A_1Rs, restrains excitatory neurotransmission, and can also act as an endogenous anticonvulsant (Muzzi et al., 2013).

Zebrafish have been widely used for the understanding of seizure modulation, with both genetic and pharmacological approaches being employed (Stewart et al., 2012; Cunliffe, 2016). Pentylenetetrazole (PTZ), a pharmacological inducer of seizures, is a noncompetitive antagonist of the gamma-aminobutyric acid ($GABA_A$) receptor complex (da Silva et al., 2016), and it has been demonstrated that it can induce seizures in larval and adult zebrafish, causing molecular, behavioral and electrographic alterations (Baraban et al., 2005; Berghmans et al., 2007; Menezes and da Silva, 2017; Menezes et al., 2018; Choo et al., 2019). Other well-characterized seizure models include kainic acid, domoic acid, the plant natural product ginkgotoxin and allyl-glycine (Lee et al., 2012; Menezes et al., 2014; Leclercq et al., 2015). The general effects observed in seizure caused by exposure to these agents (of different times, duration and intensity) include dramatically increased swimming activity, whirlpool swimming behavior, and clonus-like seizures, followed by loss of posture when the animal falls and remains immobile for a few seconds (Mussulini et al., 2013; Menezes et al., 2014). In addition, zebrafish have responded to classic anti-epileptic drugs, such as valproate, carbamazepine, gabapentin, and phenytoin (Berghmans et al., 2007; Lee et al., 2010; Siebel et al., 2010, 2013).

Studies using a PTZ-induced model of seizures in zebrafish have reinforced the involvement of adenosine signaling in seizure events. Using morpholinos that transiently block the translation of adenosine receptor transcripts, a transient intervention in these receptors in early life stages of zebrafish, promotes susceptibility to proconvulsants in a long-lasting manner, affecting animals during adulthood (Menezes et al., 2018). Inosine, a metabolite of adenosine deamination and an adenosine receptor agonist, presented anticonvulsant properties in a PTZ-induced model of seizures in zebrafish (Brillatz et al., 2018), reinforcing the beneficial effects of this nucleoside in preventing seizure events.

The use of A_1R agonists and antagonists also confirmed the anticonvulsant role promoted by the activation of this receptor in zebrafish (Siebel et al., 2015). Sustaining this finding, the administration of cyclopentyladenosine (CPA), an A_1R agonist, enhanced the latency in reaching the tonic-clonic seizure stage, inducing an anticonvulsant effect whereas DPCPX, an A_1R antagonist, decreased this latency, demonstrating a pro-convulsant effect. When evaluating the action of adenosine on A_{2A}Rs, there were no alterations in seizure parameters. In addition, zebrafish exposed to AMPCP (adenosine 5′-(a,β-methylene) diphosphate), an ecto-5'nucleotidase inhibitor, developed PTZ-induced seizures with shorter latency than control zebrafish (Siebel et al., 2015). This further demonstrates the important anticonvulsant role of adenosine via A_1Rs.

Siebel et al. (2011) showed that PTZ was able to alter ADA activity in zebrafish brain membranes. A single seizure episode reduced ecto-ADA activity; however, it did not alter ectonucleotidase and cytosolic ADA activities (Siebel et al., 2011). Seizure states with loss of posture caused by PTZ did not change ectonucleotidase but increased the ecto- and cytosolic ADA activities (Siebel et al., 2013). Antiepileptic drugs were able to reduce, at the control level, the ADA activity in zebrafish brain membranes after PTZ-induced seizures with loss of posture, and promote an increase in latency to reach the seizure (Siebel et al., 2013). Taken together, these findings demonstrate that adenosine signaling plays a role in seizure modulation in zebrafish.

5. Other neurological disorders

Zebrafish have also been used to evaluate the involvement of the purinergic system in other neurological disorders, such as autism and schizophrenia (Lara et al., 2006; Al-Mosalem et al., 2009). A social interaction deficit model developed by exposure to valproic acid in the early life stages of zebrafish induced long-lasting effects on purinergic signaling. In the adult phase, treated animals presented an increase in AMP hydrolysis while ecto-ADA activity was decreased (Zimmermann et al., 2017).

Haloperidol, a typical antipsychotic used as schizophrenia treatment, acts by relieving psychotic symptoms such as hallucinations and delusions. The acute treatment with this drug promoted a decrease in ATP hydrolysis and ecto-ADA activity in adult zebrafish (Seibt et al., 2009, 2015); however, no changes in ADP and AMP hydrolysis or cytosolic ADA were observed. The adenosine augmentation by pharmacological inhibition of adenosine kinase induced antipsychotic-like

activity in mice (Shen et al., 2012). Therefore, the effects induced by haloperidol may induce an increase in adenosine levels due to an inhibition in ecto-ADA activity as previously described (Seibt et al., 2015), contributing to the antipsychotic effects of this drug; however, it is not possible to exclude the possibility that changes in nucleotides and nucleoside levels could be an adverse effect induced by this drug.

Purinergic signaling also plays an important role in stress and anxiety. In humans, caffeine triggers anxiety, and some studies have tried to establish a relationship between anxiety and purinergic signaling. Caffeine, PACPX (1,3-dipropyl-8-(2-amino-4-chloro-phenyl)-xanthine), an A_1R antagonist, and DMPX (1,3-dimethyl-1-propargylxanthine), an A_2R antagonist, showed that the blockade of A_1Rs but not A_2Rs induces anxiety in zebrafish (Maximino et al., 2011). Another study demonstrated that A_3Rs activation leads to decreased neophobia, arousal, geotaxis and scototaxis in adult zebrafish (Maximino et al., 2015). However, A_3Rs has not yet been characterized in this species; therefore, the authors suggest that the effect of IB-MECA (methyl 1-[N6-(3-iodobenzyl)-adenin-9-yl]-b-D-ribofuronamide) on zebrafish behavior is mediated by nitric oxide and the 5-HT pathway. Additionally, Canzian et al. (2017) showed that animals exposed to an alarm substance presented an increase in erratic movements and a decrease in ecto-5′-nucleotidase activity, which could reflect a potential decrease in extracellular adenosine via the ecto-nucleotidase pathway, resulting in increased AMP levels. Also, Da Silva et al. (2015) demonstrated the involvement of adenosinergic signaling in antidepressant actions promoted by MK-801 in zebrafish. Animals exposed to MK-801 showed anxiolytic/antidepressant responses, increasing the time spent in the top area of the tanks; caffeine and DPCPX prevented these behavioral changes, reducing this swimming pattern in adult zebrafish (da Silva et al., 2015). These findings indicate that the purinergic system has a potential role in anxiety-like responses.

The association between stress and purinergic signaling has also been studied (Piato et al., 2011; Zimmermann et al., 2016). Piato et al. (2011) investigated the effects of acute restraint stress on behavior and the biochemical and molecular parameters involved in the purinergic signaling in zebrafish. The results showed, besides disturbing zebrafish behavior, increased ATP hydrolysis and decreased cytosolic ADA activity. Changes in the expression of NTPDases and adenosine receptor genes (*entpd* and *adora*, respectively) were also observed (Piato et al., 2011). Zebrafish submitted to unpredictable chronic stress demonstrated a decrease in ecto-ADA activity. On the other hand, no changes were seen in the NTPDase, ecto-5′-nucleotidase, and cytosolic ADA activities in stressed animals when compared to control. However, the evaluation of the nucleotide and nucleoside metabolism showed an increase in adenosine levels in brain membranes of zebrafish exposed to chronic stress (Zimmermann et al., 2016). Although stress and anxiety may be considered different aspects of a similar allostatic state, there are differences in the modulation of nucleotide and nucleoside-metabolizing enzymes. These differences may be a strategy to promote a physiological response and re-establish homeostasis after anxiety states or stressful events.

These findings indicate that purinergic signaling may be involved in neuropsychiatric processes through the inhibition of the enzymes responsible for the ATP hydrolysis cascade, modulating the concentration of adenine nucleotides and nucleosides in the synaptic cleft.

6. Conclusions

This mini review sheds light on the need to intensify research into purinergic signaling in zebrafish. Among the advantages of zebrafish are its small size, external fertilization and rapid development, embryo transparency, ease of experimental manipulations, highly conserved genes and similar physiological responses to those of humans. Therefore, this species has been an interesting alternative for the establishment of pharmacological and genetic models of neurological disorders such as Alzheimer's disease, Parkinson's disease, epilepsy, anxiety, stress, schizophrenia, and autism. In addition, zebrafish has external development, which could help in the investigation of the role of purinergic signaling throughout development as well as in the progression of neurological disorders. Therefore, the use of zebrafish as animal model, at both larval and adult stages, may contribute to knowledge about the actions of nucleotides and nucleosides as messengers and in the development of therapies for neurological disorders.

Declaration of Competing Interest

The authors declare no conflicts of interest.

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