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Zebrafish neurotransmitter systems as potential pharmacological and toxicological targets

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ABSTRACT

Recent advances in neurobiology have emphasized the study of brain structure and function and its association with numerous pathological and toxicological events. Neurotransmitters are substances that relay, amplify, and modulate electrical signals between neurons and other cells. Neurotransmitter signaling mediates rapid intercellular communication by interacting with cell surface receptors, activating second messenger systems and regulating the activity of ion channels. Changes in the functional balance of neurotransmitters have been implicated in the failure of central nervous system function. In addition, abnormalities in neurotransmitter production or functioning can be induced by several toxicological compounds, many of which are found in the environment. The zebrafish has been increasingly used as an animal model for biomedical research, primarily due to its genetic tractability and ease of maintenance. These features make this species a versatile tool for pre-clinical drug discovery and toxicological investigations. Here, we present a review regarding the role of different excitatory and inhibitory neurotransmitter systems in zebrafish, such as dopaminergic, serotoninergic, cholinergic, purinergic, histaminergic, nitrergic, glutamatergic, glycinergic, and GABAergic systems, and emphasizing their features as pharmacological and toxicological targets. The increase in the global knowledge of neurotransmitter systems in zebrafish and the elucidation of their pharmacological and toxicological aspects may lead to new strategies and appropriate research priorities to offer insights for biomedical and environmental research.

1. Introduction

Neurotransmitters are chemical messengers that initiate, amplify, and modulate signals between neurons and other cells in the body. Neuronal activity depends on the balance between the number of excitatory and inhibitory processes affecting it, which may occur individually or simultaneously (Prange et al., 2004). In addition, neurological and psychiatric disorders are associated with the abnormal production or function of neurotransmitters, and experimental approaches involving transporters, receptors, and enzymes in such conditions have been characterized (Raiteri, 2006). These assays include the analysis of various neurotransmitter characteristics, such as localization, function, and pharmacological properties (Raiteri, 2006). In this context, there is a growing interest in biological models to investigate the basis of neurotransmission. Although many researchers study these parameters through cell culture methods, using the whole organism allows the screening of processes that are not easily replicated in vitro, such as organ development. Furthermore, drug metabolism is an important factor for the conservation of drug activity across species. Despite that in vitro studies provide speed and efficiency to screen a larger number of compounds, whole organisms offer advantages over cell lines for chemical genetic screens, which provide information regarding tissue specificity, toxicity, and biologic availability.

The zebrafish has become a promising model in many research areas, including neuroscience, developmental biology, toxicology, transgenic research, vertebrate genome evolution, and teratology (Lele and Krone, 1996; Vascotto et al., 1997; Ivetac et al., 2000; Bowman and Zon, 2010). Additionally, it has been shown that the zebrafish genome shares similarities with the human genome (Barbazuk et al., 2000). The characterization of alternative animal models, which permits embryologic and molecular screenings, contributes to a better knowledge of neurochemical mechanisms and helps in drug development and

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screening. Besides the zebrafish has been used to screen novel compounds and small molecules as a starting point for drug discovery, it has been an emergent vertebrate model for analyses of transcriptome, proteome, and metabolome (Sukardi et al., 2010).

Neurotoxicity can result from exposure to drugs used for chemotherapy, radiation treatment, and organ transplantation as well as from food additives and environmental toxins (Parng et al., 2007). The ability to examine the nervous system and visually evaluate the brain in early stages of development makes the zebrafish an exceptional model for neurotoxicity assessments. The investigation of environmental toxins (e.g., organic compounds and heavy metals) on zebrafish neurotransmission has been used to understand the biological basis of the cumulative effects of pollutants and other chemicals. Technological advancements and knowledge of the zebrafish genome have allowed for the development and improvement of sophisticated strategies such as mutant individuals, genetic and tissue manipulation, morpholinos and microarray technology. The development of new bioassays for toxic and therapeutic endpoints in this species has contributed to the understanding of mechanisms triggered by chemical toxicity (Hill et al., 2005). These advances, associated to the simplicity of evaluating the morphological, biochemical, and physiological information at all stages of early development in juveniles and adults of both sexes, make this species ideal for identifying the adverse effects of chemical exposure. This review will focus on the role of different excitatory and inhibitory neurotransmitter systems in the zebrafish, including dopaminergic, serotoninergic, cholinergic, glutamatergic, purinergic, histaminergic, nitric oxide synthase, glycinergic, and GABAergic systems (Fig. 1). Furthermore, we will emphasize their importance and potential application for pharmacological and toxicological studies.

2. Dopamine and serotonin

The aminergic neurotransmitters, including dopamine (DA) and serotonin (5HT), mediate several important brain functions. Abnormalities in their levels have been implicated in distinct human central nervous system (CNS) diseases (Belmaker, 2008; Murray et al., 2008). Although dopaminergic neurons account for less than 1% of the total neuronal population of the brain, they have important effects on brain physiology. For example, DA regulates locomotion, cognition, emotion, and reward (Goldman-Rakic, 1998; Schultz, 2002). The effects promoted by DA are mediated by a group of G-protein-coupled receptors (Nürnberger et al., 2004). In mammals, there are five dopamine receptor (DR) subtypes that are grouped into two families, D_1 and D_2, based on pharmacological profiles and sequence similarities (Callier et al., 2003; Surmeier et al., 2007). The D_1 family consists of the D_1 and D_5 receptor subtypes, and the D_2 family comprises the D_2, D_3, and D_4 receptors (Callier et al., 2003). Dysfunction in dopaminergic neurotransmission is associated with a variety of neuropathologies, such as Parkinson's disease, Tourette syndrome, and schizophrenia (Missale et al., 1998). The neurotransmitter serotonin is an important modulator of brain physiology and behavior, and it plays a fundamental role during development and plasticity in the vertebrate CNS (Daubert and Condron, 2010). The serotonergic neurons in the mammalian CNS are primarily located in the raphe nuclei, and they innervate nearly all regions of the brain (Sallinen et al., 2009). Serotonin regulates perception, aggressiveness, anxiety, sexual behavior, appetite, vascular function, and pain (Lucki, 1998; Parsey, 2010). In addition to neural communication, serotonin plays fundamental developmental roles and influences plasticity in the vertebrate CNS (Cote et al., 2007; Fricker et al., 2005; Gaspar et al., 2003). Importantly, the dysfunction of serotonergic neurons during development or adulthood has been implicated in several psychiatric diseases, including depression, drug addiction, and schizophrenia (Lucki, 1998; Sallinen et al., 2009).

Zebrafish dopaminergic and serotonergic systems share similarities to respective mammalian systems, making this species a feasible model for evaluating the general properties of both systems (Panula et al., 2006; Flinn et al, 2008). During the last decade, the zebrafish has been suggested as a tool for the analysis of the effects of alcohol on adult brain function (Gerlai et al., 2000; Gerlai et al., 2009). Alcoholism is known to affect aminergic neurons and can lead to abnormalities in the levels of aminergic neurotransmitters, resulting in significant behavioral changes (Rodd-Henricks et al., 2000; Thielen et al., 2004). For example, intermediate doses of alcohol (0.25–0.50%, v/v), when administered acutely, were shown to increase locomotor activity and aggression (Gerlai et al., 2000). Shoaling, a form of social behavior also known as group preference, was also impaired by increasing doses of acute alcohol exposure (Gerlai et al., 2008). Moreover, behavioral responses to a predator or its computer-animated image were enhanced or impaired after acute exposure to intermediate or high alcohol doses, respectively (Gerlai et al., 2000, 2008). In addition, Chatterjee and Gerlai (2009) showed significant changes in levels of 5HT and DA and their metabolites in zebrafish after alcohol treatment (Chatterjee and Gerlai, 2009).

Dopaminergic deficiency in the zebrafish brain has been previously induced by systemic administration of catecholaminergic neurotoxins, 6-hydroxydopamine (6-OHDA) and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (Anichtchik et al., 2004). The levels of dopamine and noradrenaline decreased significantly after the injection of MPTP and 6-OHDA. These drugs also caused neurotransmitter-associated behavioral changes; for example, general locomotor activity (distance moved and velocity) was markedly decreased, and the fish altered the swimming patterns (Anichtchik et al., 2004). Silver nanoparticle consumption can alter the levels of dopamine and behavior in zebrafish. A recent report demonstrated that nervous system development is disrupted in zebrafish exposed to Ag^+ (Powers et al., 2011). Ag^+ is a developmental neurotoxin that causes persistent neurobehavioral effects, reinforcing health concerns regarding the Ag^+ that is released from silver nanoparticles. In addition, early developmental exposure to Ag^+ elevated the DA and 5HT turnover in adult zebrafish (Powers et al., 2011).

Giacomini et al. (2006) investigated the effects of antipsychotics on larval zebrafish. The antipsychotics haloperidol and fluphenazine produced hypoactivity associated with erratic swimming bouts, which were rescued by coadministration with the dopamine precursor levodopa (Giacomini et al., 2006). Clozapine, an atypical antipsychotic, also induced hypoactivity. Interestingly, this effect was prevented by the D_4 receptor selective agonist ABT-724, but not by quinpirole, a D_2/D_3 agonist, which produces hyperactivity in zebrafish larvae (Boehmler et al., 2007). The acute administration of fluoxetine, a selective serotonin reuptake inhibitor, produces a hyperlocomotor effect accompanied by diminished expression of the serotonin transporter protein and the 5-HT_{1A} receptor in the spinal cord, but not in the zebrafish larval brain (Airhart et al., 2007). Other researchers have reported that the hallucinogenic drug lysergic acid diethylamide (LSD), a nonselective serotonin receptor agonist, produces a pattern of disorganized exploration in many models, including the novel tank diving test and the scototaxis test (Grossman et al., 2010).

These studies highlight the potential role of dopaminergic and serotonergic systems in zebrafish. Further evidence is required to clarify the impact of changes in these neurotransmitter systems on brain development in this species as well as their implications for potential pharmacological targets.

3. Acetylcholine

Acetylcholine (ACh) is a signaling molecule that elicits several actions at neuromuscular junctions and in the CNS (Panula et al., 2010). This molecule activates two classes of receptors (AChRs): the ionotropic nicotinic ACh receptors (nAChRs) and G-protein-coupled muscarinic AChRs (mAChRs). Whereas the mAChRs may be involved in neurotransmission, neuromodulation (Brown, 2010), and olfactory

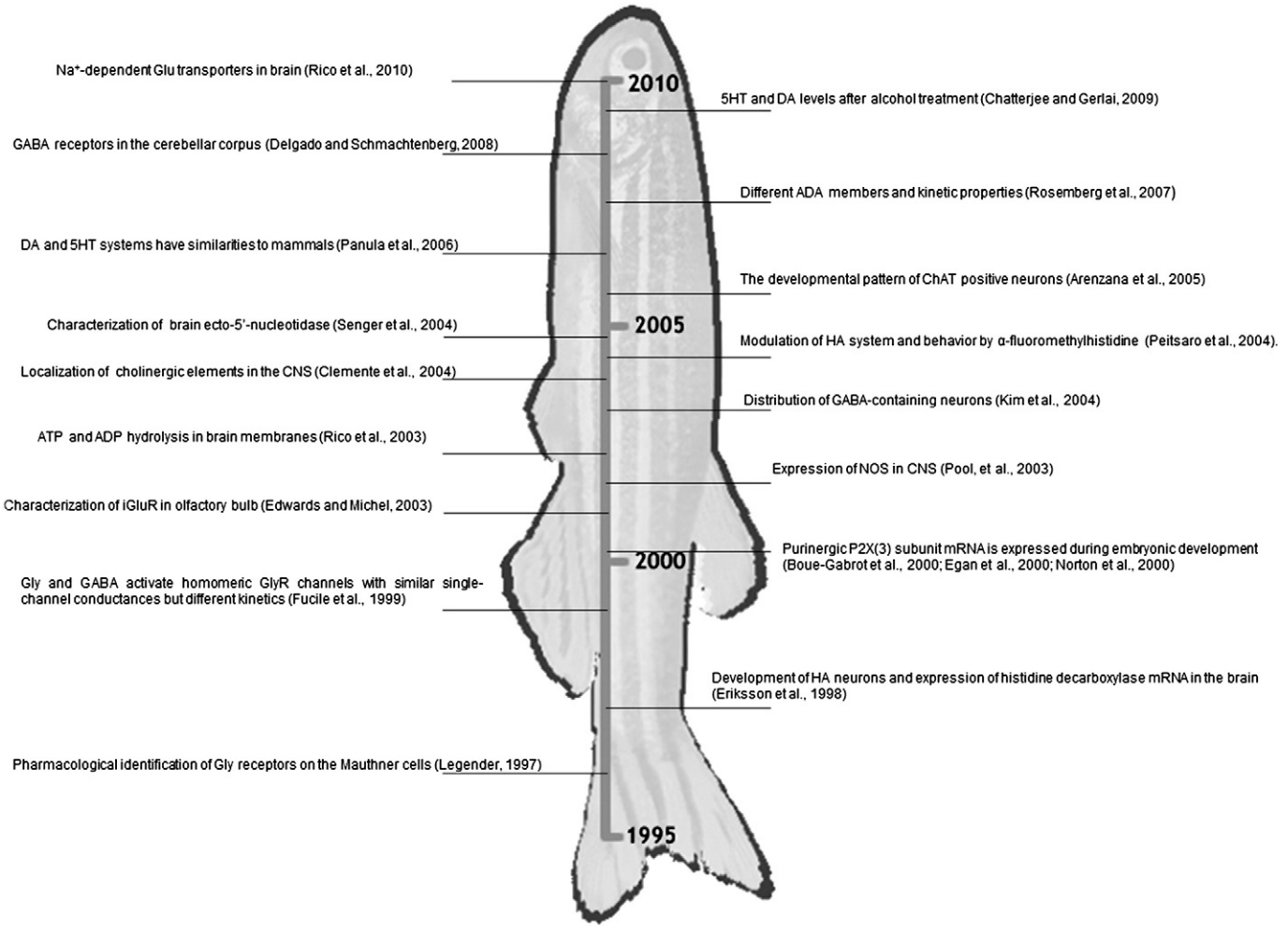

Fig. 1. Research hallmarks regarding neurotransmission in zebrafish. The timeline shows important studies related to proteins (enzymes, receptors, transporters) involved in neurotransmitter systems over the last few decades. Abbreviations: ADA, adenosine deaminase; ChAT, choline acetyltransferase; CNS, central nervous system; DA, dopamine; GABA, Gamma amino butyric acid; Gly, glycine; GlyR, glycine receptor; Glu, glutamate; HA, histamine; iGluR, ionotropic glutamate receptor; NOS, nitric oxide synthase; P2X(3), ionotropic purinergic receptor 3; 5HT, serotonin.

mechanisms (Durand et al., 1998), the nAChR plays a key role in modulating glutamate release (Alkondon et al., 1996) and memory formation (Kenney et al., 2010). Activation of nAChRs may directly depolarize cells or exert a neuromodulatory role by controlling neurotransmitter release (Vizi and Lendvai, 1999). The fine-tuned regulation of ACh-mediated signaling is performed by the activity of acetylcholinesterase (AChE, EC 3.1.1.7). This enzyme is a serine hydrolase related to the type B carboxylesterase family, which cleaves ACh into choline and acetate, effectively terminating cholinergic transmission. The de novo synthesis of ACh is dependent on choline acetyltransferase (ChAT, EC 2.3.1.6) activity, which catalyzes the reaction of acetate and choline in pre-synaptic neurons (Jamal et al., 2009).

The identification of cholinergic neurons in the zebrafish CNS has been previously reported by using specific antibodies against ChAT (Clemente et al., 2004; Kaslin et al., 2004; Mueller et al., 2004). Because of the different methodological approaches used, the anatomical identification of ChAT immunoreactive neurons differs among these studies. For example, Mueller et al. (2004) detected significant staining only in the lateral nucleus of the ventral telencephalic area, whereas Kaslin et al. (2004) observed ChAT immunoreactivity in the central, dorsal and subcommissural nuclei of the ventral telencephalic area of adults. In the diencephalon, the preoptic area, dorsal thalamus, pretectal nucleus and hypothalamus showed distinct ChAT positive staining. Prominent staining was also detected in the mesencephalon, whereas the optic tectum (OT) and tegmentum showed immunoreactive cells (Clemente et al., 2004; Kaslin et al., 2004; Mueller et al., 2004). The primary developmental pattern of ChAT-positive neurons was described for the zebrafish (Arenzana et al., 2005). In this study, it was demonstrated that, at 60 hours post-fertilization (hpf), the tegmental ChAT positive neurons may be identified within the oculomotor, trochlear and rostral tegmental nuclei, whereas the tectal cholinergic neurons develop only at 5 days post-fertilization (dpf).

The mAChRs have been characterized in the zebrafish brain by radioligand binding techniques (Williams and Messer, 2004). These authors suggested that, similar to rodents, this species might be a useful model for evaluating the role of cholinergic systems in learning, memory, and behavior. Moreover, Steele et al. (2009) showed that the M(2) muscarinic receptor plays a role in the initiation of hypoxic bradycardia in larval zebrafish at 4 dpf. The role that nicotine plays in memory and behavioral tasks has already been reported in adult zebrafish (Levin and Chen, 2004; Levin et al., 2007). In these studies, low nicotine doses significantly improved fish memory, whereas higher doses induced memory impairment (Levin and Chen, 2004). Additionally, a nicotine-induced anxiolytic effect in zebrafish has been suggested by studies that evaluate vertical swimming in the novel tank paradigm (Levin et al., 2007), and both nicotinic α7 and α4β2 receptors can be involved in this response (Bencan and Levin, 2008). Considering the effects of organophosphate pesticides, a recent study showed that the zebrafish is sensitive to chlorpyrifos exposure during development, resulting in persisting developmental neurobehavioral

effects. A putative role for AChR was suggested to trigger these effects (Eddins et al., 2010).

There is evidence suggesting that AChE activity and expression are important for regulating zebrafish brain function. The early expression of AChE in diverse cell types suggests that it may play a role during development and may thus be a target for neurotoxicity in zebrafish (Hanneman and Westerfield, 1989). Several studies have evaluated the effects of metals (Senger et al., 2006a, 2006b; Richetti et al., 2011), typical and atypical antipsychotics (Seibt et al., 2009), methanol (Rico et al., 2006), antiepileptics (Siebel et al., 2010), and ethanol (Rico et al., 2007) on AChE activity in the zebrafish brain. These data suggest that altering the activity of this enzyme may impair ACh-mediated neurotransmission in this species, supporting the idea that cholinergic signaling may be affected by toxins and drugs of abuse. Importantly, the development of strategies to maintain and/or prevent drug-induced changes in AChE activity is an interesting approach for future translational research. A recent report demonstrated that the effects of ethanol on AChE activity may be related to changes in oxidative stress parameters, which were prevented by pretreatment with taurine (Rosemberg et al., 2010a). Although the mechanisms underlying these changes in AChE activity still remain to be elucidated, these studies highlight the need to evaluate the potential effects of distinct drugs/toxins on other neurotransmitter systems. Because ATP may be co-released at the synaptic cleft with ACh, several reports have aimed to correlate modifications in cholinergic neurotransmission with changes in purinergic signaling parameters (Senger et al., 2006b; Rico et al., 2006, 2007, 2008).

Based on these data, the evaluation of cholinergic system parameters has emerged as an important strategy to assess neurochemical, behavioral, and toxicological phenotypes in both larval and adult zebrafish. Advances in the knowledge of several behavioral paradigms (Rosemberg et al., 2011) associated with pharmacological/toxicological manipulations provide useful tools for understanding how alterations in these neurotransmitter systems correlate with changes in the behavior of this species.

4. Purine nucleotides and nucleosides

Nucleosides and nucleotides exert their actions through the activation of specific membrane purinoceptors, which are divided into the two purinergic receptor families, P1 and P2 (Burnstock, 1978). Purinergic receptors are divided based on their response to specific agonists and molecular cloning (Burnstock and Kennedy, 1985). Extracellular nucleotides exert their effects through two major receptor subfamilies: P2X receptors are ligand-gated ion channels comprising a family of seven receptors, and P2Y receptors are a group of eight G-protein coupled receptors (Khakh et al., 2001; Abbracchio et al., 2006). In mammals, there are seven known P2X receptor subtypes ($P2X_{1-7}$) and eight P2Y receptor subtypes ($P2Y_1$, $P2Y_2$, $P2Y_4$, $P2Y_6$, $P2Y_{11}$, $P2Y_{12}$, $P2Y_{13}$, and $P2Y_{14}$) (Abbracchio et al., 2006). Neurotransmission through P2X receptors is considered a short-term effect and is primarily mediated through ATP binding, whereas long-term effects, such as cytotoxicity, cell proliferation, differentiation and migration, are primarily mediated through P2Y receptors, which bind both purine and pyrimidine nucleotides (Agresti et al., 2005). Considering their importance for cell signaling, the concentration of extracellular nucleotides is tightly regulated by a variety of cell surface enzymes called ectonucleotidases. These enzymes hydrolyze nucleoside triphosphates, diphosphates and monophosphates to their respective nucleosides (Zimmermann, 2001; Yegutkin, 2008). There are four major families of ectonculeotidases in mammals, namely, E-NTPDases (ectonucleoside triphosphate diphosphohydrolases), E-NPPs (ectonucleotide pyrophosphate/phosphodiesterases), alkaline phosphatases and ecto-5′-nucleotidase (Robson et al., 2006; Schetinger et al., 2007). Additionally to their role in the inactivation of purinergic signaling, ectonucleotidases have been proposed to prevent P2 receptor desensitization (Enjyoji et al., 1999) and to control the availability of ligands for nucleotide and adenosine receptors (Bonan et al., 2001). Adenosine, the product of ATP catabolism, has anticonvulsant, neuroprotective, and antinociceptive roles (Van Dycke et al, 2010; Paterniti et al, 2011). This nucleoside exerts these effects through the activation of four G-protein-coupled receptor subtypes: A_1, A_{2A}, A_{2B} and A_3 (Burnstock, 1978).

The purinergic system has been studied in zebrafish through the characterization of P2 and P1 receptors as well as the enzymes involved in the control of nucleotide and nucleoside levels. A P2X subunit cloned from the zebrafish has been identified as an ortholog of the mammalian P2X(3) subunit (Egan et al., 2000). In addition, zebrafish P2X(3) subunit mRNA is exclusively expressed at high levels in trigeminal neurons and Rohon-Beard cells during embryonic development (Boué-Grabot et al., 2000; Norton et al., 2000). Recently, it has been shown that *p2rx3.1* in ectodermal cells is involved in purinergic signaling that is essential for proper craniofacial development and sensory circuit formation in embryonic and larval zebrafish (Kucenas et al., 2009). The cloning and characterization of the zebrafish P2X(4) and P2X(5) subunits were also performed (Diaz-Hernandez et al., 2002), and a more complete analysis of the P2X family identified nine genes. Of these, six are orthologs of mammalian genes, two are paralogs of previously described zebrafish subunits, and one remains unclassified (Kucenas et al., 2003). Specifically, *p2rx2*, *p2rx3.1*, *p2rx3.2* and *p2rx8* were expressed in the trigeminal ganglia and Rohon-Beard neuronal subsets. In contrast to mammals, *p2rx2* was not expressed in hypocretin cells (Appelbaum et al., 2007). Previous studies also provide evidence for the presence of a P2Y1 receptor in zebrafish thrombocytes (Gregory and Jagadeeswaran, 2002). Regarding P1 receptors, two zebrafish A2A (*adora2a.1 and adora2a.2*) genes and one A_2B (*adora2b*) adenosine receptor gene were identified in the CNS of developing embryos. Moreover, caffeine, an A_2A adenosine receptor antagonist, is neuroprotective against the adverse effects of MPTP in zebrafish embryos, which suggests that these receptors may serve as useful targets for testing novel therapeutic strategies for the treatment of Parkinson's disease (Boehmler et al., 2009).

The NTPDase and ecto-5′-nucleotidase activities were described in zebrafish brain membranes, and these enzymes share several kinetic properties with the enzymes previously identified in mammals (Rico et al., 2003; Senger et al., 2004). Homology-based searches identified the presence of NTPDase1-6 and NTPDase8 orthologs, and the phylogeny also grouped three NTPDase2 and two NTPDase5 paralogs (Rosemberg et al., 2010b). A distinct expression profile for *entpd1-6* and *entpd8* was observed in the brain, liver, and heart of zebrafish (Rosemberg et al., 2010b), and studies also showed that *entpd3* was expressed with *p2rx8* in the hypothalamic region (Appelbaum et al., 2007). In the zebrafish retina, NTPDases1 and 2 appear to be expressed within the germinal margin, which contains proliferative and differentiating cells (Ricatti et al., 2009). Another enzyme involved in the control of purinergic signaling is adenosine deaminase, which is responsible for cleaving the neuromodulator adenosine into inosine. Two members of the ADA subfamily, ADA1 and ADA2, were described, and the evidence showed another similar protein group, called ADAL (adenosine deaminase-like). The existence of different ADA-related genes, their distinct expression patterns and a truncated *ADA2-1* isoform suggests a high degree of complexity within the zebrafish adenosinergic system (Rosemberg et al., 2007a). The kinetic properties of these enzymes in the membrane and soluble fractions from zebrafish brains were determined, and the results indicate that the presence of ADA activity is important for regulating the adenosine/inosine levels in the zebrafish CNS (Rosemberg et al., 2008).

Several studies have demonstrated that these enzymes may be a target of the neurotoxic effects induced by pesticides, alcohols, and metals. Exposure to carbofuran and malathion for seven days significantly decreased ADP and AMP hydrolysis in zebrafish brain

membranes (Senger et al., 2005). Other organic compounds, such as methanol and ethanol, also induced significant changes in extracellular nucleotide and nucleoside levels. Methanol or ethanol exposure for one hour decreased NTPDase activity and NTPDase1 and mRNA transcript levels for three NTPDase2 genes in the zebrafish brain. However, no significant alterations in ecto-5′-nucleotidase activity were observed after exposure to methanol or ethanol (Rico et al., 2006, 2008). Exposure to lead and mercury for 24 h, 96 h or 30 days caused differential inhibitory effects on ATP, ADP and AMP hydrolysis, whereas no significant changes were found in the expression of NTPDase1 and 5′-nucleotidase following 30 days of exposure to both metals (Senger et al., 2006a). Soluble ADA activity also decreased after both acute (24 h) and subchronic (96 h) exposure to mercury, whereas enzyme activity was inhibited only after subchronic exposure in brain membranes. Semiquantitative RT-PCR analysis showed that mercury chloride did not alter ADA gene expression (Senger et al., 2010). Acute copper treatment for 24 hours decreased ATP hydrolysis; however, subchronic treatment for 96 hours inhibited both NTPDase and ecto-5′-nucleotidase activities. In contrast to the findings observed for other metals, NTPDase1, NTPDase2_mg and NTPDase2_mv transcripts were decreased after copper exposure for 24 and 96 h. Subchronic copper treatment also reduced NTPDase2_mq and ecto-5′-nucleotidase expression (Rosemberg et al., 2007b). The co-existence of several enzymes in the zebrafish CNS represents a sophisticated route for the appearance and inactivation of extracellular nucleotides on the cell surface. Therefore, the regulation of the nucleotidase pathway and, consequently, of the nucleotide levels may play a modulatory role during the evolution of neurotoxicity initiated by metals, pesticides, and organic compounds. Thus, identifying toxicant-induced changes and the mechanisms by which these enzymes regulate local nucleotide and nucleoside concentrations may represent important strategies for better understanding their role as a potential target for neurotoxins.

5. Histamine

Histamine (HA) is a biogenic amine widely distributed in the human brain (Lipinski et al., 1973), and its synthesis is induced by the enzyme L-histidine descarboxylase. HA acts through at least four types of G-protein-coupled receptors in mammals: the H1, H2, H3, and H4 receptors (Liu et al., 2001). The organization of the histaminergic system (HS) appears to be similar in all vertebrates (Panula et al., 1984). The HS is involved in several brain regulatory mechanisms, including alertness and sleep, hormone regulation, circadian rhythms, locomotor activity, consciousness, memory, and eating/drinking (Schwartz et al., 1991; Haas and Panula, 2003). Furthermore, this system may be associated with neuropsychiatric diseases such as schizophrenia (Jin et al., 2009), Alzheimer's (Panula et al., 1998) and Parkinson's disease (Anichtchik et al., 2000). In the zebrafish brain, histaminergic innervations and the molecular cloning and expression of L-histidine descarboxylase have been described (Eriksson et al., 1998). The zebrafish HS resembles that of other vertebrates; however, HA concentrations are slightly lower in zebrafish brain compared to higher vertebrates (Yamatodani et al., 1991). The HA content in the adult zebrafish brain varies with circadian rhythms, with decreased concentrations during the light period, which is similar to what is observed in rodents (Mochizuki et al., 1992).

In zebrafish embryos, the first histamine-immunoreactive neurons appear in the ventral hypothalamus at about 85 hpf. At 90 h, immunoreactive fibers can be observed terminating in the dorsal telencephalon. The HS appears during the period when the larva begins actively searching for prey, suggesting that this system may play a role in alertness (Eriksson et al., 1998). The HA-immunoreactive neurons that first appear in the larva likely belong to the same population of adult neurons because they are also located in the developing ventral hypothalamus and innervate the rostrodorsal telencephalon, a major projection area in adults. In zebrafish, this area corresponds to the mammalian amygdala and hippocampus, which are densely innervated by histaminergic fibers (Eriksson et al., 1998; Peitsaro et al., 2003). The HS may have a similar role for alertness in the zebrafish tectum opticum (TeO). In addition to the TeO, the dorsal telencephalon and the torus semicircularis also receive dense histaminergic innervation (Northcutt, 1981; Meek, 1990).

The histamine H3-like receptor and the H3-related G-protein have been described in the zebrafish brain (Peitsaro et al., 2000). All three zebrafish HA receptors are expressed in the brain. Binding sites for H2 and H3 ligands were identified in zebrafish brains in areas that correspond to those in mammals (Peitsaro et al., 2000). In addition, the H1 receptor is expressed in the intestine, liver, and spleen, whereas the H2 receptor was found peripherally in the gills, heart, and spleen (Peitsaro et al., 2007).

Studies have shown that changes in HA levels alter behavior (Peitsaro et al., 2003). HA levels in the zebrafish brain can be reduced by α-fluoromethylhistidine administration, and this decrease is associated with changes in exploratory behavior and T-maze performance. These changes may be due to reduced anxiety and some memory-related mechanisms following HA depletion (Peitsaro et al, 2003). As demonstrated by Renier et al. (2007), histaminergic H1 antagonists produce a concentration-dependent reduction in immobility, with higher concentrations producing a state of complete unresponsiveness similar to general anesthesia. Because few studies exist that focus on behavior and pharmacology in the HS of zebrafish, further investigations are necessary to evaluate the role of this system in toxicity processes.

6. Nitric oxide

Nitric oxide (NO) is formed by endogenous NO synthase (NOS) and is involved in various normal, pathophysiological, and developmental events, which suggests that it participates in plasticity processes (Cramer et al., 1998; Moncada et al., 1998). NO is a free radical that is formed from L-arginine in biological tissues by three major NOS isoforms, including neuronal NOS (nNOS), endothelial NOS (eNOS) and inducible NOS (iNOS), by using nicotinamide adenine dinucleotide phosphate (NADPH) as a cofactor (Alderton et al., 2001). In teleosts, NO plays a role in the development of the CNS during the embryonic and post-embryonic life stages (Fritsche et al., 2000). Holmqvist et al. (2000) demonstrated that nNOS mRNA-expressing cell populations are closely associated with the proliferation zones that generate new cells throughout life, which include the ventricular regions of the telencephalon, diencephalon, and mesencephalon. The expression of NOS in zebrafish embryos was detected at 16 hpf in the hypothalamus, and it was present in discrete CNS locations after 3 dpf (Pool et al., 2007). Since there are few studies about the functional role of NO in zebrafish, further investigations are necessary to evaluate changes in this signaling system induced by pharmacological approaches and toxic agents.

7. Glutamate

Glutamate is the primary excitatory neurotransmitter in the vertebrate CNS. Many biological events are affected by the modulation of glutamatergic signaling (Ozawa et al., 1998; Anderson and Swanson, 2000), such as memory and learning (Izquierdo and Medina, 1997), development and aging (Segovia et al., 2001), and adaptation to the environment (Mattson et al., 2002). However, the glutamate concentration profile at the synaptic cleft is variable and may also act as an excitotoxin at high concentrations due to receptor overstimulation (Anderson and Swanson, 2000; Danbolt, 2001; Maragakis and Rothstein, 2004). Glial cells are essential for maintaining extracellular glutamate concentrations below neurotoxic levels, and this is achieved by high-affinity sodium-dependent glutamate transporters primarily present in

astrocytes (Chen and Swnason, 2003). Glutamate toxicity has been associated with neuronal death following ischemia and trauma (Choi, 1988; Ikonomidou et al., 1989), as well as with several neurodegenerative disorders, such as Huntington's and Alzheimer's diseases (Brewer, 2000; Ingram et al., 2001; Maragakis and Rothstein, 2001, 2004; Segovia et al., 2001).

Several studies have emerged that aimed at identifying and understanding the basis of glutamatergic signaling. Glutamate uptake is tightly regulated by a group of excitatory amino acid transporters (EAATs) that belong to the solute carrier family 1 (SLC1). To date, five structurally distinct subtypes of EAATs have been identified and characterized in the mammalian brain. The presence of EAAT-related sequences has been recently described by phylogenetic analysis and mRNA expression profiling in the zebrafish CNS (Rico et al., 2010). Furthermore, the evolutionary history of EAATs was also analyzed, and these members were included in the SLC1 gene family (Gesemann et al., 2010; Neuhauss et al., 2010). After these EAAT-related genes were identified, glutamate transporter activity was investigated in the zebrafish by assessing sodium-dependent glutamate uptake in distinct brain structures (Rico et al., 2010).

Hair cells are the sensory receptors for the auditory and vestibular system in zebrafish. They detect sound and movement and transmit this information through specialized ribbon synapses, which coordinate synaptic vesicles. In one study, hair cells presented a decrease in the number of ribbon-associated synaptic vesicles in zebrafish with mutations in vesicular glutamate transporter 3 (*vglut3*), indicating the involvement of the glutamate transporter during synaptic transmission (Obholzer et al., 2008). This family of proteins mediates glutamate uptake by synaptic vesicles, which is necessary for glutamatergic transmission in the retina. Other researchers reported that the zebrafish vesicular glutamate transporter 2 (*vglut2*) is expressed in retinal ganglion cells and is partially responsible for glutamatergic transmission at the retinotectal synapse (Smear et al., 2007; Demas and Cline, 2007).

Glutamate receptors are divided into two main categories: metabotropic (mGluRs) and ionotropic receptors (iGluRs). The mGluRs trigger intracellular secondary messengers through G-proteins. In contrast, the iGluRs are ligand-gated ion channels that manage rapid changes in sodium, calcium, and potassium concentrations. The subtypes of iGluRs include N-methyl-D-aspartate (NMDA), the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA) and kainate (KA). The molecular characterization and embryonic expression of the family of NMDA receptor subunit genes have already been established in zebrafish (Cox et al., 2005). Moreover, behavioral and neuroanatomical studies have shown that the brain area responsible for learning in teleost fish is the telencephalon, which is analogous to the hippocampus and amygdala in the mammalian brain (Portavella et al., 2002; Rodríguez et al., 2002). Long-term potentiation (LTP) is representative of the synaptic modification that underlies the process of learning and memory. Nam et al. (2004) demonstrated NMDA receptor-dependent LTP in the telencephalon of the zebrafish. In this context, a simple inhibitory avoidance task in adult zebrafish showed that the resulting memory is robust, long-lasting and sensitive to the NMDA-receptor antagonist MK-801, which was added to the tank water immediately after training (Blank et al., 2009).

Each iGluR subtype has unique properties, including activation/deactivation kinetics, ion permeability, voltage-dependence and kinase regulation. A variation in the subunit composition of each iGluR further contributes to the unique cellular responses elicited by glutamate (Nakanishi et al., 1994). Edwards and Michel (2003) demonstrated the pharmacological characterization of iGluRs in the olfactory bulb. This group advanced the understanding of the glutamatergic system in teleosts by characterizing the distribution of functional NMDA and KA-stimulated neurons. Furthermore, Tabor and Friedrich (2008) pharmacologically investigated the iGluR function in zebrafish olfactory bulb neuronal circuits.

Studies also exist that evaluate glutamatergic signaling beyond the CNS. There is growing interest in understanding the role of signaling molecules in visual function in zebrafish retina. Previous studies on the localization of the glutamatergic system in the zebrafish outer plexiform layer (OPL) have shown glutamate-immunoreactivity in rod and cone photoreceptors (Connaughton et al., 1999). In addition to the visual system, glutamate receptors were found in the peripheral nervous system. The activation of iGluRs on the peripheral axons of primary motor neurons mediates neurotransmitter release at the zebrafish neuromuscular junction (Todd et al., 2004). Considering the wide spectrum of biological functions involving the glutamatergic system, it becomes important to evaluate this signaling system as a target of toxicological and pharmacological agents.

8. Glycine and GABA

The correct development of the spinal cord leads to the normal control of movements and the integration of signals from the periphery. To promote this integration, several types of neurons and neurotransmitter systems must work synchronously. A balance of both excitatory (glutamate) and inhibitory (glycine and GABA) neurotransmitters are involved in this process. Glycine receptors (GlyRs) and GABA receptors are members of the ligand-gated chloride channel family. As one of the predominant inhibitory neurotransmitters in the vertebrate brain stem and spinal cord, glycine is also critically important for the regulation of interneuron differentiation during the development of the central neural network (McDearmid et al., 2006). GABA and glycine-mediated neurotransmission arise relatively early in fish development, as shown by the circuitry underlying locomotor behaviors such as the escape response and rhythmic swimming, which are established soon after the patterning of the hindbrain and spinal cord (Saint-Amant and Drapeau, 2000). Two types of postsynaptic glycinergic receptors, with different subconductances and sensibilities to picrotoxin, were pharmacologically identified on Mauthner cells in zebrafish larvae (52 hpf) (Legendre, 1997). These types of postsynaptic receptors have been identified as the determinant receptors that control synaptic events in Mauthner cells (Legendre, 1998). Relative mRNA levels from glycine transporters (GlyT1 and GlyT2), NMDA receptor glycine binding subunit (NR1.1), and the *alpha 1* subunit of the glycine receptor (GlyRα1) have also been measured in Mauthner cells (Mongeon et al., 2008). Zebrafish GlyT1 mutants initially present with dysfunction in motility; however, proper swimming behavior is later recovered by a mechanism involving glycine tolerance and reduced glycine receptor expression (Mongeon et al., 2008). Mutants that are defective in glycinergic synaptic transmission due to a lack of synaptic aggregation of GlyRs exhibit simultaneous motor neuron activation on both sides, resulting in bilateral contraction of the axial muscles (Hirata et al., 2010).

GABA-containing neurons appear in the zebrafish olfactory bulb (OB), telencephalon, tectum stratum, and in the hypothalamus (Kim et al., 2004). In the cerebellar corpus and valves of the zebrafish, GABA receptors are present in the molecular layer, Purkinje cells and groups of Golgi cells in the granular layer (Delgado and Schmachtenberg, 2008).

In zebrafish, glycine and GABA activate homomeric GlyR channels with similar single-channel conductances but different kinetics (Fucile et al., 1999). The glycinergic and GABAergic inhibitory control of motor neurons and the balance between excitatory and inhibitory synapses on interneurons and motor neurons underlies the normal functioning of locomotor circuits that produce rhythmic motor output (Grillner et al., 1995; Hultborn and Nielsen, 2007). Thus, because neurological effects can be detected by movement disorders, these systems are key candidates for neurotoxicological assessment. However, few studies contribute to the study of this topic. One report using a phenylpyrazole insecticide (fipronil) on zebrafish embryos

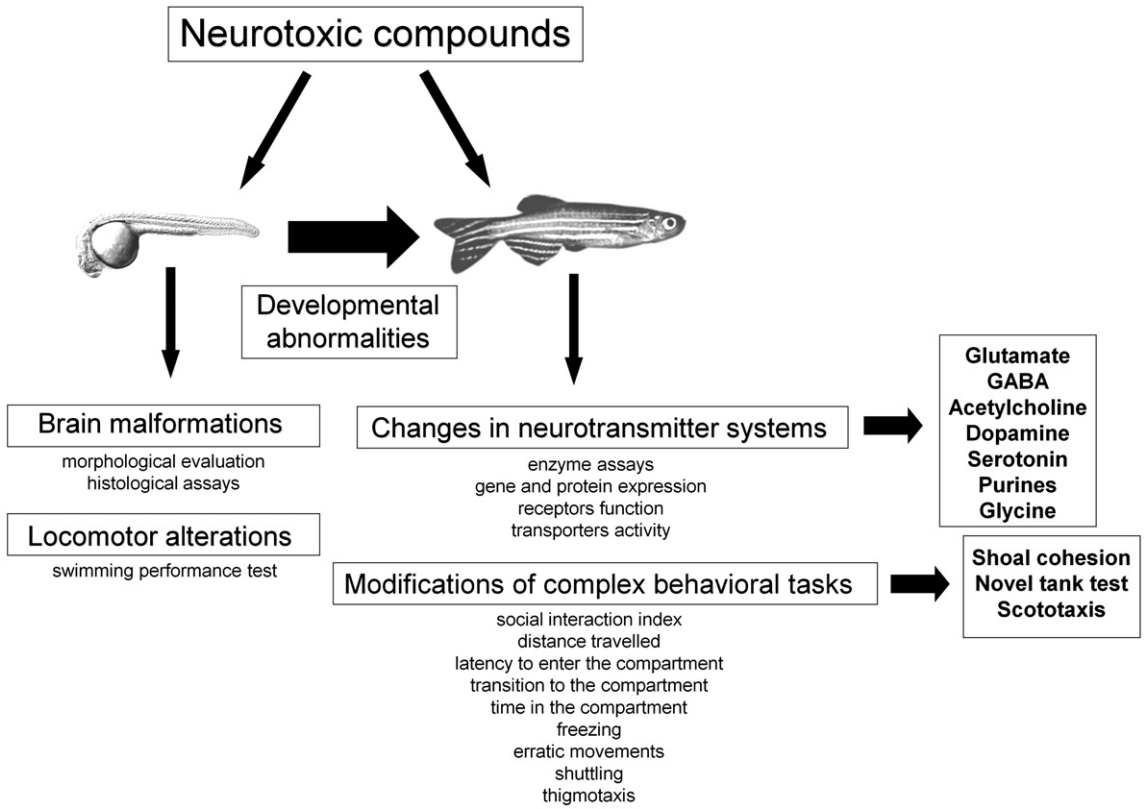

Fig. 2. The zebrafish model offers the potential to evaluate the effects of several compounds. This figure illustrates emerging approaches and perspectives for studying cellular, morphological, physiological, and behavioral aspects using larval and adult zebrafish. The strategies described are interesting tools for testing the potential neuroprotective activities of distinct compounds in a fast and large-scale manner.

shows that, although this insecticide is an inhibitor of GABA receptors, it may inhibit a structurally related GlyR subtype expressed during the development of spinal locomotor pathways in zebrafish. This inhibition of GlyR had no effect on the morphology of zebrafish embryos until 30 hpf; however, after this period, embryos began to show reduced body length, notochord degeneration, abnormal axial muscle morphology, and locomotor defects.

The use of zebrafish as a complementary vertebrate model for the evaluation of seizures induced by GABA antagonists has also emerged. Baraban et al. (2005) reported that the exposure to the common convulsant agent, pentylenetetrazole, induced changes in zebrafish behavior, neural activity and significantly increased *c-fos* expression. Moreover, it has been shown that a mind bomb mutant zebrafish presents several changes in the brain metabolism, including down-regulation of several genes necessary for GABA-mediated signaling (Hortopan et al., 2010). These approaches point the zebrafish model as an interesting system to explore how many known anti-epileptic drugs (AEDs), such as carbamazepine, sodium valproate, and phenytoin, would be detected when running such a screen (Berghmans et al., 2007).

9. Conclusion

In this review, we have highlighted the different neurotransmitter systems in zebrafish and described their pharmacological and toxicological implications. These advances reinforce the benefits that zebrafish offer as a model system, and emphasizes the research efforts undertaken to understand the function of the neurotransmitter systems in this species. These efforts have used the zebrafish as a model for the induction of neurological disorders, which has contributed to the understanding of the mechanisms involved in different neuronal dysfunctions. Due to its ability to provide rapid pharmacological and toxicological responses in different stages of development, to exhibit a complex set of behaviors and genomic similarities to mammals, it is important to reinforce that the zebrafish is a useful tool for performing preclinical assays on a large scale before pharmacological validation in rodent models. In addition, the ability to test neurotoxic compounds during early development and in adults permits the evaluation of morphological, behavioral, and neurochemical parameters and the study of the mechanisms involved in environmental and drug toxicity (Fig. 2). Therefore, the zebrafish represents an attractive organism for screening strategies used in drug discovery and neurotoxicity assays.

Conflict of interest statement

There are no competing interests.

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