Understanding taurine CNS activity using alternative zebrafish models

Nathana J. Mezzomo a,c⁎, Barbara D. Fontana a,b, Allan V. Kalueff d,e,f,g,h,i,j,k, Leonardo J.G. Barcellos c,l, Denis B. Rosemberg a,b

a Laboratory of Experimental Neuropsychobiology, Department of Biochemistry and Molecular Biology, Natural and Exact Sciences Center, Federal University of Santa Maria, 1000 Roraima Avenue, Santa Maria, RS 97105-900, Brazil
b Graduate Program in Biological Sciences: Toxilogical Biochemistry, Federal University of Santa Maria, 1000 Roraima Avenue, Santa Maria, RS 97105-900, Brazil
c Graduate Program in Pharmacology, Department of Clinical Medicine, Federal University of Santa Maria, Santa Maria, RS 97105-900, Brazil
d School of Pharmacy, Southwest University, Chongqing, China
e Scientific Research Institute of Physiology and Basic Medicine, Novosibirsk, Russia
f The International Zebrafish Neuroscience Research Consortium (ZNRC), Slidell, LA, USA
g Ural Federal University, Ekaterinburg, Russia
h ZEERI Research Center, St. Petersburg, Russia
i Institute of Translational Biomedicine, St. Petersburg State University, St. Petersburg, Russia
j Institute of Experimental Medicine, Almazov National Medical Research Centre, St. Petersburg, Russia
k Russian National Center for Radiology and Surgical Technologies, St. Petersburg, Russia
l Graduate Program in Bio-Experimentation, University of Passo Fundo(UPF), BR 285, Passo Fundo, RS, 99052-900, Brazil

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ABSTRACT

Taurine is a highly abundant “amino acid” in the brain. Although the potential neuroactive role of taurine in vertebrates has long been recognized, the underlying molecular mechanisms related to its pleiotropic effects in the brain remain poorly understood. Due to the genetic tractability, rich behavioral repertoire, neurochemical conservation, and small size, the zebrafish (Danio rerio) has emerged as a powerful candidate for neuropsychopharmacology investigation and in vivo drug screening. Here, we summarize the main physiological roles of taurine in mammals, including neuromodulation, osmoregulation, membrane stabilization, and antioxidant action. In this context, we also highlight how zebrafish models of brain disorders may present interesting approaches to assess molecular mechanisms underlying positive effects of taurine in the brain. Finally, we outline recent advances in zebrafish drug screening that significantly improve neuropsychiatric translational research and small molecule screens.

1. Introduction

Taurine (2-aminoethanesulfonic acid, \( \text{NH}_2\text{CH}_2\text{CH}_2\text{SO}_3\text{H} \)) is one of the most abundant amino acids in various tissues, including the brain (Xu et al., 2008; Schaffer et al., 2010). Unlike the classical amino acids, taurine has a sulfonic acid (instead of a carboxylic acid) in its chemical structure. As an amino sulfonic acid, taurine is not incorporated into proteins and occurs freely in vivo (Huxtable, 1992; Sirdah, 2015). However, some other mammals do not naturally produce taurine due to the lack of the key enzyme for its biosynthesis, thereby necessitating dietary supplementation to avoid taurine deficiency, which can trigger retinal degeneration (Hayes et al., 1975) and immunological deficits (Levis et al., 1990). Taurine plays a pleiotropic role by

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Corresponding authors at: Laboratory of Experimental Neuropsychobiology, Department of Biochemistry and Molecular Biology, Natural and Exact Sciences Center, Federal University of Santa Maria, 1000 Roraima Avenue, Santa Maria, RS 97105-900, Brazil.
E-mail addresses: nathanajamillemezzomo@gmail.com (N.J. Mezzomo), dbrosemberg@gmail.com (D.B. Rosemberg).

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modulating osmoregulation (Schaffer et al., 2010), membrane stability (Lambert et al., 2015), intracellular calcium metabolism (Foos and Wu, 2002) and neuronal activity (Wu and Prentice, 2010). Additionally, taurine prevents oxidative stress (Lerdweeraphon et al., 2013) and inflammation (Marcinkiewicz and Kontny, 2014), also acting as an endogenous neuroprotector (Menzie et al., 2014). Taurine uptake in mammalian cells is mediated by its specific transporter (TauT, or SLC6A6), which is responsible for regulating taurine levels in a Na+- and Cl−-dependent manner (Chen et al., 2004). However, the mechanisms involved in taurine release from the cells are still under debate. A major point is whether taurine is released from astrocytes and neurons via a volume-sensitive leak pathway, which is permeable to a range of organic osmolytes (Banerjee et al., 2008; Hansen et al., 2012). Since the exact mechanisms associated with taurine effects are unclear, studies aiming to unravel the molecular pathways underlying the physiological responses of taurine using various experimental models become important.

Recent studies have validated new models for drug screening, target identification, pharmacology, and toxicology to understand the molecular basis of human diseases (Dooley and Zon, 2006; Parng et al., 2002; Sumanas and Lin, 2004; Nishimura et al., 2015). Here, we will focus on the potential application of the zebrafish (Danio rerio) in exploring the neurobiological effects of taurine and its mechanisms of action. We emphasize that the zebrafish arises as a novel alternative/complementary model organism that may help generate cross-species and cross-domain translational insights into neuropsychiatric research in this field.

2. Putative mechanisms of taurine in biological systems

2.1. General overview

In 1827, a molecule from ox bile was isolated as Gallen-Asparagin (Tiedemann and Gmelin, 1827). However, the first report related to its current name, taurine, derived from the name of species Bos taurus and appeared only a decade later (Demarcay, 1838). The biosynthesis of taurine via the cysteine sulfenic acid pathway was reported in 1962 (Sumizu, 1962). Initially recognized functions of taurine were limited to bile salt synthesis, osmoregulation in marine invertebrates, energy storage in marine worms, and inhibition of the central nervous system (CNS) (Sumizu, 1962; Jacobsen and Smith, 1968). Although taurine was discovered two centuries ago, some of its mechanisms of action and their physiological relevance have been examined and recognized only relatively recently. Thus, our progress in untangling the mechanisms of CNS effects of taurine has been slow and fragmental.

In vivo, taurine is absorbed by the intestine and released into the bloodstream by a putative non-saturable pathway (Roig-Pérez et al., 2005; Lambert et al., 2015). Once it reaches the circulation, taurine is distributed between cells, transported by the plasma membrane transporters TauT (encoded by SLC6A6) and/or by the proton-coupled amino acid transporter 1 (PAT1, encoded by SLC36A1) (Ripps and Shen, 2012; Lambert et al., 2015). The concentrations of taurine in extracellular fluids are lower than those reported intracellularly, ranging from 10 to 100 μM (Huxtable, 1992; Schuller-Levis and Park, 2003; Marcinkiewicz and Kontny, 2014; de Luca et al., 2015). The extracellular effects of taurine are attributed to the activation of specific...
cellular targets at very low concentrations (Huxtable, 1992). Intracellular taurine levels are higher in tissues with considerable oxidative activity, such as heart (25–30 mM), lung (11–17 mM), and brain (30–40 mM) (Green et al., 1991; Sturman, 1993; Massieu et al., 2004; Hansen et al., 2006; Oliveira et al., 2010). Post-mortem analyses showed a similar distribution of taurine in human brain tissue (ranging from 0.74 to 1.45 μmol/g wet tissue), suggesting a widespread localization of taurine in the CNS structures (Okumura et al., 1960). Although taurine is considered an end metabolic product, its conversion into isethionic acid (2-hydroxyethane sulfonic acid) in the dog heart in vitro and in the rat heart and brain was described (Peck and Awapara et al., 1967; Read and Welty, 1962). However, taurine excess is usually excreted with urine or bile (Cho et al., 2000). Besides its conjugation with cholic acid, taurine has been reported in several other bound forms, such as N-methyl-taurine, taurobetaine, and N-(1-carboxyethyl)-taurine (Machlin and Pearson, 1957). The main functions of taurine, including neuromodulation, osmoregulation, membrane stabilization and antioxidant capacity, are summarized in Fig. 1.

2.2. Neuromodulation

Mounting evidence shows that the neuromodulatory action of taurine is due to its agonistic modulatory effects on central gamma-aminobutyric acid (GABA)A and glycine receptors (Zhang and Kim, 2007; Poleszak et al., 2011; Chan et al., 2014). For example, taurine can protect neurons from excitotoxicity by lowering the intracellular level of free calcium via inhibiting the reverse mode of Na+-Ca2+ exchanger, suggesting a potential interaction between taurine and N-methyl-D-aspartate (NMDA) receptor (Wu et al., 2005; Menzie et al., 2014). Chan et al. (2014) showed that taurine can inhibit NMDA receptors via multiple mechanisms to reduce glutamate-induced neurotoxicity. Since a specific taurine antagonist has not yet been described, this complicates the understanding of its specific extracellular mechanisms (Della Corte et al., 2002). In the cerebellum, taurine increases the Cl− conductance in excitable membranes, causing hyperpolarization in neurons and reducing their excitability (Conte-Camerino et al., 1987). These data strongly support the idea that taurine may modulate several second messenger systems and counteract the actions of glutamate, thereby preventing excitotoxicity.

2.3. Osmoregulation and membrane stabilization

Regulation of cell volume is an intrinsic property of any living cell, which have a tendency to swell or shrink, adjusting their internal osmotic pressure. Volume-regulated ion channels counteract cell swelling due to changes in osmolarity by releasing osmolytes to the extracellular milieu (Hoffmann et al., 2009; Sirianant et al., 2016). Thus, osmoregulation plays a crucial role in normal CNS function during cell growth, division, and migration. Recent data revealed that leucine-rich repeat-containing 8A (LRRC8A) is an essential component of the volume-regulated anion channel (VRAC) in astrocytes (Voss et al., 2014). This channel is permeable for a wide variety of anions, amino acids, and organic osmolytes, such as taurine (Nilius, 2004), which has been suggested as an osmoregulator in various species (Simpson et al., 1959; Walz and Allen, 1987; Oja and Saransaari, 1996). Indeed, hippocampus exposed to oxidative stress showed a significant taurine efflux via VRAC in rodents (Tucker and Olson, 2010). Since taurine release was mimicked in synaptosomal preparations, distinct mechanisms and/or cellular sources may contribute to the release of taurine in vivo (Haskew-Layton et al., 2008). Moreover, the specific mechanisms of taurine in osmoregulation seem to occur due to an antihypertensive effect via vasodilatation by reducing adrenergic and angiotensin II actions and calcium-induced vasospasm (de Luca et al., 2015).

Taurine also acts as a membrane stabilizer at physiological concentrations (Huxtable and Bressler, 1973), modulating the excitability of neuronal membranes by interfering with membrane-Ca2+ interactions. Taurine interacts with sites related to anion transport and water influx (Lazarewicz et al., 1985; Wu et al., 2005; Das et al., 2012) and with the polyunsaturated fatty acids and phospholipids (Yorek et al., 1984). Stabilizing effects of taurine on the sarcoplasmic reticulum membranes (Huxtable and Bressler, 1973) and brain synaptosomes (Pasantes-Morales and Moran et al., 1981; Lazarewicz et al., 1985; Wu et al., 2005) have been reported. One possible mechanism underlying such membrane stabilization may involve changes in phospholipid methyltransferase activity, an enzyme which controls phosphatidyl-ethanolamine (PE) and phosphatidylycerine (PC) content in membranes. Hamaguchi et al. (1991) reported that taurine increases PE/PC ratio, thereby altering the fluidity of cellular membrane which improves its resistance.

2.4. Antioxidant activity

Taurine has important intracellular antioxidant functions in different tissues, including neurons (Hansen et al., 2006), where it acts by lowering the production of oxidants and/or boosting the antioxidant protection (Rosemberg et al., 2010; Shimada et al., 2015). In vitro, taurine can interact directly with some oxidant radicals (peroxyl radical, anion superoxide, nitric oxide and peroxynitrite), thereby exerting a scavenger effect at physiological intracellular concentrations (Oliveira et al., 2010). During inflammation, stimulated neutrophils release large amounts of taurine that can rapidly react with hypochlorous acid to form taurine-chloramine. This conjugate provides a detoxification mechanism, which protects against neutrophil-induced cytotoxicity (Marcinkiewicz and Konny, 2014). Taurine-chloramine is taken up into the cells and further concentrated in the mitochondria, where it changes the membrane potential, promotes mitochondrial swelling, and triggers apoptosis via caspase-9 activation (Klamt and Shacter, 2005). Moreover, taurine-chloramine has anti-inflammatory activities per se, since it inhibits the production of nitric oxide, tumor necrosis factor alpha (TNF-α), IL-6, IL-8, and suppresses NF-kB synthesis (Agca et al., 2014; Kim et al., 2011; Konny et al., 2000).

However, despite its important role in controlling the pro-oxidant/antioxidant balance (Ariuoma et al., 1988; Gürrer et al., 2001; Parildar-Karpuzoğlu et al., 2008; Das et al., 2012), more studies are needed to explain how intracellular taurine modulates cellular redox profile.

3. The use of zebrafish in neuropsychiatric research

3.1. General overview

The zebrafish is a freshwater teleost fish native to Southeast Asia. Their small size, easy maintenance, low cost, easy breeding, and translucent embryos were instrumental in introducing the zebrafish to biomedicine (Rico et al., 2011; Parker et al., 2012; Stewart et al., 2014; 2015). Importantly, both larvae and adult zebrafish are easier to care of (than rodents) and need a little space to work, constituting important characteristics to perform medium/high throughput screens (Bilotta et al., 1999; Rico et al., 2011; Kalueff et al., 2013). The drug delivery method is also a practical aspect of this model since chemical compounds can be added to the tank water and be promptly absorbed by the immersed zebrafish through gills (Rosemberg et al., 2012; Tran et al., 2015). The zebrafish has already proven to be a powerful animal model for genetic, developmental and pharmacological screening, and they exhibit multiple behaviors including social, affective, and defensive responses that may be useful for interactive neurophenotyping (Gerlai, 2003; Guo, 2004; Blaser and Vira, 2014).

3.2. Recent approaches to zebrafish use in behavioral neuroscience

The zebrafish promise as an alternative organism for modeling human diseases has been empowered by its recently sequenced genome (Howe et al., 2013). Around 70% of zebrafish genes share a high degree
of homology with their mammalian orthologs (MacRae and Peterson, 2015). Despite considerable neuroanatomical differences between mammals and teleosts, mounting evidence shows that zebrafish possess several brain areas with homologous functions (Ullmann et al., 2010; Randlett et al., 2015). For example, the lateral pallium of the telencephalic area of zebrafish is responsible for memory processes, while the habenula is associated with fear responses, similar to hippocampus and amygdala, respectively (Perathoner et al., 2016; Agetsuma et al., 2010). Zebrafish are fully capable of cognitive processing and complex decision-making, showing analogous behavioral responses and high sensitivity to pharmacological agents (Sison et al., 2006; Parker et al., 2012; Oliveira, 2013).

To extrapolate experimental data from animal models to humans in translational neuroscience, the investigation of different validity criteria is imperative (van der Staay et al., 2009). Validation of a certain model is a scientific approach that improves its reproducibility and consistency (Vervliet and Raes, 2013). For example, the construct validity evaluates how a specific process, trait or state reflects theoretical assumptions. In other words, it correlates mechanistic similarities between the model and the clinical condition (Willner, 1991). While face validity refers to conserved phenomenological and symptomatological similarities of features, the predictive validity implies the extrapolation of the effects of a certain manipulation from one species to another (van der Staay and Steckler, 2002; Willner, 1991). Although construct validity has been considered the most important criterion for animal models, both face and predictive validities establish a network association of drug effects, behavioral phenotypes, and etiology to unravel molecular pathways associated with clinical conditions (van der Staay et al., 2009). During the last decade, the predictive, face, and construct validity of different behavioral tasks has been established for zebrafish. Various complex behaviors have already been reported for this species, such as aggression (Gerlai et al., 2006; Fontana et al., 2015), long- and short-term memory (Blank et al., 2009; Cognato et al., 2012; Jia et al., 2014), object discrimination (May et al., 2016) and color preference (Bault et al., 2015). Zebrafish have also been used to investigate behavioral- and molecular-related features of Alzheimer’s disease (Bortolotto et al., 2015; Lee and Freeman, 2016), Parkinson’s disease (Sarah Babu et al., 2016), schizophrenia (Giacomotto et al., 2016), epilepsy (Grone et al., 2016), obesity (Den Broeder et al., 2015), diabetes (Sarras et al., 2015), endocrine and other metabolic dysfunctions (Alderman and Vijayan, 2012; Alsop and Vijayan, 2008; Baimonte et al., 2015). Together, these aspects reinforce the growing significance of zebrafish translational neuroscience studies, as summarized in Table 1 and Fig. 2.

4. Taurine effects in zebrafish models

4.1. General overview

Early works by Michel and Lubomudrov (1995) have evaluated the specificity and sensitivity of the olfactory organ of adult zebrafish to amino acids, bile acid, and steroid odors using the electro-olfactogram recording protocol. Although taurine-conjugated bile acids (taurocholic acid, taurochenodeoxycholic acid, taurolithocholic acid-3-sulfate) were more effective odors than other molecules, later works provided the molecular characterization of the receptors for amino acid and bile salt odors in adult zebrafish. Michel and Derbridge (1997) showed that zebrafish cells express specific odorant receptor gene subfamilies that mediate the chemical perception of taurine-conjugated odors. David-Watine et al. (1999) isolated a novel subunit (αZ1) of glycine receptor of zebrafish, with a high degree of homology between its amino acid sequence with the mammalian α1 subunit, while M4 and C-terminal domains were more similar to the α2/α3 subunit. Additionally, taurine acts as a potent agonist of αZ1 receptor subunit, suggesting that glycine receptor may mediate its effects in zebrafish (David-Watine et al., 1999).

Zebrafish TauT protein has 625 amino acids and presents a high molecular homology to the mouse, rat, and human orthologs (72%, 74%, and 73%, respectively). Besides, its heterologous expression in mammalian cells shows that taurine uptake in zebrafish occurs in a Na\(^+\)/K\(^-\)-dependent manner and presents substrate selectivity, substrate affinity, ion dependence, and stoichiometry similar to those of mammalian TauTs (Kozlowski et al., 2008). As a maternally derived molecule, TauT mRNA is evident in the 1–4 cell-stage embryo. Later, during embryogenesis, TauT transcripts are detected in the retina, heart, brain, kidneys, and somites (Kozlowski et al., 2008). Furthermore, the zebrafish genome contains two LRRCSA orthologs (lrrc8aα and lrrc8ab) that share 87% identity with human LRRCSA (Yamada et al., 2016). Molecular experiments also revealed that cysteine sulfenic acid decarboxylase (CSAD), the rate-limiting enzyme in the de novo biosynthesis of taurine is detected in yolk, syncytial layer, and various embryonic tissues (e.g. notochord, brain, retina, pronephric duct, liver, and pancreas) (Chang et al., 2013). Interestingly, TauT knockdown delays embryo development by inducing apoptosis in brain and spinal cord cells (Kozlowski et al., 2008), while reduced csad expression decreases embryonic taurine levels and increases early mortality and cardiac anomalies (Chang et al., 2013). Taken together, these results suggest an evolutionarily conserved function of taurine in vertebrate species, raising the possibility to assess the mechanisms underlying its actions in different cell types.

Neurobehavioral data have shown that zebrafish acutely exposed to taurine at 42, 150, and 400 mg/L display an anxiolytic-like profile without changes in locomotion. In addition, 150 mg/L taurine reduced risk assessment episodes, suggesting that, like in rodents, taurine is anxiolytic in zebrafish (Mezzomo et al., 2016). Thus, the use of different experimental models emerges as an interesting approach to clarify the neurochemical pathways associated with taurine effects in CNS.

4.2. Actions of taurine in the acute effects of ethanol

As already mentioned, taurine has important antioxidant properties (Aruoma et al., 1988; Green et al., 1991; Oliveira et al., 2010; Shimada et al., 2015; Patel et al., 2016). Ethanol elevates reactive oxygen species that are strongly associated with many alcohol-related diseases (Albano, 2006). Ethanol can be oxidized by alcohol dehydrogenase, microsomal ethanol oxidation system (MEOS), and catalase. These enzymes produce its reactive metabolite, acetaldehyde, which affects ethanol-mediated responses and impairs the antioxidant defense system (Lieber, 1997; Zima et al., 2001; Quertemont and Didone, 2006; Das et al., 2007).

Ethanol also influences zebrafish cognition, stress sensitivity, impulsivity, attention, and aggression (Parker et al., 2012). Recent zebrafish studies show the protective role of taurine in acute ethanol exposure (Rosemberg et al., 2010), as taurine pretreatment lowers acetylcholinesterase activity and lipid peroxidation in fish brain. Further analyses revealed that taurine antagonizes the effects of alcohol in zebrafish (Rosemberg et al., 2012), since it prevents anxiolytic action following a 20-min, and abolished locomotor impairment following a 60-min exposure. Thus, the administration of taurine prior to ethanol maintains redox homeostasis and modulates the enzyme responsible for terminating the cholinergic transmission in vivo. Moreover, similar to mammals, taurine exerts antioxidant and neuroprotective effects in zebrafish.

Usually, energy drinks have high levels of taurine and their consumption with alcoholic beverages are common, constituting a public health concern (Marczinski and Fillmore, 2014). Although there is a large body of evidence showing the interactions between energy drinks and ethanol intake, their actions and behavioral effects in different organisms are still controversial. In humans, the ingestion of alcohol plus energy drink attenuated the perception of headache, weakness, dry mouth, and impairment of motor coordination. However, objective measures of motor coordination and visual reaction time, as well as the
<table>
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**Table 1** Overview of the existing experimental protocols for modeling different brain-related disorders in zebrafish.

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**Abbreviations:** AD = Alzheimer’s disease; APP = amyloid-precursor protein; APPo = (2R)-amino-5-phosphonovaleric acid; APV = (2R)-amino-5-phosphonovaleric acid; CNQX = 6-cyano-7-nitroquinoxaline-2,3-dione; CRF = Corticotropin Releasing Factor; DISC1 = Disrupted in schizophrenia 1; KA = Kainic acid; MK-801 = Dizocilpine; MPTP = 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; NMDA = N-methyl-D-aspartate; NRG1 = Neuregulin; PEN = Presymptomatic Neurotoxin; P301L = Presymptomatic Neurotoxin; PTZ = pentylenetetrazole; SCN1A = sodium voltage-gated channel alpha subunit 1; SCZ = Schizophrenia.
breath alcohol concentration, did not corroborate these subjective effects (Ferreira et al., 2006). Interestingly, when different doses of energy drinks and ethanol were coadministered in Swiss mice, 10.71 ml/kg of energy drink antagonized the depressant effects of high ethanol doses (Ferreira et al., 2004). Since energy drinks are complex mixtures of taurine, caffeine, and other compounds, it is difficult to state whether these effects result from interaction among molecules or if they are specifically associated with taurine.

Furthermore, as agonists of GABA A receptors promote agonistic behaviors (Miczek et al., 1995; 2003; Zarrabian et al., 2016), the association of taurine and ethanol may influence aggressive behavior. Using the mirror-induced aggression task, Fontana et al., 2015 showed behavioral effects of taurine in zebrafish cotreated with 0.25% ethanol for 1 h. At 42 and 400 mg/L, taurine increased aggression, whereas 150 mg/L abolished the agonistic behavior, showing a biphasic response for ethanol-induced aggression. Although the mechanisms of taurine neurobehavioral responses are not fully understood, the use of zebrafish continues to foster innovative research into the underlying mechanisms of taurine action and its potential for preventing ethanol-induced CNS deficits.

5. Taurine and neurological disorders

The development of new therapies for CNS disorders is slow, expensive and ineffective (Newman et al., 2011). Furthermore, behavioral biomarkers of neurodegeneration are often challenging to quantify in both clinical and experimental (animal) model systems (Menzie et al., 2014; MacRae and Peterson, 2015; Nunes et al., 2016).

Taurine is an endogenous brain substance with robust neuromodulatory properties (Wu and Prentice, 2010; Chan et al., 2014) that has been often described as an inhibitory neurotransmitter. The classic description of neurotransmitter determines that its synthesis must occur in the presynaptic neuron and that the molecule must be stored in synaptic vesicles. A neurotransmitter should be present in the axon terminal at presynapse and its release must be essentially diffused across the synaptic cleft, binding to specific receptors on the postsynaptic side. Importantly, the neurotransmitter released at synaptic cleft must cause changes in the postsynaptic potential and a specific mechanism to remove it from the synaptic cleft should be present (Hanretta and Lombardini 1987; Lodish et al., 2000). Concerning the five basic criteria that allow classifying a certain molecule as a neurotransmitter, several aspects have supported a putative existence of the taurinergic system in the CNS.

First, taurine and/or its synthesizing enzyme are often concentrated presynaptically in neuronal terminals (Wu et al., 1979; Wu 1982; Magnusson et al., 1989; Wu and Prentice, 2010). Secondly, stimulated taurine release occurs both in a calcium-dependent and independent manners (Philibert et al., 1989; Wu and Prentice, 2010). Taurine also modulates neurotransmission by eliciting inhibitory neurotransmission through GABA A and glycine receptors (Okamoto et al., 1983; Albrecht and Schousboe, 2005; Wu et al., 2008), also inhibiting NDMA receptors (Wu et al., 2005; Menzie et al., 2014; Chan et al., 2014). Specific taurine receptors have been suggested (with a specific Kd in nM range) as distinct from GABA A, GABA B, and glycine receptors, since using agonists or antagonists of these receptors has little effect on taurine binding (Frosini et al., 2003; Wu et al., 1992; Wu and Prentice, 2010). Finally, the CNS expresses transporter systems (TauT and VRAC) able to regulate taurine influx and efflux, respectively (Banerjee et al., 2008; Hansen et al., 2012; Martin 1992; Kozlowski et al., 2008).

In summary, while taurine meets major criteria to be a neurotransmitter in the vertebrate CNS, it cannot yet be classified as a classical neurotransmitter due to unclear storage at synaptic vesicles and a lack of specific cloned taurine receptor. Because neurodegenerative diseases share common fundamental pathophysiology, including glutamate excitotoxicity, calcium imbalance and oxidative stress, which individually or collectively results in cell death (Menzie et al., 2014), taurine may serve as a promising therapeutic target for several neurological disorders.

5.1. Taurine and Alzheimer’s disease

Alzheimer’s disease (AD) strongly correlates with synaptic degeneration and neuronal death in limbic structures followed by escalating cognitive decline and social dependence, eventually culminating in death (Caltagirone et al., 2012, Menzie et al., 2014; Carretti et al., 2015). It is characterized by the deposition of a 39–43 amino acid residue peptide, amyloid beta (Aβ), in the brains of affected individuals (Louzada et al., 2004; Oz et al., 2009). The neuropathological markers of intracellular neurofibrillary tangles (NFTs) are composed of hyperphosphorylated tau protein and neuronal cell loss, particularly affecting the cholinergic system (Braak and Braak, 1998; Newman et al., 2011; Menzie et al., 2014). There is a strong association between Aβ peptide with AD pathogenesis, and blockade of glutamate receptors prevents Aβ-induced neuronal death (Lipton and Rosenberg, 1994; Mattson,
Recent data showed that taurine prevents Aβ neurotoxicity via activation of GABA<sub>A</sub> receptors (Louzada et al., 2004), suggesting that taurine-related modulation of glutamate and GABA<sub>A</sub> receptors can be an interesting therapeutic approach for treating AD.

Because taurine concentrations are 3–4 times higher in the developing than in the mature brain (Miller et al., 2000), it may play a role during brain development and/or aging (Banay-Schwartz et al., 1989). In aged mice, chronic treatment with taurine ameliorates age-dependent memory deficits (El Idrissi, 2008), corroborating the pleiotropic role of exogenous taurine. Indeed, taurine increases the levels of GABA, glutamate, and the expression of glutamic acid decarboxylase (GAD) and neuropeptide somatostatin. As these effects are opposite from those naturally occurring during aging, taurine supplementation may correct age-related decline in cognitive functions (El Idrissi, 2008).

The beneficial properties of taurine have been shown in a transgenic mouse model of AD, rescuing cognitive deficits without affecting cognitively normal mice (Kim et al., 2014). Histopathological studies found that taurine increases the proliferation of adult neural stem/progenitor cells from the subventricular zone in vitro (Hernandez-Benitez et al., 2012; Ramos-Mandujano et al., 2014), showing a potential role in adult neurogenesis. Furthermore, taurine also reduced activated microglia and increased the survival of newborn neurons, resulting in a net increase of neurogenesis in adult specimens (Gebara et al., 2015). Together, these data support a beneficial role of taurine in hippocampal neurogenesis during brain aging in vivo.

Some pharmacological agents, such as donepezil, rivastigmine, tatractate, galantamine HBr, memantine, and the psychostimulant modafnil, have been used as cognitive enhancers (Mehlman, 2004). Considering the lack of effective treatments, questions regarding the validity and utility of the existing animal models have emerged. Mice are the dominant vertebrate model for modeling AD-related phenotypes but the use of non-mammalian organisms emerges as a simple strategy for studying neuropsychiatric disorders. Transgenic, knockout, and morpholino zebrafish models have enabled a better understanding of the genetic mechanisms associated with CNS dysfunctions (Tomasiwicz et al., 2002; Paquet et al., 2009; Formella et al., 2012), thereby serving as valuable tools to investigate the effects of taurine in forward genetics-based studies.

Zebrafish cells express genes corresponding to those mutated in human familial AD, amyloid-β precursor protein (APP), appa and appb (Musa et al., 2001; Joshi et al., 2009; Newman et al., 2011). Orthologs to human of presenilin (PSEN1 and PSEN2), psen1 and psen2, respectively (Wilson and Lardelli, 2013) and prion protein (PRP), prp1, and prp2 have also been described (Kaiser et al., 2012). The loss of zebrafish appa and appb function by morpholino knockdown resulted in reduced body length and defective convergent extension movements during gastrulation in embryos. These defects are rescued by wild-type human amyloid-β precursor protein mRNA, but not by the Swedish mutant amyloid-β precursor protein, known to cause familial AD (Joshi et al., 2009; Xi et al., 2011; Song and Pimplikar, 2012). Injection of antisense morpholino to reduce APP levels in zebrafish embryos caused convergent extension defects, defective axonal outgrowth of facial branchiomotor and spinal motor neurons (Song and Pimplikar, 2012). These findings demonstrate that zebrafish provide a powerful system to delineate APP functions in vivo and to analyze differences in the activity of various mutant forms of the amyloid-β precursor protein.

Taurine may aid cognitive impairment and inhibit Aβ related damages, since it reduced cognitive deficits in APP/PS1 transgenic mouse model of AD for 6 weeks in both Y-maze and passive avoidance tests. In the cortex of APP/PS1 mice, taurine slightly decreased the insoluble fraction of Aβ (Kim et al., 2014). In rodents, taurine is able to recover memory impairments induced by alcohol, pentobarbital, sodium nitrite, and cycloheximide without any observable effects on other behaviors including motor coordination, exploration, and locomotor activity (Vohra and Hui, 2000). Moreover, the intracerebroventricular administration of taurine protects from hypoxia-induced learning impairment (Malcangio et al., 1989). Intravenously administered taurine significantly improves post-injury functional impairments caused by traumatic brain injury (Su et al., 2014). Taurine is also able to rescue age-dependent loss of visual discrimination (Suge et al., 2007) and to ameliorate the cognitive impairment and abnormal acetylcholinesterase activity in streptozotocin-induced dementia model (Javed et al., 2013). Since taurine presents a cognitive enhancing phenotype in mouse models, the zebrafish arises as a logical non-mammalian candidate for studies of taurine role in behavioral and neurotranscognitive functions.

### 5.2. Taurine and Parkinson’s disease

Parkinson’s disease (PD) is recognized as the second most common progressive neurodegenerative disorder after AD (Driver et al., 2009; Shulman et al., 2011; Ricciardi et al., 2015). Patients with PD show degenerative loss of dopaminergic nigrostriatal neurons, intracytoplasmic Lewy bodies (LBs) and intra-axonal Lewy neurites (LN)s composed of fibrillar aggregated α-synuclein (Spillantini et al., 1998). Clinically, PD is a motor disorder dominated by bradykinesia, rigidity, resting tremor, and postural instability responsive to dopaminergic replacement therapy (Calabresi et al., 2013). Besides these motor symptoms, the existence of a cognitive impairment has been largely attributed to an inability to retrieve information from long-term memory storages (Ricciardi et al., 2015) and to a deficit of acquisition (Kehagia et al., 2010).

Similar to other age-related neurodegenerative disorders, the dopaminergic neurons that degenerate in PD express glutamate receptors and are vulnerable to excitotoxicity (Miranda et al., 1997). Despite the crucial role of dopamine in PD pathogenesis, taurine may also be involved in modulating the nigrostriatal system (Bianchi et al., 1998; Zhang et al., 2015). Taurine potently protects neurons in culture against the toxicity of Aβ, glutamate, kainate, and NMDDA (El Idrissi and Trenkner et al., 1999; Louzada et al., 2004). Although the neuroinhibitory actions of taurine in the CNS have long been known (Zukin et al., 1974; Chung et al., 2012; Menzie et al., 2014), its molecular mechanisms are still debated. Some studies suggest taurine neuromodulation of the nigrostriatal system (Bianchi et al., 1996; Ye et al., 1997), as high taurine levels are found in the striatum (Palkovits et al., 1986), substanția nigra (Dray and Straughan, 1974), and in GABAergic terminals from the striatum to the substantia nigra (Bianchi et al., 1998). The age-related decline in taurine concentrations strongly correlates with the striatal dopaminergic loss (Dawson et al., 1999), and changes in taurine concentrations may contribute to neuronal degeneration (Chung et al., 2012). Since taurine may improve the protection of dopaminergic cells via direct and indirect effects on excitotoxicity and by inhibiting the firing of GABAergic cells (Ye et al., 1997), compounds that modulate GABAergic activity should be explored as neuroprotectors against glutamatergic excitotoxicity.

A great advantage of the zebrafish model system is the ability to provide an in vivo test of toxicity and to screen potential protective molecules in a medium-to-high throughput manner. Extensive information is available regarding the CNS pattern and the neurotransmitter systems in zebrafish, which show important similarities to the human CNS (Bretaud et al., 2011; Wager and Russell, 2013). Another interesting feature concerns the dopaminergic system in this species, which has already been characterized in both embryonic and adult stages (Panula et al., 2010). Several neurodegenerative diseases have been modeled in zebrafish using mutant forms of MAPT (Bai et al., 2006; Tomasiwicz et al., 2002), SOD1 (Ramesh et al., 2010), and HTT (Williams et al., 2008). It is also possible to observe PD-like phenotypes in zebrafish treated with a dopaminergic neuron-selective toxin indicating the existence of functionally equivalent circuitry (Wager and Russell, 2013). Conversely, the effects of PD neurotoxins or PD genes in zebrafish should be assessed considering the potential impact of variation in genetic context on spontaneous motor behavior, gene
expression levels, the number of dopaminergic neurons, susceptibility to neurotoxins, and the effect of gene knockdown (Bretau et al., 2011). Thus, the zebrafish may serve as a tempting tool to investigate the gene–environment interactions following taurine treatment, aiming at our improved understanding of PD pathogenesis and its pharmacotherapy.

5.3. Taurine and epilepsy

Epilepsy is characterized by the recurrence of unprovoked seizures that cause neurological deficits (Fisher et al., 2005; Banerjee et al., 2009). The epileptic seizures seem to occur via common cellular mechanisms and networks (McCormick and Contreras, 2001) involving sudden and abnormal discharges of neurons (Fisher et al., 2005; Dayapoglu and Tan, 2016). Their treatment consists mainly of conventional anti-epileptic drugs (AEDs) that act by inhibiting the sodium currents or enhancing of GABAergic inhibition (Czajkowski et al., 2005). Since current AEDs do not exert a significant control of seizures in 30% of patients, the search for novel therapeutic molecules is needed (Torres-Hernandez et al., 2015).

Taurine may be a useful agent for treating epilepsy since it modulates neurotransmission and inhibits neuronal excitation (Sarasara and Oja, 2008). Elevated taurine is found in serum of patients with epilepsy, while lower amounts are detected in brain tissue (Wilson et al., 1996; Sejima et al., 1997; Gaby, 2007). Moreover, low taurine brain content may prolong seizure activity, and correlates with the onset of epileptic episodes (Oja and Kontro, 1983). On the other hand, agents that induce seizures in animal models elevate taurine levels in the brain, suggesting a possible adaptive protective mechanism to counter glutamatergic excitotoxicity (Vezzani and Schwarz, 1985).

Although mechanisms of taurine action in epilepsy are not fully understood, it can reduce seizure episodes as a neuroprotector (Barbeau et al., 1975; Izumi et al., 1975; Durelli et al., 1976, 1977; van Underwesd and Tan, 2016). Their treatment consists mainly of conventional anti-epileptic drugs (AEDs) that act by inhibiting the sodium currents or enhancing of GABAergic inhibition (Czajkowski et al., 2005). Since current AEDs do not exert a significant control of seizures in 30% of patients, the search for novel therapeutic molecules is needed (Torres-Hernandez et al., 2015).

Seizure episodes in zebrafish can also be modeled using classical convulsant drugs (e.g. pentylenetetrazole (PTZ) and kainic acid) (Alfar et al., 2011; Baraban et al., 2005; Mussulini et al., 2013). Animals display abnormal locomotor activity and corkscrew swimming (a behavioral phenotype that closely resembles tonic-clonic seizures). Pineda et al. (2011) studied the brain electrical activity using electroencephalogram (EEG) recordings in adult zebrafish exposed to PTZ for 35 min. The authors observed an increase of high amplitude sharp transients analogous to the human interictal epileptiform discharges (Pineda et al., 2011). Since the seizure-like behavior occurs simultaneously with alterations of EEG in adult zebrafish exposed to the same PTZ conditions, a direct correlation of abnormal behavior and electrical activity in brain tissue was likely (Mussulini et al., 2013). Because there are no data regarding EEG recordings in kainic acid model, more studies are necessary to validate this model. In sum, the use of both larval and adult zebrafish to investigate the effects of taurine represents a refinement of the existent rodent protocols, showing a promising relevance to evaluate the mechanisms of taurine in epileptic models with medium/high throughput capabilities.

5.4. Taurine and schizophrenia

Schizophrenia is a serious mental disorder characterized by positive (e.g. hallucinations, delusions) and negative symptoms (e.g. social withdrawal, anhedonia). Patients usually present a confused mental state, disruption of social engagement and emotional expression, and the lack of motivation (Heinrichs, 2003, Jenkins 2013; Nasyrov et al., 2015). Modulating inflammatory response and redox activity, changes in taurine and glutathione (GSH) metabolism are involved in the pathophysiology of schizophrenia (Schuller-Levis and Park, 2003; Haddad and Harb, 2005). Taurine levels are increased in the prefrontal cortex of patients with schizophrenia, and this rise correlates with illness duration (Shirayama et al., 2010). Moreover, altered taurine levels were detected in patients with acute polymorphic psychosis and depression (Nordin and Sjodin, 2006; Samuelsson et al., 2011).

Mounting evidence supports the hypofunction of a subpopulation of cortico-limbic NMDA receptors in schizophrenia (Coyle 2006). Given the role of NMDA receptors in the reward circuitry and in substance dependence, it is reasonable to link a dysfunction of the NMDA receptor dysfunction with schizophrenia (Coyle et al., 2002; Coyle and Tsai, 2004; Coyle 2006). In the last decade, the zebrafish have emerged as a model organism in behavioral pharmacology and neuroscience of cognitive dysfunction (Blaser and Vira, 2014). Using the zebrafish, researchers may combine genetic strategies (gene knockdown, mutants, transgens) for examining the impact of altered dopamine signaling in neuropsychiatric disorders (Souza and Tropepe, 2011). Furthermore, the underlying genetic mechanisms mediating the neurogenesis of the dopaminergic system are also well conserved between zebrafish and fish.
mammals (Filippi et al., 2007; Ryu et al., 2007).

Although atypical brain functioning has been associated with neuropsychiatric and neurodegenerative conditions, there are few animal models available to study schizophrenia-related behavioral and cognitive deficits. The administration of dizocilpine (MK-801), which acts as an antagonist of the NMDA receptor, elicits a behavioral syndrome in rodents, which is similar to schizophrenia symptoms in humans (Clineschiedt et al., 1982; Deutsch et al., 1997). Similarly, zebrafish exposed to MK-801 present psychotic-like hyperlocomotion, which can be attenuated by antipsychotics (Seibt et al., 2010, 2011, 2012; Maaswinkel et al., 2013). Interestingly, MK-801 elicits anxiolytic-like effects and the presence of olanzapine potentiated this effect (Seibt et al., 2010). Another study showed that pharmacological manipulation of glutamate neurotransmission with MK-801 reduces memory formation, but does not affect memory retrieval in short or long-term memory assays in zebrafish larvae (Andersson et al., 2015).

Additionally, overt changes in social interaction occur in several neuropsychiatric disorders. Zimmermann et al., 2016 investigated the actions of MK-801 on social preference and in the mirror-induced aggression task in zebrafish. The authors showed that MK-801 decreased time spent near conspecifics and increase the time close to the opponent image, suggesting a modulatory role in the approach/avoidance response. The treatment with carbocetan, an oxytocin receptor agonist, reestablished the behavioral phenotypes altered by MK-801 in both tests (Zimmermann et al., 2016). In sum, these results suggest that the exposure to MK-801 is highly attractive for assessing behavioral deficits and can serve as an interesting model for screening potential neuroprotectors. Considering the evolutionarily conserved molecular targets for MK-801 in zebrafish, this species can be a suitable vertebrate to perform pharmacological investigations in medium-to-high-throughput screening protocols. Due to its antagonism of glutamatergic signalling, taurine emerges as a candidate molecule to counteract the neurochemical and behavioral actions of MK-801 and other antiglutamatergic drugs in zebrafish, as well as for testing potential antiglutamatergic effects of taurine.

6. Taurine and stress-related disorders

A biological hallmark of stress response is the activation of the hypothalamic pituitary-adrenal (HPA) axis, triggering a “fight or flight” response with enhanced activation of the sympathetic nervous system when facing a dangerous situation, such as a predator, an accident, or a natural disaster (McEwen, 2007; Li and Hu, 2016). In teleost fish, cortisol is released from interrenal cells (adrenal gland homolog) during stress following activation of the hypothalamus–pituitary–interrenal (HPi) axis (Alsp and Vijayan, 2008; Alderman and Vijayan, 2012; Biaimonte et al., 2015). Various stressors rapidly increase whole-body cortisol in zebrafish, reaching significant levels after 15 min (Barcellos et al., 2007; Barcellos et al., 2016; Ramsay et al., 2009).

Although stress response is adaptive, an excessive adrenocortical and autonomic function is harmful to health and survival. Dysregulation of the HPA axis is associated with some psychiatric disorders (e.g. depression, posttraumatic stress disorder, anxiety) (Newport and Nemeroff, 2003; Holsboer et al., 2000; Walker et al., 2013, Moreno-Peral et al., 2014) and other biomedical conditions, including Type II diabetes, hypertension, chronic fatigue syndrome and fibromyalgia (Bruehl et al., 2007; Wirtz et al., 2007; Wingenfeld et al., 2008; Galli et al., 2009).

Although the role of taurine in the neurobiology of stress is still poorly understood, TauT can be affected by distinct extracellular stimuli. For example, murine monocyte cell line RAW264.7 treated with 12-O-tetradecanoylphorbol 13-acetate (TPA) show a marked reduction in TauT activity, which was reversed by steroid hormones (Kim et al., 1998). In a rat stress-induced hypertension model, animals treated with 200 mg/kg/day taurine and stressed for 3 weeks contain more angiotensin converting enzyme 2 (ACE2) than non-stressed and stressed groups (Lv et al., 2015). These data implicate taurine in the regulation of the HPA axis and renin-angiotensin-aldoosterone system in stress-induced hypertension. In a randomized double-blind clinical trial, patients orally treated for 21 days with 1998 mg/day of a taurine analog acamprosate, markedly reduced alcohol consumption (Hammargerg et al., 2009). Given the influence of HPA on craving responses (Kiefer et al., 2006), these findings highlight the importance of using different experimental models to assess the neurobiological actions of taurine.

The relationship of taurine levels with distinct behavioral tests following acute stress in zebrafish has been previously investigated. Musthag et al. (2014) submitted zebrafish to a netting stress for 15 min and further exposed the animals to the open field and light-dark tests. The authors observed changes in the metabolome with a significant increase in taurine levels when exposed to the light-dark apparatus vs. open field, regardless of experimentally evoked stress. However, since both tests may naturally cause various levels of stress (Kysil et al., 2017), studies aiming to assess the behavioral effects of taurine per se are imperative. In this context, as already mentioned, Mezzomo et al. (2016) reported an anxiolytic-like effect of taurine in zebrafish, since it increases the time spent in, and transitions to, the lit area following their acute treatment. These neurobehavioral data reinforce that anxiolytic effects of taurine depend on experimental task and, thus, future evaluation is needed to clarify whether taurine may display an anti-stress psychotropic activity in the species.

7. Conclusions

In summary, we emphasize the importance of further validation of zebrafish models to investigate the beneficial effects of taurine in the brain, and their underlying molecular mechanisms. Modeling both adult and larval zebrafish endophenotypes using automated videotracking systems associated with the measurement of biochemical and molecular endpoints has a great relevance to understand the pleiotropic actions of taurine in vertebrates. Since zebrafish embryos are transparent and larvae models can use multiple animals in a same battery test (Best and Alderton, 2008; Best et al., 2008; Creton, 2009), protocols that evaluate the pharmacokinetics and the central mechanisms of taurine during development can be refined further. Adult fish display a wider spectrum of quantifiable behavioral phenotypes and well-developed motor, sensory and endocrine systems susceptible to environmental challenges (Burne et al., 2011; Cachah et al., 2010; Egan et al., 2009; Grossman et al., 2010; Norton and Bally-Cuif, 2016; Webb et al., 2009; Stewart et al., 2010, 2011a, 2011b). As shown in Table 2, although both adult and larval zebrafish models present some methodological limitations, they are particularly well suited for assessing the effects of taurine at behavioral and molecular levels in different experimental models of brain-related disorders. Thus, the use of zebrafish fosters translational neuroscience studies and in vivo pharmacological screening of taurine action in the CNS.

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Extensive genomic information available on AD and PD-related genes of zebrafish. There are few animal models available to study seizure-like behaviors, but do not share the manifestation of tonic-clonic seizures as observed using EEG recordings in adult and larvae. Genetic mechanisms mediating the neurogenesis of the dopaminergic system are well conserved between zebrafish and mammals. Most of the models do not properly show evidence of significant permanent neuronal loss, a characteristic observed in age-related neurodegenerative disorders.

<table>
<thead>
<tr>
<th>Brain disorders</th>
<th>Phenotypes</th>
<th>Strategy for treatment</th>
<th>Potential Tau actions</th>
<th>Translational validity of the zebrafish model</th>
<th>Protocol limitations</th>
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</thead>
<tbody>
<tr>
<td>Alzheimer's disease</td>
<td>Deterioration of the cognitive function with &quot;fibers&quot; and &quot;small military&quot; foci. Deposition of a 39-43 amino acid residue peptide, known as Aβ, in the brain.</td>
<td>Use of cognitive enhancers to improve memory (e.g. donepezil, rivastigmine, galantamine, memantine, and the psychostimulant modafinil).</td>
<td>Tau prevents the neurotoxicity of Aβ and via activation of GABA&lt;sub&gt;4&lt;/sub&gt; receptors.</td>
<td>The neuronal structure possesses typical features observed in mammals.</td>
<td>High degree of physiological conservation regarding the mechanisms of action of different neurotransmitters. Extensive genomic information available on AD and PD-related genes of zebrafish.</td>
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<tr>
<td>Parkinson's disease</td>
<td>Degenerative loss of dopaminergic nigrostriatal neurons.</td>
<td>Levodopa (L-dopa), a dopamine precursor, has a good therapeutic action.</td>
<td>Tau increases the survival of newborn neurons, resulting in a significant increase of neurogenesis. Neurprotective effect against glutamatergic excitotoxicity (probably unrelated with the blockade of glutamate receptors).</td>
<td>Marked behavioral changes (e.g. changes in locomotion and anxiety-like behavior). Manifestation of tonic-clonic seizures as observed using EEG recordings in adult and larvae.</td>
<td>Drugs like PTZ and kainic acid induce seizure-like behaviors, but do not share the same mechanisms to induce seizures. Since there are no data regarding EEG recordings in kainic acid model, more studies are necessary to improve construct validity of the model.</td>
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<tr>
<td>Epilepsy</td>
<td>Presence of intracytoplasmic LBs and intra-axonal LNs. Sudden and abnormal discharges of neurons that may cause irreversible damage in the brain or even lead to death when not properly treated.</td>
<td>Conventional anti-epileptic drugs (AEDs) that exert their effects by inhibiting the sodium currents or by enhancing GABAergic inhibition.</td>
<td>Tau appears to modulate the neurotransmission by causing hyperpolarization and by inhibiting the firing of neurons.</td>
<td>Genetic mechanisms mediating the neurogenesis of the dopaminergic system are well conserved between zebrafish and mammalian.</td>
<td>Drugs like PTZ and kainic acid induce seizure-like behaviors, but do not share the same mechanisms to induce seizures. Since there are no data regarding EEG recordings in kainic acid model, more studies are necessary to improve construct validity of the model.</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>Disturbance of glutamate and dopamine metabolism, but the mechanisms of this disease are still unclear. Antipsychotics drugs, chlorpromazine, a &quot;phenothiazine antipsychotic&quot; and &quot;dopamine inhibitor&quot;.</td>
<td>Antagonists of serotonin 2A receptor (SHT&lt;sub&gt;2A&lt;/sub&gt;), which decreases extrapyramidal effects.</td>
<td>Changes in Tau and GSH metabolism can be involved in the pathophysiology of the schizophrenia. These substances are important regulators of the redox balance and modulate inflammatory responses.</td>
<td>Changes in locomotion, anxiety-like behavior, memory and social behavior have been described for zebrafish. Similar to humans, cortisol is the main stress hormone in zebrafish, making it an attractive model organism for assessing the behavioral, neurochemical, physiological, and epigenetic effects of stressors. Excessive genomic information available on stress-related response genes of zebrafish during ontogeny.</td>
<td>Although the measurement of whole body cortisol is consistent with stress response, measuring circulating cortisol in larvae and adult specimens is difficult (but cortisol can be quantified in tank water as it is secreted with urine).</td>
</tr>
<tr>
<td>Stress-related disorders</td>
<td>Activation of the HPA/ HPI axis, triggering a &quot;fight or flight&quot; response with enhanced activation of the sympathetic nervous system. Anxiolytic and antidepressant drugs (e.g. fluoxetine and buspirone inhibit stress-related changes).</td>
<td></td>
<td>Tau can regulate HPA axis and alter renin-angiotensin-aldosterone system playing a role in preventing stress-induced hypertension. Tau has anxiolytic-like effects in zebrafish (see Mezzomo et al., 2016). Tau could serve as an alternative treatment since it is an organic osmolyte able to regulate cell volume.</td>
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</table>

Abbreviations: Tau = Taurine; Aβ = amyloid beta; LBs = Lewy bodies; LNs = Lewy neurites; AD = Alzheimer's disease; PD = Parkinson's disease; EEG = electroencephalogram; PTZ = pentylenetetrazole; GSH = glutathione; NMDA = N-methyl-D-aspartate; HPA = hypothalamic pituitary-adrenal axis; HPI = hypothalamus–pituitary–interrenal axis.
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