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Understanding taurine CNS activity using alternative zebrafish models

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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, $NH_2CH_2CH_2SO_3H$) 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; Suárez et al., 2016). Since taurine is synthesized endogenously from methionine and cysteine in the presence of vitamin B_6, it is considered a "semi-essential amino acid" in humans (Puerta et al., 2010; Das et al., 2012; Sirdah, 2015).

The biosynthesis of taurine is highly variable between individuals depending on nutritional state, protein intake, and cysteine accessibility (Huxtable, 1992; de Luca et al., 2015). The availability of cysteine is dependent on the metabolic equilibrium between homocysteine and methionine, via folic acid, vitamin B_{12} and the enzyme activity of methyltetrahydrofolate reductase (de Luca et al., 2015). Since biosynthetic capacity of taurine is limited in humans, an alternative source is dietary intake with meat and seafood (Salze and Davis, 2015).

In humans, intracellular concentrations of taurine range between 5–20 μmol/g in various tissues, including cardiac and skeletal muscle, retina, and brain (Huxtable, 1992; Ripps and Shen, 2012; de Luca et al., 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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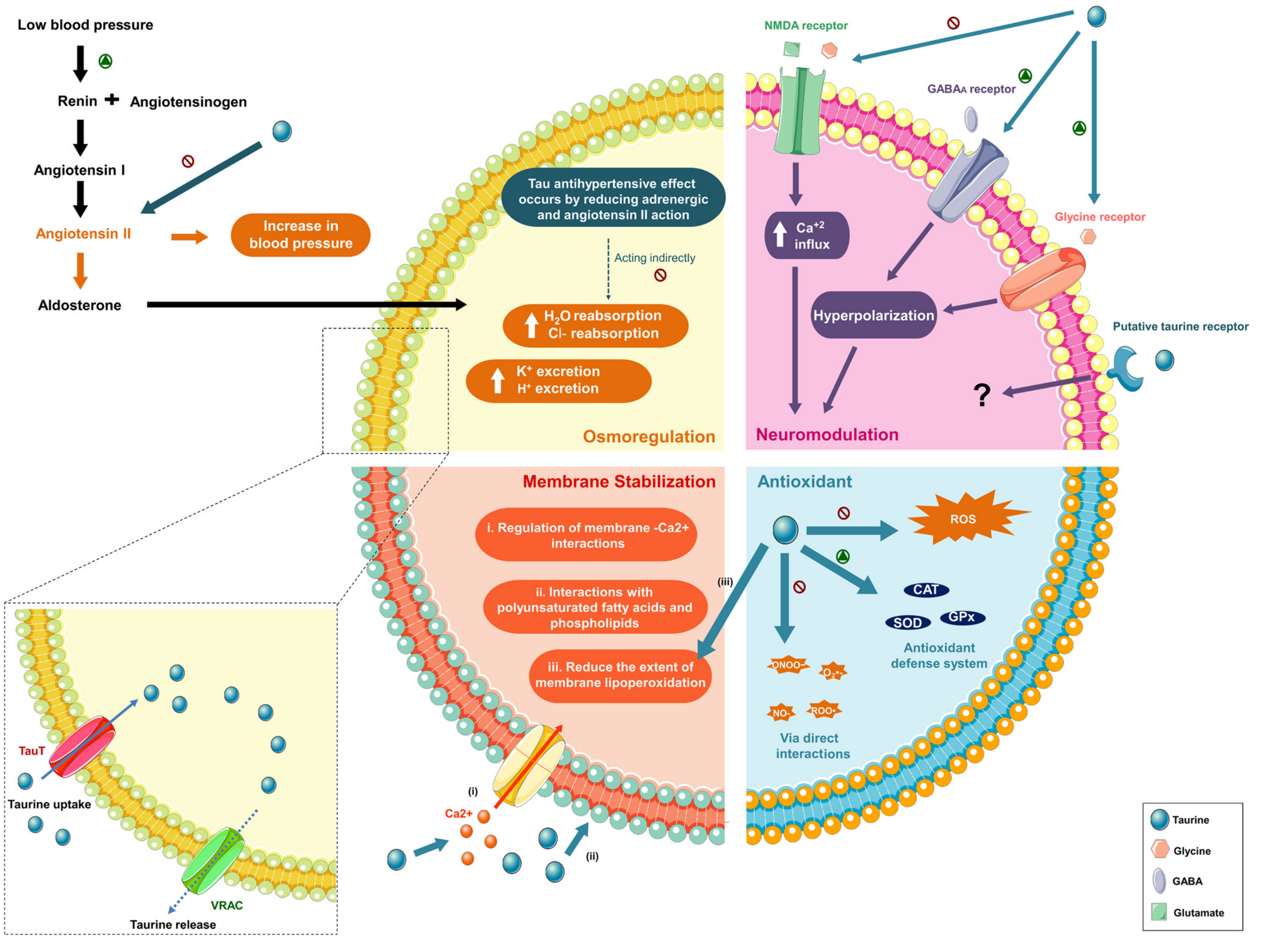

Fig. 1. Mechanisms of taurine action *in-vivo* include its role in osmoregulation, neuromodulation, membrane stabilization and antioxidant defense. The cartoon illustrates taurine transporters **(TauT and VRAC)**, as well as the putative taurine receptor, and the potential modulatory effects of taurine in the brain.

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, 2000; 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 sulfinic 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 blood stream 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 μmoles/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 convertion 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^+–Ca^{2+} 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 8 A (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-Ca^{2+} 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 phosphatidylethanolamine (PE) and phosphatidylcholine (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 Kontny, 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-inflamatory activities *per se*, since it inhibits the production of nitric oxid, tumor necrosis factor alpha (TNF-α), IL-6, IL-8, and suppresses NF-kB synthesis (Agca et al., 2014; Kim et al., 2011; Kontny et al., 2000).

However, despite its important role in controlling the pro-oxidant-antioxidant balance (Aruoma et al., 1988; Gürer 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 multple 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 manipiulation 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., 2000; 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 (Sarath 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; Baiamonte 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 odorants using the electro-olfactogram recording protocol. Although taurine-conjugated bile acids (taurocholic acid, taurochenodeoxycholic acid, taurolithocholic acid-3-sulfate) were more effective odorants than other molecules, later works provided the molecular characterization of the receptors for amino acid and bile salt odorants in adult zebrafish. Michel and Derbidge (1997) showed that zebrafish cells express specific odorant receptor gene subfamilies that mediate the chemical perception of taurine-conjugated odorants. 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 LRRC8A orthologs (*lrrc8aa* and *lrrc8ab*) that share 87% identity with human LRRC8A (Yamada et al., 2016). Molecular experiments also revealed that cysteine sulfinic 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 1
Overview of the existing experimental protocols for modeling different brain-related disorders in zebrafish.

Brain disorder	Experimental protocol	Mechanism	Characteristics	References
Alzheimer's disease	Knockdown for APP, *appa* and *appb*	Antisense morpholino to reduce APP levels in zebrafish embryos.	Induces a defective axonal outgrowth of facial branchiomotor and spinal motor neurons.	Musa et al. (2001), Joshi et al. (2009)
	Knockdown for *psn* genes	Antisense morpholino causing down-regulation of *Notch* target gene, *her6* expression and increased expression of *neurogenin 1* (ngn1) mRNA.	Somite defects, defective brain development, altered gene expression and CNS impairments.	Nornes et al. (2003)
	Knockdown for *Pen-2*	Antisense morpholino causing the reduction of *islet-1* positive neurons.	Induces a p53-dependent apoptotic pathway that contributes to neuronal death.	Campbell et al. (2006)
	Transgenic models (4R-Tau-GFP, 4R/0N tau or TAU- P301L)	Insertion of mutant genes that leads to alterations in TAU protein.	TAU phosphorylation, TAU accumulation resembling tangles and neuronal death.	Tomasiewicz et al. (2002)
	Cholinergic neurotoxins (scopolamine, pilocarpine and physostigmine)	Muscarinic receptor agonist or antagonist, or acetylcholinesterase inhibitor effects.	Impairs acquisition of passive avoidance response, retention of the learned response and suppressed the electrically evoked field potentials in the telencephalon of the adult zebrafish.	Richetti et al. (2011), Eddins et al. (2010), Kim et al. (2010)
	Glutamatergic neurotoxins (MK-801, ketamine, APV, memantine, kainate, domoate and CNQX)	NMDA-receptor antagonist, KA receptor agonist or AMPA-receptor antagonist effects.	Induces neuronal damage/death by the over activation of the glutamate receptors.	Swain et al. (2004), Zakhary et al. (2011), Nam et al. (2004), Best et al. (2008), Alfaro et al. (2011), Tiedeken et al. (2005)
Parkinson's disease	Knockdown for *PINK*1	Antisense morpholino to reduce PINK1 levels in zebrafish. PINK1 is the second most common cause of autosomal recessive PD.	Fewer central dopaminergic neurons and alterations of mitochondrial function, including increases in caspase-3 activity and reactive oxygen species levels.	Anichtchik et al. (2008)
	Dopaminergic neurotoxins (MPTP, rotenone and paraquat)	Inhibited mitochondrial complex I activity leading to oxidative stress, impaired energy metabolism, proteasomal dysfunction, and, eventually, dopamine neuronal loss.	Fewer erratic movements, increased freezing bouts and altered regulation of PD-related genes.	Bretaud et al. (2004), Sarath Babu et al. (2016)
Epilepsy	SCN1A mutant gene	Haploinsufficiency of the voltage-gated sodium channel.	Induces conditions like Dravet syndrome, including severe cognitive incapacity and drug-resistant seizure.	Escayg and Goldin, (2010), Saitoh et al. (2012)
	Mind-bomb mutant	Disturbed E3 ubiquitin ligase activity and a downregulation of GABA-related gene transcripts.	Defects of brain development which lead animals to spontaneous seizures when adults.	Hortopan and Baraban (2011)
	OCRL1 homolog mutant gene	The specific mechanics are currently unclear.	Induces symptoms like Lowe syndrome, causing hyperthermia-induced seizures.	Ramirez et al. (2012) Oltrabella et al. (2015)
	GABAergic neurotoxin (PTZ)	$GABA_A$-receptor antagonist effects.	Induces seizure-like behaviors and abnormal brain physiology.	Baraban et al. (2005), Pineda et al. (2011), Mussulini, et al. (2013)
	Glutamatergic neurotoxin (KA)	Increases glutamatergic signaling.	Induces seizure-like behaviors.	Alfaro et al. (2011)
Schizophrenia	Knockdown for *DISC1* and *NRG1*	Impairs specification of olig2-positive cells in the hindbrain and other brain regions.	Defects of oligodendrocyte development and loss of olig2-positive cerebellar neurons.	Wood et al. (2009)
	Glutamatergic neurotoxin (MK-801)	NMDA-receptor antagonist effects.	Causes SCZ-like symptoms, characterized by hyperlocomotion, memory deficits, and social impairments, which can be attenuated by antipsychotics.	Seibt et al. (2010, 2011, 2012) Maaswinkel et al. (2013)
Stress-related disorders	Acute stress	Exposure to natural stressors (e.g. alarm substance, chase with net, restraint stress).	Induce anxiety-like behavior and increase whole-body cortisol levels.	Quadros et al. (2016), Canzian et al. (2017), Dal Santo et al. (2014)
	Chronic stress	Exposure to unpredictable natural stressors (e.g. social isolation, exposure to predator, crowding)	Induces anxiety-like behavior, modulates *crf* gene expression, and increases whole-body cortisol levels.	Piato et al. (2011)

Abbreviations: AD = Alzheimer's disease; APP = *amyloid-β precursor protein*; 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*; PD = Parkinson's disease; PEN = *presenilin enhancer*; PINK1 = *putative kinase 1*; PS = *presenilin*; PTZ = pentylenetetrazole; SCN1A = sodium voltage-gated channel alpha subunit 1; SCZ = Schizoprenia.

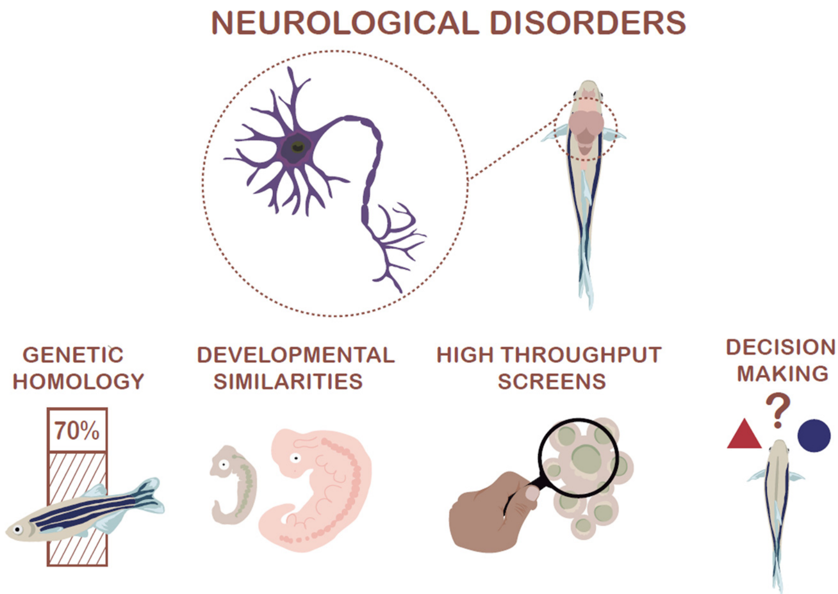

Fig. 2. Schematic diagram showing advantageous features of zebrafish to investigate the underlying mechanisms involved in CNS disorders.

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 presynaptic in neuronal terminals (Wu et al., 1979; Wu 1982; Magnusson et al., 1989; Wu and Prentice, 2010). Second, 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; Carrettiero 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, 2003). Recent data showed that taurine prevents Aβ neurotoxicity via activation of $GABA_A$ receptors (Louzada et al., 2004), suggesting that taurine-related modulation of glutamate and $GABA_A$ 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 donezepil, rivastigmine tartrate, galantamine HBr, memantine, and the psychostimulant modafinil, 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 (Tomasiewicz 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 rescued 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 ageing-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 neurocognitive 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 (LNs) composed of fibrillary 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 by 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 NMDA (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), substantia 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; Tomasiewicz 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 contextual on spontaneous motor behavior, gene expression levels, the number of dopaminergic neurons, susceptibility to neurotoxins, and the effect of gene knockdown (Bretaud 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; Dayapoğlu 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 (Czapinski 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-Hernández et al., 2015).

Taurine may be a useful agent for treating epilepsy since it modulates neurotransmission and inhibits neuronal excitation (Saransaari 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 counteract glutamatergic excitotoxicity (Vezzani and Schwarcz, 1985).

Although mechanisms of taurine action in epilepsy are not fully understood, it can reduce seizure episodes as a neuroprotector (Barbeau, 1973, 1975; Izumi et al., 1975; Durelli et al., 1976, 1977; van Gelder et al., 1977; Frigyesi and Lombardini, 1979). For example, mice pretreated with 43 mg/kg taurine show longer onset of tonic seizures after kainate administration, also reducing tonic-clonic convulsions, mortality rate, and neuronal cell death in the hippocampus (El Idrissi et al., 2003). The likely role of inhibitory neurotransmission via $GABA_A$ activation and modulation of calcium influx in the limbic system was further supported in vitro, revealing a neuroprotective action of taurine in neuronal cultures against kainic acid excitotoxicity (also see similar results in Junyent et al., (2009)). Finally, since taurine has antioxidant properties, it can play a protective role in epilepsy by modulating intracellular redox profile. In general, seizure episodes induce neurodegeneration, which can be directly associated with lipid peroxidation of brain membranes and protein carbonylation occurred due to an increased production of free radicals and / or reduced defense mechanisms (Gomes et al., 2011).

Given the potential protective role of taurine in animal models, clinical trials also began (Barbeau and Donaldson, 1973; Pennetta et al., 1977; Mongiovi, 1978; Airaksinen et al., 1980). Anticonvulsant action of taurine in humans (2 weeks 1.5–7.5 g daily) **rescued** seizures in 5 out of 9 patients (König et al., 1977). Noteworthy, the majority of these studies date to 1970s and all clinical trials had a small number of patients with different types of epilepsies. These studies also failed to characterize variations in taurine doses and to evaluate the possible synergic/additive effects with classical anticonvulsant medications. However, during the last decade, models have gained importance for studying the neurobiology of epilepsy. The genetic screening in zebrafish has been used to identify genes associated with specific disorders and behaviors (e.g. epilepsy). For example, N-Ethyl-*N*-nitrosourea generated model of Dravet syndrome, caused by mutated SCN1, SCN8 or HCN1 genes, represents a severe form of childhood epilepsy with intellectual disability, drug-resistant seizures and unexpected deaths. The zebrafish *scn1a* mutants display a haploinsufficiency for the voltage-gated sodium channel which is likely the main cause for Dravet-like phenotype in this genetic animal model (Escayg and Goldin, 2010; Saitoh et al., 2012; Griffin et al., 2016). The use of zebrafish for modeling monogenic epilepsy disorders is promising for searching novel candidates to the treatment of epilepsy since these mutants are also sensitive to various clinically used AEDs (Baraban et al., 2013). Additionally, mutations of the zebrafish OCRL1 homolog gene make the organism propense to undergo hyperthermia-induced seizures (Ramirez et al., 2012; Oltrabella et al., 2015). High-throughput mutagenesis efforts aiming to mutate each gene in zebrafish are already ongoing and will provide an incomparable resource for characterizing additional epilepsy models (Grone and Baraban, 2015; Kettleborough et al., 2013; Moens et al., 2008) and these zebrafish mutants represent important tools for assessing spontaneous seizures in a simple vertebrate system. Another model for epilepsy described is the *mind-bomb* mutant, which displays disturbed E3 ubiquitin ligase activity and a downregulation of GABA-related gene transcripts that result in a defect of brain development, showing spontaneous seizures (Hortopan et al., 2010; Hortopan and Baraban, 2011).

Seizure episodes in zebrafish can also be modeled using classical convulsant drugs (e.g. pentylenetetrazole (PTZ) and kainic acid) (Alfaro 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 larvae 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; Nasyrova 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 Sjödin, 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, transgenics) 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 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 (Clineschmidt 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 carbetocin, 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 signaling, 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 (Alsop and Vijayan, 2008; Alderman and Vijayan, 2012; Baiamonte 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 monocytic 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-aldosterone 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 (Hammarberg 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. Mushtaq 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 anxyolitic effects of taurine depend on experimental task and, thus, future evaluation is needed to clarify whether taurine may display an antistress 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 larvae 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; Cachat et al., 2010; Egan et al., 2009; Grossman et al., 2010; Norton and Bally-Cuif, 2010; 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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Table 2
Effects of taurine (Tau) as potential adjunct treatment for brain disorders, in the context of the use and limitations of zebrafish models.

Brain disorders	Phenotypes	Strategy for treatment	Potential Tau actions	Translational validity of the zebrafish model	Protocol limitations
Alzheimer's disease	Deterioration of the cognitive functions with "fibers" and "small military" foci.	Use of cognitive enhancers to improve memory (e.g. donezepil, rivastigmine tartrate, galantamine HBr, memantine, and the psychostimulant modafinil).	Tau prevents the neurotoxicity of Aβ and via activation of $GABA_A$ receptors.	The neuronal structure possesses typical features observed in mammals.	Most of the models do not properly show evidence of significant permanent neuronal loss, a characteristic observed in age-related neurodegenerative disorders.
	Deposition of a 39-43 amino acid residue peptide, known as Aβ, in the brain		Tau increases the survival of newborn neurons, resulting in a significant increase of neurogenesis.	High degree of physiological conservation regarding the mechanisms of action of different neurotransmitters.	
Parkinson's disease	Degenerative loss of dopaminergic nigrostriatal neurons.	Levodopa (L-dopa), a dopamine precursor, has a good therapeutic action.	Neuroprotective effect against glutamatergic excitotoxicity (probably unrelated with the blockade of glutamate receptors).	Extensive genomic information available on AD and PD-related genes of zebrafish.	
	Presence of intracytoplasmic LBs and intra-axonal LNs.		Neuromodulator in the nigrostriatal system.	Marked behavioral changes (e.g. changes in locomotion and anxiety-like behavior).	
Epilepsy	Sudden and abnormal discharges of neurons that may cause irreversible damage in the brain or even lead to death when not properly treated.	Conventional anti-epileptic drugs (AEDs) that exert their effects by inhibiting the sodium currents or by enhancing GABAergic inhibition.	Tau appears to modulate the neurotransmission by causing hyperpolarization and by inhibiting the firing of neurons.	Manifestation of tonic-clonic seizures as observed using EEG recordings in adult and larvae.	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.
Schizophrenia	Disturbance of glutamate and dopamine metabolism, but the mechanisms of this disease are still unclear.	Antipsychotic drugs, chlorpromazine, a "phenothiazine antipsychotic" and "dopamine inhibitor".	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.	Genetic mechanisms mediating the neurogenesis of the dopaminergic system are well conserved between zebrafish and mammalian.	There are few animal models available to study behavioral and cognitive deficits and possible pharmacological interventions so far.
		Antagonists of serotonin 2 A receptor ($5HT_{2A}$), which decreases extrapyramidal effects.	Tau may antagonize glutamatergic effects and counteract NMDA receptor activation.	Changes in locomotion, anxiety-like behavior, memory and social behavior have been described for zebrafish.	
Stress-related disorders	Activation of the HPA/ HPI axis, triggering a "fight or flight" response with enhanced activation of the sympathetic nervous system.	Anxiolytic and antidepressant drugs (e.g. fluoxetine and buspirone inhibit stress-related changes).	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.	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. Extensive genomic information available on stress-related response genes of zebrafish during ontogeny.	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).

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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References

Agca, C.A., Tuzcu, M., Hayirli, A., Sahin, K., 2014. Taurine ameliorates neuropathy via regulating NF-κB and Nrf2/HO-1 signaling cascades in diabetic rats. Food Chem. Toxicol. 71, 116–121.

Agetsuma, M., Aizawa, H., Aoki, T., Nakayama, R., Takahoko, M., Goto, M., Sassa, T., Amo, R., Shiraki, T., Kawakami, K., Hosoya, T., Higashijima, S., Okamoto, H., 2010. The habenula is crucial for experience-dependent modification of fear responses in zebrafish. Nat. Neurosci. 13 (11), 1354–1356.

Airaksinen, E.M., Oja, S.S., Marnela, K.-M., Leino, E., Pääkkönen, L., 1980. Effects of taurine treatment on epileptic patients. Prog. Clin. Biol. Res. 39, 157–166.

Albano, E., 2006. Alcohol, oxidative stress and free radical damage. Proc. Nutr. Soc. 65 (3), 278–290.

Albrecht, J., Schousboe, A., 2005. Taurine interaction with neurotransmitter receptors in the CNS: an update. Neurochem. Res. 30 (12), 1615–1621.

Alderman, S.L., Vijayan, M.M., 2012. 11b-Hydroxysteroid dehydrogenase type 2 in zebrafish brain: a functional role in hypothalamus-pituitary-interrenal axis regulation. J. Endocrinol. 215, 393–402.

Alfaro, J.M., Ripoll-Gómez, J., Burgos, J.S., 2011. Kainate administered to adult zebrafish causes seizures similar to those in rodent models. Eur. J. Neurosci. 33 (7), 1252–1255.

Alsop, D., Vijayan, M.M., 2008. The zebrafish stress axis: molecular fallout from the teleostspecific genome duplication event. Gen. Comp. Endocrinol. 161, 62–66 in press.

Andersson, M.A., Ek, F., Olsson, R., 2015. Using visual lateralization to model learning and memory in zebrafish larvae. Sci. Rep. 5, 8667.

Anichtchik, O., Diekmann, H., Fleming, A., Roach, A., Goldsmith, P., Rubinsztein, D.C., 2008. Loss of PINK1 function affects development and results in neurodegeneration in zebrafish. J. Neurosci. 28 (33), 8199–8207.

Aruoma, O.I., Halliwell, B., Hoey, B.M., Butler, J., 1988. The antioxidant action of taurine, hypotaurine and their metabolic precursors. Biochem J. 256 (1), 251–255.

Bai, Q., Mullet, S.J., Garver, J.A., Hinkle, D.A., Burton, E.A., 2006. Zebrafish DJ-1 is evolutionarily conserved and expressed in dopaminergic neurons. Brain Res. 1113, 33–44.

Baiamonte, M., Brennan, C.H., Vinson, G.P., 2015. Sustained action of developmental ethanol exposure on the cortisol response to stress in Zebrafish Larvae and Adults. Zebrafish Larvae and adults. PLoS ONE 10 (4), e0124488.

Banay-Schwartz, M., Lajtha, A., Palkovits, M., 1989. Changes with aging in the levels of amino acids in rat CNS structural elements. II. Taurine and small neutral amino acids. Neurochem. Res. 14, 563–570.

Banerjee, P.N., Filippi, D., Allen Hauser, W., 2009. The descriptive epidemiology of epilepsy-a review. Epilepsy Res. 85 (1), 31–45.

Banerjee, R., Vitvitsky, V., Garg, S.K., 2008. The undertow of sulfur metabolism on glutamatergic neurotransmission. Trends Biochem Sci. 33 (9), 413–419.

Baraban, S.C., Dinday, M.T., Hortopan, G.A., 2013. Drug screening in Scn1a zebrafish mutant identifies clemizole as a potential Dravet syndrome treatment. Nat. Commun. 4, 2410.

Baraban, S.C., Taylor, M.R., Castro, P.R., Baier, H., 2005. Pentylenetetrazole induced changes in zebrafish behavior, neural activity and c-fos expression. Neuroscience. 131, 759–768.

Barbeau, A., 1973. Zinc, taurine, and epilepsy. Trans. Am. Neurol. Assoc. 98, 1–3.

Barbeau, A., Donaldson, J., 1973. Taurine in epilepsy. Lancet. 2, 387.

Barbeau, A., Inoue, N., Tsukada, Y., Butterworth, R.F., 1975. The neuropharmacology of taurine. Life Sci. 17, 669–677.

Barcellos, H.H., Kalichak, F., da Rosa, J.G., Oliveira, T.A., Koakoski, G., Idalencio, R., de Abreu, M.S., Giacomini, A.C., Fagundes, M., Variani, C., Rossini, M., Piato, A.L., Barcellos, L.J., 2016. Waterborne aripiprazole blunts the stress response in zebrafish. Sci. Rep. 22 (6), 37612.

Barcellos, L.J.G., Ritter, F., Kreutz, L.C., Quevedo, R.M., Silva, L.B., Bedin, A.C., Finco, J.A., Cericato, L., 2007. Whole-body cortisol increases after direct and visual contact with a predator in zebrafish, Danio rerio. Aquaculture 272, 774–778.

Bault, Z.A., Peterson, S.M., Freeman, J.L., 2015. Directional and color preference in adult zebrafish: implications in behavioral and learning assays in neurotoxicology studies. J. Appl. Toxicol. 35 (12), 1502–1510.

Best, J.D., Alderton, W.K., 2008. Zebrafish: an in vivo model for the study of neurological diseases. Neuropsychiatr. Dis. Treat. 4, 567–576.

Best, J.D., Berghmans, S., Hunt, J.J., Clarke, S.C., Fleming, A., Goldsmith, P., Roach, A.G., 2008. Nonassociative learning in larval zebrafish. Neuropsychopharmacology. 33, 1206–1215.

Bianchi, L., Bolam, J.P., Galeffi, F., Frosini, M., Palmi, M., Sgaragli, G., Della Corte, L., 1996. In vivo release of taurine from rat neostriatum and substantia nigra. Adv. Exp. Med. Biol. 403, 427–433.

Bianchi, L., Colivicchi, M.A., Bolam, J.P., Della Corte, L., 1998. The release of amino acids from rat neostriatum and substantia nigra in vivo: a dual microdialysis probe analysis. Neuroscience. 87 (1), 171–180.

Bilotta, J., Saszik, S., DeLorenzo, A.S., Hardesty, R.H., 1999. Establishing and maintaining a low-cost zebrafish breeding and behavioral research facility. Behav. Res. Methods Instrum. Comput. 31 (1), 178–184.

Blank, M., Guerim, L.D., Cordeiro, R.F., Vianna, M.R., 2009. A one-trial inhibitory avoidance task to zebrafish: rapid acquisition of an NMDA-dependent long-term memory. Neurobiol Learn Mem. 92 (4), 529–534.

Blaser, R.E., Vira, D.G., 2014. Experiments on learning in zebrafish (Danio rerio): a promising model of neurocognitive function. Neurosci. Biobehav. Rev. 42, 224–231.

Bortolotto, J.W., Melo, G.M., Cognato, Gde, P., Vianna, M.R., Bonan, C.D., 2015. Modulation of adenosine signaling prevents scopolamine-induced cognitive impairment in zebrafish. Neurobiol. Learn. Mem. 118, 113–119.

Braak, H., Braak, E., 1998. Evolution of neuronal changes in the course of Alzheimer's disease. J. Neural Transm. 53, 127–140.

Bretaud, S., Lee, S., Guo, S., 2004. Sensitivity of zebrafish to environmental toxins implicated in Parkinson's disease. Neurotoxicol. Teratol. 26 (6), 857–864.

Bretaud, S., MacRaild, S., Ingham, P.W., Bandmann, O., 2011. The influence of the zebrafish genetic background on Parkinson's disease-related aspects. Zebrafish. 8 (3), 103–108.

Bruehl, H., Rueger, M., Dziobek, I., Sweat, V., Tirsi, A., Javier, E., Arentoft, A., Wolf, O.T., Convit, A., 2007. Hypothalamic-Pituitary-Adrenal axis dysregulation and memory impairments in type 2 diabetes. J. Clin. Endocrinol. Metab. 92 (7), 2439–2445.

Burne, T., Scott, E., van Swinderen, B., Hilliard, M., Reinhard, J., Claudianos, C., Eyles, D., McGrath, J., 2011. Big ideas for small brains: what can psychiatry learn from worms, flies, bees and fish? Mol. Psychiatry 16, 7–16.

Cachat, J., Stewart, A., Grossman, L., Gaikwad, S., Kadri, F., Chung, K.M., Wu, N., Wong, K., Roy, S., Suciu, C., Goodspeed, J., Elegante, M., Bartels, B., Elkhayat, S., Tien, D., Tan, J., Denmark, A., Gilder, T., Kyzar, E., Dileo, J., Frank, K., Chang, K., Utterback, E., Hart, P., Kalueff, A.V., 2010. Measuring behavioral and endocrine responses to novelty stress in adult zebrafish. Nat. Protoc. 5 (11), 1786–1799.

Calabresi, P., Castrioto, A., Di Filippo, M., Picconi, B., 2013. New experimental and clinical links between the hippocampus and the dopaminergic system in Parkinson's disease. Lancet Neurol. 12 (8), 811–821.

Caltagirone, C., Ferrannini, L., Marchionni, N., Nappi, G., Scapagnini, G., Trabucchi, M., 2012. The potential protective effect of tramiprosate (homotaurine) against Alzheimer's disease: a review. Aging Clin. Exp. Res. 24 (6), 580–587.

Campbell, W.A., Yang, H., Zetterberg, H., Baulac, S., Sears, J.A., Liu, T., Wong, S.T., Zhong, T.P., Xia, W., 2006. Zebrafish lacking Alzheimer presenilin enhancer 2 (Pen-2) demonstrate excessive p53-dependent apoptosis and neuronal loss. J. Neurochem. 96 (5), 1423–1440.

Canzian, J., Fontana, B.D., Quadros, V.A., Rosemberg, D.B., 2017. Conspecific alarm substance differently alters group behavior of zebrafish populations: putative involvement of cholinergic and purinergic signaling in anxiety- and fear-like responses. Behav. Brain Res. 1 (320), 255–263.

Carrettiero, D.C., Santiago, F.E., Motzko-Soares, A.C., Almeida, M.C., 2015. Temperature and toxic Tau in Alzheimer's disease: new insights. Temperature (Austin) 2 (4), 491–498.

Chan, C.Y., Sun, H.S., Shah, S.M., Agovic, M.S., Friedman, E., Banerjee, S.P., 2014. Modes of direct modulation by taurine of the glutamate NMDA receptor in rat cortex. Eur. J. Pharmacol. 728, 167–175.

Chang, Y.C., Ding, S.T., Lee, Y.H., Wang, Y.C., Huang, M.F., Liu, I.H., 2013. Taurine homeostasis requires de novo synthesis via cysteine sulfinic acid decarboxylase during zebrafish early embryogenesis. Amino Acids. 44 (2), 615–629.

Chen, S.W., Kong, W.X., Zhang, Y.J., Li, Y.L., Mi, X.J., Mu, X.S., 2004. Possible anxiolytic effects of taurine in the mouse elevated plusmaze. Life Sci. 75, 1503–1511.

Cho, K.H., Kim, E.S., Chen, J.D., 2000. Taurine intake and excretion in patients undergoing long term enteral nutrition. Adv. Exp. Med. Biol. 483, 605–612.

Chung, M.C., Malatesta, P., Bosquesi, P.L., Yamasaki, P.R., Santos, J.L., Vizioli, E.O., 2012. Advances in drug design based on the amino acid approach: taurine analogues for the treatment of CNS diseases. Pharmaceuticals (Basel). 5 (10), 1128–1146.

Clineschmidt, B.V., Martin, G.E., Bunting, P.R., Papp, N.L., 1982. Central sympathomimetic activity of (+)-5-methyl-10,11-dihydro-5H-dibenzo [d]cyclohepten- 5,10-imine (MK-801), a substance with potent anticonvulsant, central sympathomimetic, and apparent anxiolytic properties. Drug. Dev. Res. 2, 135–145.

Cognato, G.P., Bortolotto, J.W., Blazina, A.R., Christoff, R.R., Lara, D.R., Vianna, M.R., Bonan, C.D., 2012. Y-Maze memory task in zebrafish (Danio rerio): the role of glutamatergic and cholinergic systems on the acquisition and consolidation periods. Neurobiol Learn Mem. 98 (4), 321–328.

Conte-Camerino, D., Franconi, F., Mambrini, M., Bennardini, F., Failli, P., Bryant, S.H., Giotti, A., 1987. The action of taurine on chloride conductance and excitability characteristics of rat striated muscle fibers. Pharmacol. Res. Commun. 19 (10), 685–701.

Coyle, J.T., 2006. Glutamate and schizophrenia: beyond the dopamine hypothesis. Cell. Mol. Neurobiol. 26 (4-6), 365–384.

Coyle, J.T., Tsai, G., 2004. The NMDA receptor glycine modulatory site: a therapeutic target for improving cognition and reducing negative symptoms in schizophrenia. Psychopharmacology (Berl.) 174, 32–38.

Coyle, J.T., Tsai, G., Goff, D.C., 2002. Ionotropic glutamate receptors as therapeutic targets in schizophrenia. Curr. Drug. Targets CNS Neurol. Disord. 1, 183–189.

Creton, R., 2009. Automated analysis of behavior in zebrafi sh larvae. Behav. Brain Res. 203, 127–136.

Czapinski, P., Blaszczyk, B., Czuczwar, S.J., 2005. Mechanisms of action of antiepileptic drugs. Curr. Top. Med. Chem. 5 (1), 3–14.

Dal Santo, G., Conteratoa, G.M.M., Barcellos, L.J.G., Rosemberg, D.B., Piato, A.L., 2014. Acute restraint stress induces an imbalance in the oxidative status of the zebrafish brain. Neurosci. Lett. 13 (558), 103–108.

Das, J., Roy, A., Sil, P.C., 2012. Mechanism of the protective action of taurine in toxin and drug induced organ pathophysiology and diabetic complications: a review. Folia

Microbiol. (Dordrecht Netherlands) 3 (12), 1251–1264.
Das, S.K., Hiran, K.R., Mukherjee, S., Vasudevan, D.M., 2007. Oxidative stress is the primary event: effects of ethanol consumption in brain. Indian J. Clin. Biochem. 22 (1), 99–104.
David-Watine, B., Goblet, C., de Saint Jan, D., Fucile, S., Devignot, V., Bregestovski, P., Korn, H., 1999. Cloning, expression and electrophysiological characterization of glycine receptor alpha subunit from zebrafish. Neuroscience. 90 (1), 303–317.
Dawson, R., Jr, Pelleymounter, M.A., Cullen, M.J., Gollub, M., Liu, S., 1999. An age-related decline in striatal taurine is correlated with a loss of dopaminergic markers. Brain Res. Bull. 48 (3), 319–324.
Dayapoğlu, N., Tan, M., 2016. Clinical nurses' knowledge and attitudes toward patients with epilepsy. Epilepsy Behav. 61, 206–209.
de Luca, A., Pierno, S., Camerino, D.C., 2015. Taurine: the appeal of a safe amino acid for skeletal muscle disorders. J. Transl. Med. 13, 243.
Della Corte, L., Crichton, R.R., Duburs, G., Nolan, K., Tipton, K.F., Tirzitis, G., Ward, R.J., 2002. The use of taurine analogues to investigate taurine functions and their potential therapeutic applications. Amino Acids. 23 (4), 367–379.
Demarcay, H., 1838. Ueber die Natur der Galle. Annalen der Pharmacie 27 (3), 270–291.
Den Broeder, M.J., Kopylova, V.A., Kamminga, L.M., Legler, J., 2015. Zebrafish as a model to study the role of peroxisome proliferating-activated receptors in adipogenesis and obesity. PPAR Res. 358029.
Deutsch, S.I., Rosse, R.B., Mastropaolo, J., 1997. Behavioral approaches to the functional assessment of NMDA-mediated neural transmission in intact mice. Clin. Neuropharmacol. 20, 375–384.
Dooley, K., Zon, L.I., 2000. Zebrafish: a model system for the study of human disease. Curr. Opin. Genet. Dev. 10 (3), 252–256.
Dray, A., Straughan, D.W., 1974. Proceedings: evaluation of iontophoretic N-methylbicuculline and other inhibitory amino-acid antagonists in rat brain stem. Br. J. Pharmacol. 51 (1), 133P–134P.
Driver, J.A., Logroscino, G., Gaziano, J.M., Kurth, T., 2009. Incidence and remaining lifetime risk of Parkinson disease in advanced age. Neurology 72 (5), 432–438.
Durelli, L., Mutani, R., Delsedime, M., Quattrocolo, G., Buffa, C., Mazzarino, M., Fumero, S., 1976. Electroencephalographic and biochemical study of the antiepileptic actions of taurine administered by cortical superfusion. Exp. Neurol. 52, 30–39.
Durelli, L., Mutani, R., Quattrocolo, G., Delsedime, M., Buffa, C., Fassio, F., Valentini, C., Fumero, S.S., 1977. Relationships between electroencephalographic pattern and biochemical picture of the cobalt epileptogenic lesion after cortical superfusion with taurine. Exp. Neurol. 54, 489–503.
Eddins, D., Cerutti, D., Williams, P., Linney, E., Levin, E.D., 2010. Zebrafish provide a sensitive model of persisting neurobehavioral effects of developmental chlorpyrifos exposure: comparison with nicotine and pilocarpine effects and relationship to dopamine deficits. Neurotoxicol Teratol. 32, 99–108.
Egan, R.J., Bergner, C.L., Hart, P.C., Cachat, J.M., Canavello, P.R., Elegante, M.F., Elkhayat, S.I., Bartels, B.K., Tien, A.K., Tien, D.H., Mohnot, S., Beeson, E., Glasgow, E., Amri, H., Zukowska, Z., Kalueff, A.V., 2009. Understanding behavioral and physiological phenotypes of stress and anxiety in zebrafish. Behav. Brain Res. 205 (1), 38–44.
El Idrissi, A., 2008. Taurine improves learning and retention in aged mice. Neurosci. Lett. 436, 19–22.
El Idrissi, A., Messing, J., Scalia, J., Trenkner, E., 2003. Prevention of epileptic seizures by taurine. Adv. Exp. Med. Biol. 526, 515–525.
El Idrissi, A., Trenkner, E., 1999. Growth factors and taurine protect against excitotoxicity by stabilizing calcium homeostasis and energy metabolism. J. Neurosci. 19 (21), 9459–9468.
Escayg, A., Goldin, A.L., 2010. Sodium channel SCN1A and epilepsy: mutations and mechanisms. Epilepsia 51, 1650–1658.
Ferreira, S.E., de Mello, M.T., Pompéia, S., de Souza-Formigoni, M.L., 2006. Effects of energy drink ingestion on alcohol intoxication. Alcohol. Clin. Exp. Res. 30 (4), 598–605.
Ferreira, S.E., Hartmann Quadros, I.M., Trindade, A.A., Takahashi, S., Koyama, R.G., Souza-Formigoni, M.L., 2004. Can energy drinks reduce the depressor effect of ethanol? An experimental study in mice. Physiol Behav. 82 (5), 841–847.
Filippi, A., Dürr, K., Ryu, S., Willaredt, M., Holzschuh, J., Driever, W., 2007. Expression and function of nr4a2, lmx1b, and pitx3 in zebrafi sh dopaminergic and noradrenergic neuronal development. BMC Dev. Biol. 7, 135.
Fisher, R.S., Harding, G., Erba, G., Barkley, G.L., Wilkins, A., Epilepsy Foundation of America Working Group, 2005. Photic- and pattern-induced seizures: a review for the Epilepsy Foundation of America Working Group. Epilepsia 46 (9), 1426–1441.
Fontana, B.D., Meinerz, D.L., Rosa, L.V., Mezzomo, N.J., Silveira, A., Giuliani, G.S., Quadros, V.A., Filho, G.L., Blaser, R.E., Rosemberg, D.B., 2015. Modulatory action of taurine on ethanol-induced aggressive behavior in zebrafish. Pharmacol. Biochem. Behav. 141, 18–27.
Foos, T.M., Wu, J.Y., 2002. The role of Taurine in Central nervous system and the modulation of intracellular calcium homeostasis. Neurochem. Res. 27, 21–26.
Formella, I., Scott, E.K., Burne, T.H., Harms, L.R., Liu, P.Y., Turner, K.M., Cui, X., Eyles, D.W., 2012. Transient knockdown of tyrosine hydroxylase during development has persistent effects on behaviour in adult zebrafish (Danio rerio). PLoS One 7 (8), e42482.
Frigyesi, T.L., Lombardini, J.B., 1979. Augmentation of thalamomotor cortico - cerebellar epileptogenesis by taurine and its antagonism by diphenylhydantoin. Life Sci. 24, 1251–1259.
Frosini, M., Sesti, C., Saponara, S., Ricci, L., Valoti, M., Palmi, M., Machetti, F., Sgaragli, G., 2003. A specific taurine recognition site in the rabbit brain is responsible for taurine effects on thermoregulation. Br. J. Pharmacol. 139, 487–494.
Gaby, A.R., 2007. Natural approaches to epilepsy. Altern. Med. Rev. 12 (1), 9–24.
Galli, U., Gaab, J., Ettlin, D.A., Ruggia, F., Ehlert, U., Palla, S., 2009. Enhanced negative feedback sensitivity of the hypothalamus-pituitary-adrenal axis in chronic myogenous facial pain. Eur. J. Pain 13 (6), 600–605.
Gebara, E., Udry, F., Sultan, S., Toni, N., 2015. Taurine increases hippocampal neurogenesis in aging mice. Stem Cell. Res. 14 (3), 369–379.
Gerlai, R., 2003. Zebrafish: an uncharted behavior genetic model. Behav. Genet. 33, 461–468.
Gerlai, R., Lahav, M., Guo, S., Rosenthal, A., 2000. Drinks like a fish: zebra fish (Danio rerio) as a behavior genetic model to study alcohol effects. Pharmacol. Biochem. Behav. 4, 773–782.
Giacomotto, J., Carroll, A.P., Rinkwitz, S., Mowry, B., Cairns, M., Becker, T.S., 2016. Developmental suppression of schizophrenia-associated miR-137 alters sensorimotor function in zebrafish. Transl. Psychiatry 6, e818.
Gomes, T.K.C., Oliveira, S.L., Ataide, T.R., Trindade Filho, E.M., 2011. The role of the ketogenic diet on oxidative stress present in experimental epilepsy. J. Epilepsy Clin. Neurophysiol. 17 (2), 54–64.
Green, T.R., Fellman, J.H., Eicher, A.L., Pratt, K.L., 1991. Antioxidant role and subcellular location of hypotaurine and taurine in human neutrophils. Biochim. Biophys. Acta 1073 (1), 91–97.
Griffin, A., Krasniak, C., Baraban, S.C., 2016. Advancing epilepsy treatment through personalized genetic zebrafish models. Prog. Brain Res. 226, 195–207.
Grone, B.P., Baraban, S.C., 2015. Animal models in epilepsy research: legacies and new directions. Nat. Neurosci. 18 (3), 339–343.
Grone, B.P., Marchese, M., Hamling, K.R., Kumar, M.G., Krasniak, C.S., Sicca, F., Santorelli, F.M., Patel, M., Baraban, S.C., 2016. Epilepsy, behavioral abnormalities, and physiological comorbidities in syntaxin-binding protein 1 (STXBP1) mutant zebrafish. PLoS One 11 (3), e0151148.
Grossman, L., Utterback, E., Stewart, A., Gaikwad, S., Chung, K., Suciu, C., Wong, K., Elegante, M., Elkhayat, S., Tan, J., Gilder, T., Wu, N., DiLeo, J., Cachat, J., Kalueff, A.V., 2010. Characterization of behavioral and endocrine effects of LSD on zebrafish. Behav. Brain Res. 214 (2), 277–284.
Guo, S., 2004. Linking genes to brain, behavior and neurological diseases: what can we learn from zebrafish? Genes Brain Behav. 3, 63–74.
Gürer, H., Ozgünes, H., Saygin, E., Ercal, N., 2001. Antioxidant effect of taurine against lead-induced oxidative stress. Arch. Environ. Contam. Toxicol. 41 (4), 397–402.
Haddad, J.J., Harb, H.L., 2005. L-gamma-Glutamyl-L-cysteinyl-glycine (glutathione; GSH) and GSH-related enzymes in the regulation of pro-and anti-inflammatory cytokines: a signaling transcriptional scenario for redox (y)immunologic sensor(s)? Mol. Immunol. 42, 987–1014.
Hamaguchi, T., Azuma, J., Schaffer, S., 1991. Interaction of taurine with methionine: inhibition of myocardial phospholipid methyltransferase. J. Cardiovasc. Pharmacol. 18 (2), 224–230.
Hammarberg, A., Nylander, I., Zhou, Q., Jayaram-Lindström, N., Reid, M.S., Franck, J., 2009. The effect of acamprosate on alcohol craving and correlation with hypothalamic pituitary adrenal (HPA) axis hormones and beta-endorphin. Brain Res. 11 (1305) Suppl:S2-6.
Hanretta, A.T., Lombardini, J.B., 1987. Is taurine a hypothalamic neurotransmitter?: A model of the differential uptake and compartmentalization of taurine by neuronal and glial cell particles from the rat hypothalamus. Brain Res. 434 (2), 167–201.
Hansen, S.H., Andersen, M.L., Birkedal, H., Cornett, C., Wibrand, F., 2006. The important role of taurine in oxidative metabolism. Adv. Exp. Med. Biol. 583, 129–135.
Hansen, D.B., Friis, M.B., Hoffmann, E.K., Lambert, I.H., 2012. Downregulation of the taurine transporter TauT during hypo-osmotic stress in NIH3T3 mouse fibroblasts. J. Membr. Biol. 245 (2), 77–87.
Haskew-Layton, R.E., Rudkouskaya, A., Jin, Y., Feustel, P.J., Kimelberg, H.K., Mongin, A.A., 2008. Two distinct modes of hypoosmotic medium-induced release of excitatory amino acids and taurine in the rat brain in vivo. PLoS One 3 (10), e3543.
Hayes, K.C., Carey, R.E., Schmidt, S.Y., 1975. Retinal degeneration associated with taurine deficiency in the cat. Science 188 (4191), 949–951.
Heinrichs, R.W., 2003. Historical origins of schizophrenia: two early madmen and their illness. J. Hist. Behav. Sci. 39 (4), 349–363.
Hernandez-Benitez, R., Ramos-Mandujano, G., Pasantes-Morales, H., 2012. Taurine stimulates proliferation and promotes neurogenesis of mouse adult cultured neural stem/progenitor cells. Stem Cell. Res. 9, 24–34.
Hoffmann, E.K., Lambert, I.H., Pedersen, S.F., 2009. Physiology of cell volume regulation in vertebrates. Physiol. Rev. 89 (1), 193–277.
Holsboer, F., 2000. The corticosteroid receptor hypothesis of depression. Neuropsychopharmacology 23, 5.
Hortopan, G.A., Baraban, S.C., 2011. Aberrant expression of genes necessary for neuronal development and notch signaling in an epileptic mind bomb zebrafish. Dev. Dyn. 240, 1964–1976.
Hortopan, G.A., Dinday, M.T., Baraban, S.C., 2010. Spontaneous seizures and altered gene expression in GABA signaling pathways in a mind bomb mutant zebrafish. J. Neurosci. 30, 13718–13728.
Howe, K., Clark, M.D., Torroja, C.F., Torrance, J., Berthelot, C., Muffato, M., Collins, J.E., Humphray, S., McLaren, K., Matthews, L., McLaren, S., Sealy, I., Caccamo, M., Churcher, C., Scott, C., Barrett, J.C., Koch, R., Rauch, G.J., White, S., Chow, W., Kilian, B., Quintais, L.T., et al., 2013. The zebrafish reference genome sequence and its relationship to the human genome. Nature 496 (7446), 498–503.
Huxtable, R., Bressler, R., 1973. Effect of taurine on a muscle intracellular membrane. Biochim. Biophys. Acta 323 (4), 573–583.
Huxtable, R.J., 1992. Physiological actions of taurine. Physiol. Rev. 72, 101–163.
Izumi, K., Igisu, H., Fukuda, T., 1975. Effects of edentate on seizures suppressing actions of taurine and GABA. Brain Res. 88, 576–579.
Jacobsen, J.G., Smith, L.H., 1968. Biochemistry and physiology of taurine and taurine derivatives. Physiol. Rev. 48, 424–511.
Javed, H., Khan, A., Vaibhav, K., Moshahid Khan, M., Ahmad, A., Ejaz, Ahmad M.,

Ahmad, A., Tabassum, R., Islam, F., Safhi, M.M., Islam, F., 2013. Taurine ameliorates neurobehavioral, neurochemical and immunohistochemical changes in sporadic dementia of Alzheimer's type (SDAT) caused by intracerebroventricular streptozotocin in rats. Neurol. Sci. 34, 2181–2192.
Jenkins, T.A., 2013. Perinatal complications and schizophrenia: involvement of the immune system. Front.Neurosci 7, 110.
Jia, J., Fernandes, Y., Gerlai, R., 2014. Short-term memory in zebrafish (Danio rerio). Behav. Brain Res. 270, 29–36.
Joshi, P., Liang, J.O., DiMonte, K., Sullivan, J., Pimplikar, S.W., 2009. Amyloid precursor protein is required for convergent-extension movements during Zebrafish development. Dev. Biol. 335, 1–11.
Junyent, F., Utrera, J., Romero, R., Pallàs, M., Camins, A., Duque, D., Auladell, C., 2009. Prevention of epilepsy by taurine treatments in mice experimental model. J. Neurosci. Res. 87, 1500–1508.
Kaiser, D.M., Acharya, M., Leighton, P.L., Wang, H., Daude, N., Wohlgemuth, S., Shi, B., Allison, W.T., 2012. Amyloid beta precursor protein and prion protein have a conserved interaction affecting cell adhesion and CNS development. PLoS One 7 (12), e51305.
Kalueff, A.V., Gebhardt, M., Stewart, A.M., Cachat, J.M., Brimmer, M., Chawla, J.S., Craddock, C., Kyzar, E.J., Roth, A., Landsman, S., Gaikwad, S., Robinson, K., Baatrup, E., Tierney, K., Shamchuk, A., Norton, W., Miller, N., Nicolson, T., Braubach, O., Gilman, C.P., Pittman, J., Rosemberg, D.B., Gerlai, R., Echevarria, D., Lamb, E., Neuhauss, S.C., Weng, W., Bally-Cuif, L., Schneider, H., 2013. Zebrafish neuroscience research consortium, 2013. Towards a comprehensive catalog of zebrafish behavior 1.0 and beyond. Zebrafish 10 (1), 70–86.
Kehagia, A.A., Barker, R.A., Robbins, T.W., 2010. Neuropsychological and clinical heterogeneity of cognitive impairment and dementia in patients with parkinson's disease. Lancet Neurol. 9 (12), 1200–1213.
Kettleborough, R.N., Busch-Nentwich, E.M., Harvey, S.A., Dooley, C.M., de Bruijn, E., van Eeden, F., Sealy, I., White, R.J., Herd, C., Nijman, I.J., Fényes, F., Mehroke, S., Scahill, C., Gibbons, R., Wali, N., Carruthers, S., Hall, A., Yen, J., Cuppen, E., Stemple, D.L., 2013. A systematic genome-wide analysis of zebrafish protein-coding gene function. Nature 496, 494–497.
Kiefer, F., Jahn, H., Otte, C., Naber, D., Wiedemann, K., 2006. Hypothalamic-Pituitary-Adrenocortical axis activity: a target of pharmacological anticraving treatment? Biol. Psychiatry 60, 74–76.
Kim, B.S., Cho, I.S., Park, S.Y., Schuller-Levis, G., Levis, W., Park, E., 2011. Taurine chloramine inhibits NO and TNF-α production in zymosan plus interferon-γ activated RAW 264.7 cells. J. Drugs Dermatol. 10 (6), 659–665.
Kim, H.W., Lee, E.J., Shim, M.J., Kim, B.K., 1998. Effects of steroid hormones and cyclosporine A on taurine-transporter activity in the RAW264.7 cell line. Adv. Exp. Med. Biol. 442, 247–254.
Kim, H.Y., Kim, H.V., Yoon, J.H., Kang, B.R., Cho, S.M., Lee, S., Kim, J.Y., Kim, J.W., Cho, Y., Woo, J., Kim, Y., 2014. Taurine in drinking water recovers learning and memory in the adult APP/ PS1 mouse model of Alzheimer's disease. Sci. Rep. 4, 7467.
Kim, Y.H., Lee, Y., Lee, K., Lee, T., Kim, Y.J., Lee, C.J., 2010. Reduced neuronal proliferation by proconvulsant drugs in the developing zebrafish brain. Neurotoxicol. Teratol. 32, 551–557.
Klamt, F., Shacter, E., 2005. Taurine chloramine, an oxidant derived from neutrophils, induces apoptosis in human B lymphoma cells through mitochondrial damage. J. Biol. Chem. 280 (22), 21346–21352.
König, P., Kriechbaum, G., Presslich, O., Schubert, H., Schuster, P., Sieghart, W., 1977. Orale Taurinmedikation bei therapieresistenten Epilepsien. Klin. Wochenschr. 89, 111–113.
Kontny, E., Szczepańska, K., Kowalczewski, J., Kurowska, M., Janicka, I., Marcinkiewicz, J., Maśliński, W., 2000. The mechanism of taurine chloramine inhibition of cytokine (interleukin-6, interleukin-8) production by rheumatoid arthritis fibroblast-like synoviocytes. Arthritis Rheum. 43 (10), 2169–2177.
Kozlowski, D.J., Chen, Z., Zhuang, L., Fei, Y.J., Navarre, S., Ganapathy, V., 2008. Molecular characterization and expression pattern of taurine transporter in zebrafish during embryogenesis. Life Sci. 82 (19-20), 1004–1011.
Kysil, E.V., Meshalkina, D.A., Frick, E.E., Echevarria, D.J., Rosemberg, D.B., Maximino, C., Lima, M.G., Abreu, M.S., Giacomini, A.C., Barcellos, L.J.G., Song, C., Kalueff, A.V., 2017. Comparative analyses of zebrafish anxiety-like behavior using conflict-based novelty tests. Zebrafish 14 (3).
Lambert, I.H., Kristensen, D.M., Holm, J.B., Mortensen, O.H., 2015. Physiological role of taurine – from organism to organelle. Acta Physiol. 213, 191–212.
Lazarewicz, J.W., Noremberg, K., Lehmann, A., Hamberger, A., 1985. Effects of taurine on calcium binding and accumulation in rabbit hippocampal and cortical synaptosomes. Neurochem. Int. 7 (3), 421–427.
Lee, J., Freeman, J.L., 2016. Embryonic exposure to 10 μg L-1 lead results in female-specific expression changes in genes associated with nervous system development and function and alzheimer's disease in aged adult zebrafish brain. Metallomics 8 (6), 589–596.
Lerdweeraphon, W., Wyss, J.M., Boonmars, T., Roysommutil, S., 2013. Perinatal taurine exposure affects adult oxidative stress. J. Physiol. Regul. Integr. Comp. Physiol. 305, R95–R97.
Levis, G.S., Mehta, P.D., Rudelli, R., Sturman, J., 1990. Immunologic Consequences of taurine in cats. J. Leukoc. Biol. 47, 321–331.
Li, X., Hu, L., 2016. The role of stress regulation on neural plasticity in pain chronification. Neural Plast. 1–9 Article ID 6402942.
Lieber, C.S., 1997. Ethanol metabolism, cirrhosis and alcoholism. Clin. Chim. Acta. 257 (1), 59–84.
Lipton, S.A., Rosenberg, P.A., 1994. Excitatory amino acids as a final common pathway for neurologic disorders. N. Engl. J. Med. 330, 613–622.
Lodish, H., Berk, A., Zipursky, S.L., 2000. Molecular Cell Biology: Section 21.4 Neurotransmitters, Synapses, and Impulse Transmission, 4th ed. W. H. Freeman, New York.
Louzada, P.R., Paula Lima, A.C., Mendonca-Silva, D.L., Noël, F., De Mello, F.G., Ferreira, S.T., 2004. Taurine prevents the neurotoxicity of beta-amyloid and glutamate receptor agonists: activation of GABA receptors and possible implications for Alzheimer's disease and other neurological disorders. FASEB J. 18 (3), 511–518.
Lv, Q., Dong, G., Cao, S., Wu, G., Feng, Y., Mei, L., Lin, S., Yang, Q., Yang, J., Hu, J., 2015. Effects of taurine on blood index of hypothalamic pituitary adrenal (HPA) axis of stress-induced hypertensive rat. Adv. Exp. Med. Biol. 803, 613–621.
Maaswinkel, H., Zhu, L., Weng, W., 2013. Assessing social engagement in heterogeneous groups of zebrafish: a New paradigm for autism-like behavioral responses. PLoS One 8 (10), e75955.
Machlin, L.J., Pearson, P.B., 1957. Metabolism of taurine in the growing chicken. Arch. Biochem. Biophys. 70, 35–42.
MacRae, C.A., Peterson, R.T., 2015. Zebrafish as tools for drug discovery. Nat. Rev. Drug. Discov. 14 (10), 721–731.
Magnusson, K.R., Clements, J.R., Wu, J.Y., Beitz, A.J., 1989. Colocalization of taurine and cysteine sulfinic acid decarboxylase-like immunoreactivity in the hippocampus of the rat. Synapse 4, 55–69.
Malcangio, M., Bartolini, A., Ghelardini, C., Bennardini, F., Malmberg-Aiello, P., Franconi, F., Giotti, A., 1989. Effect of ICV taurine on the impairment of learning, convulsions and death caused by hypoxia. Psychopharmacology (Berl.) 98, 316–320.
Marcinkiewicz, J., Kontny, E., 2014. Taurine and inflammatory diseases. Amino Acids 46, 7–20.
Martin, D.L., 1992. Synthesis and release of neuroactive substances by glial cells. Glia 5, 81–94.
Marczinski, C.A., Fillmore, M.T., 2014. Energy drinks mixed with alcohol: what are the risks? Nutr. Rev. 72 (1), 98–107.
Massieu, L., Montiel, T., Robles, G., Quesada, O., 2004. Brain amino acids during hyponatremia in vivo: clinical observations and experimental studies. Neurochem. Res. 29, 73–81.
Mattson, M., 2003. Excitotoxic and excitoprotective mechanisms: abundant targets for the prevention and treatment of neurodegenerative disorders. Neuromol. Med. 3, 65–94.
May, Z., Morrill, A., Holcombe, A., Johnston, T., Gallup, J., Fouad, K., Schalomon, M., Hamilton, T.J., 2016. Object recognition memory in zebrafish. Behav. Brain Res. 296, 199–210.
McCormick, D.A., Contreras, D., 2001. On the cellular and network bases of epileptic seizures. Annu. Rev. Physiol. 63, 815–846.
McEwen, B.S., 2007. Physiology and neurobiology of stress and adaptation: Central role of the brain. Physiol Rev. 87, 873–904.
Mehlman, M.J., 2004. Cognition-Enhancing drugs. Milbank Q. 82 (3), 483–506.
Menzie, J., Pan, C., Prentice, H., Wu, J.Y., 2014. Taurine and central nervous system disorders. Amino Acids 46 (1), 31–46.
Mezzomo, N.J., Silveira, A., Giuliani, G.S., Quadros, V.A., Rosemberg, D.B., 2016. The role of taurine on anxiety-like behaviors in zebrafish: a comparative study using the novel tank and the light-dark tasks. Neurosci. Lett. 613, 19–24.
Michel, W.C., Derbidge, D.S., 1997. Evidence of distinct amino acid and bile salt receptors in the olfactory system of the zebrafish, Danio rerio. Brain Res. 764 (1-2), 179–187.
Michel, W.C., Lubomudrov, L.M., 1995. Specificity and sensitivity of the olfactory organ of the zebrafish, Danio rerio. J. Comp. Physiol. 177 (2), 191–199.
Miczek, K.A., Fish, E.W., De Bold, J.F., 2003. Neurosteroids, GABAA receptors, and escalated aggressive behavior. Horm Behav. 44 (3), 242–257.
Miczek, K.A., Weerts, E.M., Vivian, J.A., Barros, H.M., 1995. Aggression, anxiety and vocalizations in animals: GABAA and 5-HT anxiolytics. Psychopharmacology (Berl). 121 (1), 38–56.
Miller, T.J., Hanson, R.D., Yancey, P.H., 2000. Developmental changes in organic osmolytes in prenatal and postnatal rat tissues. Comp. Biochem. Physiol. A Mol. Integr. Physiol. 125, 45–56.
Miranda, A.F., Boegman, R.J., Beninger, R.J., Jhamandas, K., 1997. Protection against quinolinic acid-mediated excitotoxicity in nigrostriatal dopaminergic neurons by endogenous kynurenic acid. Neurosci.78 967–975.
Moens, C.B., Donn, T.M., Wolf-Saxon, E.R., Ma, T.P., 2008. Reverse genetics in zebrafish by TILLING. Brief. Funct. Genom. Proteom. 7, 454–459.
Mongiovi, A., 1978. Contributo clinico al controllo dell'epilessia com taurina. Riv. Neurol. 48, 305–325.
Moreno-Peral, P., Conejo-Cerón, S., Motrico, E., Rodríguez-Morejón, A., Fernández, A., García-Campayo, J., Roca, M., Serrano-Blanco, A., Rubio-Valera, M., Bellón, J.Á., 2014. Risk factors for the onset of panic and generalised anxiety disorders in the general adult population: a systematic review of cohort studies. J. Affect Disord. 168, 337–348.
Musa, A., Lehrach, H., Russo, V.A., 2001. Distinct expression patterns of two zebrafish homologues of the human APP gene during embryonic development. Dev. Genes Evol. 211, 563–567.
Mushtaq, M.Y., Marçal, R.M., Champagne, D.L., Kooy, F.V., Verpoorte, R., Choi, Y.H., 2014. Effect of acute stresses on zebra Fish (Danio rerio) metabolome measured by NMR-Based metabolomics. Planta Med. 80, 1227–1233.
Mussulini, B.H., Leite, C.E., Zenki, K.C., Moro, L., Baggio, S., Rico, E.P., Rosemberg, D.B., Dias, R.D., Souza, T.M., Calcagnotto, M.E., Campos, M.M., Battastini, A.M., de Oliveira, D.L., 2013. Seizures induced by pentylenetetrazole in the adult zebrafish: a detailed behavioral characterization. PLoS One 8 (1), e54515.
Nam, R.H., Kim, W., Lee, C.J., 2004. NMDA receptordependent long-term potentiation in the telencephalon of the zebrafish. Neurosci. Lett. 370, 248–251.
Nasyrova, R.F., Ivashchenko, D.V., Ivanov, M.V., Neznanov, N.G., 2015. Role of nitric oxide and related molecules in schizophrenia pathogenesis: biochemical, genetic and clinical aspects. Front. Physiol. 6, 139.
Newman, M., Verdile, G., Martins, R.N., Lardelli, M., 2011. Zebrafish as a tool in

Alzheimer's disease research. Biochim. Biophys. Acta 1812 (3), 346–352.
Newport, D.J., Nemeroff, C.B., 2003. Neurobiology of posttraumatic stress disorder. FOCUS Summer (I) 3, 313–321.
Nilius, B., 2004. Is the volume-regulated anion channel VRAC a "water-permeable" channel? Neurochem. Res. 29 (1), 3–8.
Nishimura, Y., Murakami, S., Ashikawa, Y., Sasagawa, S., Umemoto, N., Shimada, Y., Tanaka, T., 2015. Zebrafish as a systems toxicology model for developmental neurotoxicity testing. Congenit. Anom. (Kyoto) 55 (1), 1–16.
Nordin, C., Sjödin, I., 2006. Altered CSF taurine function in pathological gambling. Psychiatry Res. 40, 473–474.
Nornes, S., Groth, C., Camp, E., Ey, P., Lardelli, M., 2003. Developmental control of Presenilin1 expression, endoproteolysis, and interaction in zebrafish embryos. Exp. Cell. Res. 289 (1), 124–132.
Norton, W., Bally-Cuif, L., 2010. Adult zebrafish as a model organism for behavioural genetics. BMC Neurosci. 11, 90.
Nunes, A.K., Rapôso, C., de Oliveira, W.H., Thomé, R., Verinaud, L., Tovar-Moll, F., Peixoto, C.A., 2016. Phosphodiesterase-5 inhibition promotes remyelination by MCP-1/CCR-2 and MMP-9 regulation in a cuprizone-induced demyelination model. Exp. Neurol. 275, 143–153.
Oja, S.S., Kontro, P., 1983. Taurine. In: 2nd ed. In: Lajtha, A. (Ed.), Handbook of Neurochemistry, vol. 3. Plenum Press, New York, pp. 501–533.
Oja, S.S., Saransaari, P., 1996. Taurine as a neuromodulator and osmoregulator. Metab. Brain 11, 153–164.
Okamoto, K., Kimura, H., Sakai, Y., 1983. Taurine-induced increase of the Cl conductance of cerebellar Purkinje cell dendrites in vitro. Brain Res. 259, 319–323.
Okumura, N., Otsuki, S., Kameyama, A., 1960. Studies on free amino acids in human brain. J. Biochem. (Tokyo) 47, 315–320.
Oliveira, M.W., Minotto, J.B., de Oliveira, M.R., Zanotto-Filho, A., Behr, G.A., Rocha, R.F., Moreira, J.C., Klamt, F., 2010. Scavenging and antioxidant potential of physiological taurine concentrations against different reactive oxygen/nitrogen species. Pharmacol. Rep. 62 (1), 185–193.
Oliveira, R.F., 2013. Mind the fish: zebrafish as a model in cognitive social neuroscience. Front. Neural Circ. 7, 131.
Oltrabella, F., Pietka, G., Ramirez, I.B., Mironov, A., Starborg, T., Drummond, I.A., Hinchliffe, K.A., Lowe, M., 2015. The Lowe syndrome protein OCRL1 is required for endocytosis in the zebrafish pronephric tubule. PLoS Genet. 11, e1005058.
Oz, M., Lorke, D.E., Petroianu, G.A., 2009. Methylene blue and Alzheimer's disease. Biochem Pharmacol. 78 (8), 927–932.
Palkovits, M., Elekes, I., Láng, T., Patthy, A., 1986. Taurine levels in discrete brain nuclei of rats. J. Neurochem. 47 (5), 1333–1335.
Panula, P., Chen, Y.C., Priyadarshini, M., Kudo, H., Semenova, S., Sundvik, M., Sallinen, V., 2010. The comparative neuroanatomy and neurochemistry of zebrafish CNS systems of relevance to human neuropsychiatric diseases. Neurobiol. Dis. 40, 46–57.
Paquet, D., Bhat, R., Sydow, A., Mandelkow, E.M., Berg, S., Hellberg, S., Fälting, J., Distel, M., Köster, R.W., Schmid, B., Haass, C., 2009. A zebrafish model of tauopathy allows in vivo imaging of neuronal cell death and drug evaluation. J. Clin. Invest. 119, 1382–1395.
Parildar-Karpuzoğlu, H., Mehmetçik, G., Ozdemirler-Erata, G., Doğru-Abbasoğlu, S., Koçak-Toker, N., Uysal, M., 2008. Effect of taurine treatment on pro-oxidant-antioxidant balance in livers and brains of old rats. Pharmacol. Rep. 60 (5), 673–678.
Parker, M.O., Millington, M.E., Combe, F.J., Brennan, C.H., 2012. Housing conditions differentially affect physiological and behavioural stress responses of zebrafish, as well as the response to anxiolytics. PLoS One 7 (4), e34992.
Parng, C., Seng, W.L., Semino, C., McGrath, P., 2002. Zebrafish: a preclinical model for drug screening. Assay. Drug. Dev. Technol. 1, 41–48.
Pasantes-Morales, H., Moran, J., 1981. Taurine as a neuromodulator: its action on calcium fluxes and neurotransmitter release. In: Tapia, R., Cotman, C.W. (Eds.), Regulatory Mechanisms of Synaptic Transmission. Plenum Press, New York, pp. 141–154.
Patel, S.N., Pandya, K., Clark, G.J., Parikh, M.C., Lau-Cam, C.A., 2016. Comparison of taurine and pantoyltaurine as antioxidants in vitro and in the central nervous system of diabetic rats. Exp. Toxicol. Pathol. 68 (2–3), 103–112.
Peck Jr, E.J., Awapara, J., 1967. Formation of taurine and isethionic acid in rat brain. Biochim. Biophys. Acta 141, 499–506.
Pennetta, R., Masi, G., Perniola, T., Ferrannini, E., 1977. Valutazione elettroclinica dell'azione antiepilettica della taurina. Acta Neurol. (Napoli) 32, 316–322.
Perathoner, S., Cordero-Maldonado, M.L., Crawford, A.D., 2016. Potential of zebrafish as a model for exploring the role of the amygdala in emotional memory and motivational behavior. J. Neurosci. Res. 94 (6), 445–462.
Philibert, R.A., Rogers, K.L., Dutton, G.R., 1989. K+-evoked taurine efflux from cerebellar astrocytes: on the roles of Ca2+ and Na++. Neurochem Res. 14 (1), 43–48.
Piato, Â.L., Capiotti, K.M., Tamborski, A.R., Oses, J.P., Barcellos, L.J., Bogo, M.R., Lara, D.R., Vianna, M.R., Bonan, C.D., 2011. Unpredictable chronic stress model in zebrafish (Danio rerio): behavioral and physiological responses. Prog. Neuropsychopharmacol. Biol. Psychiatry 35 (2), 561–567.
Pineda, R., Beattie, C.E., Hall, C.W., 2011. Recording the adult zebrafish cerebral field potential during pentylenetetrazole seizures. J. Neurosci. Methods 200 (1), 20–28.
Poleszak, E., Katarzyna, S., Aleksandra, S., Wróbel, A., Szewczyk, B., Kasperek, R., Blicharska, E., Nowak, G., Wlaz, P., 2011. Involvement of NMDA receptor complex inthe anxiolytic-like effects of chlordiazepoxide in mice. J. Neural. Transm. 118, 857–864.
Puerta, C., Arrieta, F.J., Balsa, J.A., Botella-Carretero, J.I., Zamarrón, I., Vázquez, C., 2010. Taurine and glucose metabolism: a review. Nutr. Hosp. 25 (6), 910–919.
Quadros, V.A., Silveira, A., Giuliani, G.S., Didonet, F., Silveira, A.S., Nunes, M.E., Silva, T.O., Loro, V.L., Rosemberg, D.B., 2016. Strain- and context-dependent behavioural responses of acute alarm substance exposure in zebrafish. Behav. Processes. 122, 1–11.
Quertemont, E., Didone, V., 2006. Role of acetaldehyde in mediating the pharmacological and behavioral effects of alcohol. Alcohol. Res. Health 29 (4), 258–265.
Ramesh, T., Lyon, A.N., Pineda, R.H., Wang, C., Janssen, P.M.L., Canan, B.D., Burghes, A.H., Beattie, C.E., 2010. A genetic model of amyotrophic lateral sclerosis in zebrafish displays phenotypic hallmarks of motoneuron disease. Dis. Model. Mech. 3, 652–662.
Ramirez, I.B., Pietka, G., Jones, D.R., Divecha, N., Alia, A., Baraban, S.C., Hurlstone, A.F., Lowe, M., 2012. Impaired neural development in a zebrafish model for Lowe syndrome. Hum. Mol. Genet. 21, 1744–1759.
Ramos-Mandujano, G., Hernandez-Benitez, R., Pasantes-Morales, H., 2014. Multiple mechanisms mediate the taurine-induced proliferation of neural stem/progenitor cells from the subventricular zone of the adult mouse. Stem Cell. Res. 12, 690–702.
Ramsay, J.M., Feist, G.W., Varga, Z.M., Westerfield, M., Kent, M.L., Schreck, C.B., 2009. Whole-body cortisol response of zebrafish to acute net handling stress. Aquaculture 297 (1-4), 157–162.
Randlett, O., Wee, C.L., Naumann, E.A., Nnaemeka, O., Schoppik, D., Fitzgerald, J.E., Portugues, R., Lacoste, A.M., Riegler, C., Engert, F., Schier, A.F., 2015. Whole-brain activity mapping onto a zebrafish brain atlas. Nat. Methods 12 (11), 1039–1046.
Read, W.O., Welty, J.D., 1962. Synthesis of taurine and isethionic acid by dog heart slices. J. Biol. Chem. 237, 1521–1522.
Ricciardi, L., Pomponi, M., Demartini, B., Ricciardi, D., Morabito, B., Bernabei, R., Bentivoglio, A.R., 2015. Emotional awareness, relationship quality, and satisfaction in patients with Parkinson's disease and their spousal caregivers. J. Nerv. Ment. Dis. 203 (8), 646–649.
Richetti, S.K., Blank, M., Capiotti, K.M., Piato, A.L., Bogo, M.R., Vianna, M.R., Bonan, C.D., 2011. Quercetin and rutin prevent scopolamine-induced memory impairment in zebrafish. Behav. Brain Res. 217, 10–15.
Rico, E.P., Rosemberg, D.B., Seibt, K.J., Capiotti, K.M., Da Silva, R.S., Bonan, C.D., 2011. Zebrafish neurotransmitter systems as potential pharmacological and toxicological targets. Neurotoxicol. Teratol. 33 (6), 608–617.
Ripps, H., Shen, W., 2012. Taurine: a “very essential” amino acid. Mol. Vis. 18, 2673–2686.
Roig-Pérez, S., Moretó, M., Ferrer, R., 2005. Transepithelial taurine transport in caco-2 cell monolayers. J. Membr. Biol. 204 (2), 85–92.
Rosemberg, D.B., Braga, M.M., Rico, E.P., Loss, C.M., Córdova, S.D., Mussulini, B.H., Blaser, R.E., Leite, C.E., Campos, M.M., Dias, R.D., Calcagnotto, M.E., de Oliveira, D.L., Souza, D.O., 2012. Behavioral effects of taurine pretreatment in zebrafish acutely exposed to ethanol. Neuropeptides (Oxford United Kingdom) 63 (4), 613–623.
Rosemberg, D.B., da Rocha, R.F., Rico, E.P., Zanotto-Filho, A., Dias, R.D., Bogo, M.R., Bonan, C.D., Moreira, J.C., Klamt, F., Souza, D.O., 2010. Taurine prevents enhancement of acetylcholinesterase activity induced by acute ethanol exposure and decreases the level of markers of oxidative stress in zebrafish brain. Neuroscience 171 (3), 683–692.
Ryu, S., Mahler, J., Acampora, D., Holzschuh, J., Erhardt, S., Omodei, D., Simeone, A., Driever, W., 2007. Orthopedia homeodomain protein is essential for diencephalic dopaminergic neuron development. Curr. Biol. 17, 873–880.
Saitoh, M., Shinohara, M., Hoshino, H., Kubota, M., Amemiya, K., Takanashi, J.L., Hwang, S.K., Hirose, S., Mizuguchi, M., 2012. Mutations of the SCN1A gene in acute encephalopathy. Epilepsia 53, 558–564.
Salze, G.P., Davis, D.A., 2015. Taurine: a critical nutrient for future fish feeds. Aquaculture 437, 215–229.
Samuelsson, M., Vainikka, L., Öllinger, K., 2011. Glutathione in the blood and cerebrospinal fluid: a study in healthy male volunteers. Neuropeptides 45, 287–292.
Saransaari, P., Oja, S.S., 2008. Taurine in neurotransmission. In: 3rd ed. In: Vizi, E.S. (Ed.), Handbook of Neurochemistry and Molecular Neurobiology, Neurotransmitter Systems, vol. 2. Springer, New York, pp. 325–342.
Sarath Babu, N.S., Murthy, C.L., Kakara, S., Sherma, R., Swamy, C.V., Idris, M.M., 2016. Methyl-4-phenyl-1,2,3,6-tetrahydropyridine induced Parkinson’s disease in zebrafish. Proteomics 16 (9), 1407–1420.
Sarras, M.P., Jr, Leontovich, A.A., Intine, R.V., 2015. Use of zebrafish as a model to investigate the role of epigenetics in propagating the secondary complications observed in diabetes mellitus. Comp. Biochem. Physiol. C Toxicol. Pharmacol. 178, 3–7.
Schaffer, S.W., Jong, C.J., Ramila, K.C., Azuma, J., 2010. Physiological roles of taurine in heart and muscle. J. Biomed. Sci. 17, S2.
Schuller-Levis, G.B., Park, E., 2003. Taurine: new implications for an old amino acid. FEMS Microbiol. Lett. 226 (2), 195–202.
Seibt, K.J., Oliveira, R.L., Rosember, D.B., Savio, L.E.B., Scherer, E.B.S., Schmitz, F., Wyse, A.T.S., Bonan, C.D., 2012. MK-801 alters Na++, K+-ATPase activity and oxidative status in zebrafish brain: reversal by antipsychotic drugs. J. Neural Transm. 119, 661–667.
Seibt, K.J., Oliveira, R.L., Zimmermann, F.F., Capiotti, K.M., Bogo, M.R., Ghisleni, G., Bonan, C.D., 2010. Antipsychotic drugs prevent the motor hyperactivity induced by psychotomimetic MK-801 in zebrafish (*Danio rerio*). Behav. Brain Res. 214, 417–422.
Seibt, K.J., Piato, A.L., Oliveira, R.L., Capiotti, K.M., Vianna, M.R., Bonan, C.D., 2011. Antipsychotic drugs reverse MK-801-induced cognitive and social interaction deficits in zebrafish (*Danio rerio*). Behav. Brain Res. 224, 135–139.
Sejima, H., Ito, M., Kishi, K., Tsuda, H., Shiraishi, H., 1997. Regional excitatory and inhibitory amino acid concentrations in pentylenetetrazol kindling and kindled rat brain. Brain Dev. 19, 171–175.
Shimada, K., Jong, C.J., Takahashi, K., Schaffer, S.W., 2015. Role of ROS production and turnover in the antioxidant activity of taurine. Adv. Exp. Med. Biol. 803, 581–596.
Shirayama, Y., Obata, T., Matsuzawa, D., Nonaka, H., Kanazawa, Y., Yoshitome, E., Ikehira, H., Hashimoto, K., Iyo, M., 2010. Specific metabolites in the medial prefrontal cortex are associated with the neurocognitive deficits in schizophrenia: a preliminary study. Neuro Image 49, 2783–2790.
Shulman, J.M., De Jager, P.L., Feany, M.B., 2011. Parkinson's disease: genetics and

pathogenesis. Annu. Rev. Pathol. 6, 193–222.
Simpson, J.W., Allen, K., Awapara, J., 1959. Free amino acids in some aquatic invertebrates. Biol. Bull. 117, 371–381.
Sirdah, M.M., 2015. Protective and therapeutic effectiveness of taurine in diabetes mellitus: a rationale for antioxidant supplementation. Diab. Metab. Syndr. 9 (1), 55–64.
Sirianant, L., Ousingsawat, J., Wanitchakool, P., Schreiber, R., Kunzelmann, K., 2016. Cellular volume regulation by anoctamin 6: Ca^{2+}, phospholipase A2 and osmosensing. Pflugers Arch. 468 (2), 335–349.
Sison, M., Cawker, J., Buske, C., Gerlai, R., 2006. Fishing for genes influencing vertebrate behavior: zebrafish making headway. Lab Anim (NY) 35 (5), 33–39.
Song, P., Pimplikar, S.W., 2012. Knockdown of amyloid precursor protein in zebrafish causes defects in motor axon outgrowth. PLoS One 7 (4), e34209.
Souza, B.R., Tropepe, V., 2011. The role of dopaminergic signalling during larval zebrafish brain development: a tool for investigating the developmental basis of neuropsychiatric disorders. Rev. Neurosci. 22 (1), 107–119.
Spillantini, M.G., Crowther, R.A., Jakes, R., Hasegawa, M., Goedert, M., 1998. Alpha-Synuclein in filamentous inclusions of Lewy bodies from Parkinson's disease and dementia with Lewy bodies. Proc. Natl. Acad. Sci. U. S. A. 95 (11), 6469–6473.
Stewart, A., Kadri, F., DiLeo, J., Chung, K., Cachat, J., Goodspeed, J., et al., 2010. The developing utility of zebrafish in modeling neurobehavioral disorders. Int. J. Comp. Psychol. 23, 104–121.
Stewart, A., Wong, K., Cachat, J., Gaikwad, S., Kyzar, E., Wu, N., Hart, P., Piet, V., Utterback, E., Elegante, M., Tien, D., Kalueff, A.V., 2011b. Zebrafish models to study drug abuse-related phenotypes. Rev. Neurosci. 22 (1), 95–105.
Stewart, A., Wu, N., Cachat, J., Hart, P., Gaikwad, S., Wong, K., Utterback, E., Gilder, T., Kyzar, E., Newman, A., Carlos, D., Chang, K., Hook, M., Rhymes, C., Caffery, M., Greenberg, M., Zadina, J., Kalueff, A.V., 2011a. Pharmacological modulation of anxiety-like phenotypes in adult zebrafish behavioral models. Prog. Neuropsychopharmacol. Biol. Psychiatry 35 (6), 1421–1431.
Stewart, A.M., Braubach, O., Spitsbergen, J., Gerlai, R., Kalueff, A.V., 2014. Zebrafish models for translational neuroscience research: from tank to bedside. Trends Neurosci. 37 (5), 264–278.
Stewart, A.M., Ullmann, J.F., Norton, W.H., Parker, M.O., Brennan, C.H., Gerlai, R., Kalueff, A.V., 2015. Molecular psychiatry of zebrafish. Mol. Psychiatry 20 (1), 2–17.
Sturman, J.A., 1993. Taurine in development. Physiol. Rev. 73, 119–147.
Su, Y., Fan, W., Ma, Z., Wen, X., Wang, W., Wu, Q., Huang, H., 2014. Taurine improves functional and histological outcomes and reduces inflammation in traumatic brain injury. Neuroscience 266, 56–65.
Suárez, L.M., Muñoz, M.D., Martín Del Río, R., Solís, J.M., 2016. Taurine content in different brain structures during ageing: effect on hippocampal synaptic plasticity. Amino Acids 48 (5), 1199–1208.
Suge, R., Hosoe, N., Furube, M., Yamamoto, T., Hirayama, A., Hirano, S., Nomura, M., 2007. Specific timing of taurine supplementation affects learning ability in mice. Life Sci. 81, 1228–1234.
Sumanas, S., Lin, S., 2004. Zebrafish as a model system for drug target screening and validation. Drug. Discov. Today: Targets 3 (3), 89–96.
Sumizu, K., 1962. Oxidation of hypotaurine in rat liver. Biochim. Biophys. Acta 63, 210–212.
Swain, H.A., Sigstad, C., Scalzo, F.M., 2004. Effects of dizocilpine (MK-801) on circling behavior, swimming activity, and place preference in zebrafish (Danio rerio). Neurotoxicol. Teratol. 26, 725–729.
Tiedeken, J.A., Ramsdell, J.S., Ramsdell, A.F., 2005. Developmental toxicity of domoic acid in zebrafish (Danio rerio). Neurotoxicol. Teratol. 27 (5), 711–717.
Tiedemann, F., Gmelin, L., 1827. Einige neue Bestandtheile der Galle des Ochsen. Annalen der Physik 85 (2), 326–337.
Tomasiewicz, H.G., Flaherty, D.B., Soria, J.P., Wood, J.G., 2002. Transgenic zebrafish model of neurodegeneration. J. Neurosci. Res. 70, 734–745.
Torres-Hernández, B.A., Del Valle-Mojica, L.M., Ortíz, J.G., 2015. Valerenic acid and Valeriana officinalis extracts delay onset of Pentylenetetrazole (PTZ)-Induced seizures in adult Danio rerio (Zebrafish). BMC Complem. Altern. Med. 15, 228.
Tran, S., Nowicki, M., Chatterjee, D., Gerlai, R., 2015. Acute and chronic ethanol exposure differentially alters alcohol dehydrogenase and aldehyde dehydrogenase activity in the zebrafish liver. Prog. Neuropsychopharmacol. Biol. Psychiatry. 56, 221–226.
Tucker, B., Olson, J.E., 2010. Glutamate receptor-mediated taurine release from the hippocampus during oxidative stress. J. Biomed. Sci. 17 (1), S10.
Ullmann, J.F., Cowin, G., Kurniawan, N.D., Collin, S.P., 2010. A three-dimensional digital atlas of the zebrafish brain. Neuroimage 51 (1), 76–82.
van der Staay, F.J., Arndt, S.S., Nordquist, R.E., 2009. Evaluation of animal models of neurobehavioral disorders. Behav. Brain Funct. 5, 11.
van der Staay, F.J., Steckler, T., 2002. The fallacy of behavioral phenotyping without standardisation. Genes Brain Behav. 1 (1), 9–13.
van Gelder, N.M., Koyama, I., Jasper, H.H., 1977. Taurine treatment of spontaneous chronic epilepsy in a cat. Epilepsia 18, 45–54.
Vervliet, B., Raes, F., 2013. Criteria of validity in experimental psychopathology: application to models of anxiety and depression. Psychol. Med. 43 (11), 2241–2244.
Vezzani, A., Schwarcz, R., 1985. A noradrenergic component of quinolinic acid-induced seizures. Exp. Neurol. 90 (1), 254–258.
Vohra, B.P., Hui, X., 2000. Improvement of impaired memory in mice by taurine. Neural Plast. 7, 245–259.
Voss, F.K., Ullrich, F., Münch, J., Lazarow, K., Lutter, D., Mah, N., Andrade-Navarro, M.A., von Kries, J.P., Stauber, T., Jentsch, T.J., 2014. Identification of LRRC8 heteromers as an essential component of the volume-regulated anion channel VRAC. Science 344 (6184), 634–638.
Wager, K., Russell, C., 2013. Mitophagy and neurodegeneration: the zebrafish model system. Autophagy 9 (11), 1693–1709.
Walker, E.F., et al., 2013. Cortisol levels and risk for psychosis: initial findings from the North American prodrome longitudinal study. Biol. Psychiatry 74, 410–417.
Walz, W., Allen, A.F., 1987. Evaluation of the osmoregulatory function of taurine in brain cells. Exp. Brain 68, 290–298.
Webb, K.J., Norton, W.H., Trumbach, D., Meijer, A.H., Ninkovic, J., Topp, S., et al., 2009. Zebrafish reward mutants reveal novel transcripts mediating the behavioral effects of amphetamine. Genome Biol. 10, R81.
Williams, A., Sarkar, S., Cuddon, P., Ttofi, E.K., Saiki, SSiddiqi, F.H., Jahreiss, L., Fleming, A., Pask, D., Goldsmith, P., 2008. Novel targets for Huntington's disease in an mTOR-independent autophagy pathway. Nat. Chem. Biol. 4, 295–305.
Willner, P., 1991. Behavioural models in psychopharmacology. In: Willner, P. (Ed.), Behavioural Models in Psychopharmacology. Cambridge University Press, Cambridge 3 ± 18.
Wilson, C.L., Maidment, N.T., Shomer, M.H., Behnke, E.J., Ackerson, L., Fried, I., Engel Jr, J., 1996. Comparison of seizure related amino acid release in human epileptic hippocampus versus a chronic, kainate rat model of hippocampal epilepsy. Epilepsy Res. 26, 245–254.
Wilson, L., Lardelli, M., 2013. The development of an in vivo γ-secretase assay using zebrafish embryos. J. Alzheimers Dis. 36 (3), 521–534.
Wingenfeld, K., Heim, C., Schmidt, I., Wagner, D., Meinlschmidt, G., Hellhammer, D.H., 2008. HPA axis reactivity and lymphocyte glucocorticoid sensitivity in fibromyalgia syndrome and chronic pelvic pain. Psychosom. Med. 70 (1), 65–72.
Wirtz, P.H., Känel von, R., Emini, L., Ruedisueli, K., Groessbauer, S., Maercker, A., Ehlert, U., 2007. Evidence for altered hypothalamus-pituitary-adrenal axis functioning in systemic hypertension: blunted cortisol response to awakening and lower negative feedback sensitivity. Psychoneuroendocrinology 32 (5), 430–436.
Wood, J.D., Bonath, F., Kumar, S., Ross, C.A., Cunliffe, V.T., 2009. Disrupted-in-schizophrenia 1 and neuregulin 1 are required for the specification of oligodendrocytes and neurones in the zebrafish brain. Hum. Mol. Genet. 18, 391–404.
Wu, H., Jin, Y., Wei, J., Jin, H., Sha, D., Wu, J.Y., 2005. Mode of action of taurine as a neuroprotector. Brain Res. 1038 (2), 123–131.
Wu, J., Kohno, T., Georgiev, S.K., Ikoma, M., Ishii, H., Petrenko, A.B., Baba, H., 2008. Taurine activates glycine and gamma-aminobutyric acid A receptors in rat substantia gelatinosa neurons. Neuro Rep. 19, 333–337.
Wu, J.Y., 1982. Purification and characterization of cysteic/cysteine sulfinic acids decarboxylase and L-glutamate decarboxylase in bovine brain. Proc. Natl. Acad. Sci. U. S. A. 79, 4270–4274.
Wu, J.Y., Moss, L.G., Chen, M.S., 1979. Tissue and regional distribution of cysteic acid decarboxylase in bovine brain. A new assay method. Neurochem. Res. 4, 201–212.
Wu, J.Y., Prentice, H., 2010. Role of Taurine in the central nervous system. J. Biomed. Sci. 17, S1.
Wu, J.Y., Tang, X.W., Tsai, W.H., 1992. Taurine receptor: kinetic analysis and pharmacological studies. Adv. Exp. Med. Biol. 315, 263–268.
Xi, Y., Noble, S., Ekker, M., 2011. Modeling neurodegeneration in zebrafish. Curr. Neurol. Neurosci. Rep. 11 (3), 274–282.
Xu, Y.J., Arneja, A.S., Tappia, P.S., Dhalla, N.S., 2008. The potential health benefits of taurine in cardiovascular disease. Exp. Clin. Cardiol. 13 (2), 57–65.
Yamada, T., Wondergem, R., Morrison, R., Yin, V.P., Strange, K., 2016. Leucine-rich repeat containing protein LRRC8A is essential for swelling-activated Cl- currents and embryonic development in zebrafish. Physiol Rep. 4 (19) pii: e12940.
Ye, G., Tse, A.C., Yung, W., 1997. Taurine inhibits rat substantia nigra pars reticulata neurons by activation of GABA- and glycine-linked chloride conductance. Brain Res. 749 (1), 175–179.
Yorek, M.H., Strom, D.K., Spector, A.A., 1984. Effect of membrane polyunsaturation on carrier-mediated transport in cultured retinoblastoma cells: alterations in taurine uptake. J. Neurochem. 42, 254–261.
Zakhary, S.M., Ayubcha, D., Ansari, F., Kamran, K., Karim, M., Leheste, J.R., Horowitz, J.M., Torres, G., 2011. A behavioral and molecular analysis of ketamine in zebrafish. Synapse 65, 160–167.
Zarrabian, S., Farahizadeh, M., Nasehi, M., Zarrindast, M.R., 2016. The role of CA3 GABAA receptors on anxiolytic-like behaviors and avoidance memory deficit induced by NMDA receptor antagonists. J. Psychopharmacol. 30 (2), 215–223.
Zhang, C.G., Kim, S.J., 2007. Taurine induces anti-anxiety by activatingstrychnine-sensitive glycine receptor in vivo. Annu. Nutr. Metab. 51, 379–386.
Zhang, L., Yuan, Y., Tong, Q., Jiang, S., Xu, Q., Ding, J., Zhang, L., Zhang, R., Zhang, K., 2015. Reduced plasma taurine level in Parkinson's disease: association with motor severity and levodopa treatment. Int. J. Dev. Neurosci. Early Online: 1–7.
Zima, T., Fialová, L., Mestek, O., Janebová, M., Crkovská, J., Malbohan, I., Stípek, S., Mikulíková, L., Popov, P., 2001. Oxidative stress, metabolism of ethanol and alcohol-related diseases. J. Biomed. Sci. 8 (1), 59–70.
Zimmermann, F.F., Gaspary, K.V., Siebel, A.M., Bonan, C.D., 2016. Oxytocin reversed MK-801-induced social interaction and aggression deficits in zebrafish. Behav. Brain Res. 15 (311), 368–374.
Zukin, S.R., Young, A.B., Snyder, S.H., 1974. Gamma-aminobutyric acid binding to receptor sites in the rat central nervous system. Proc. Natl. Acad. Sci. U. S. A. 71 (12), 4802–4807.