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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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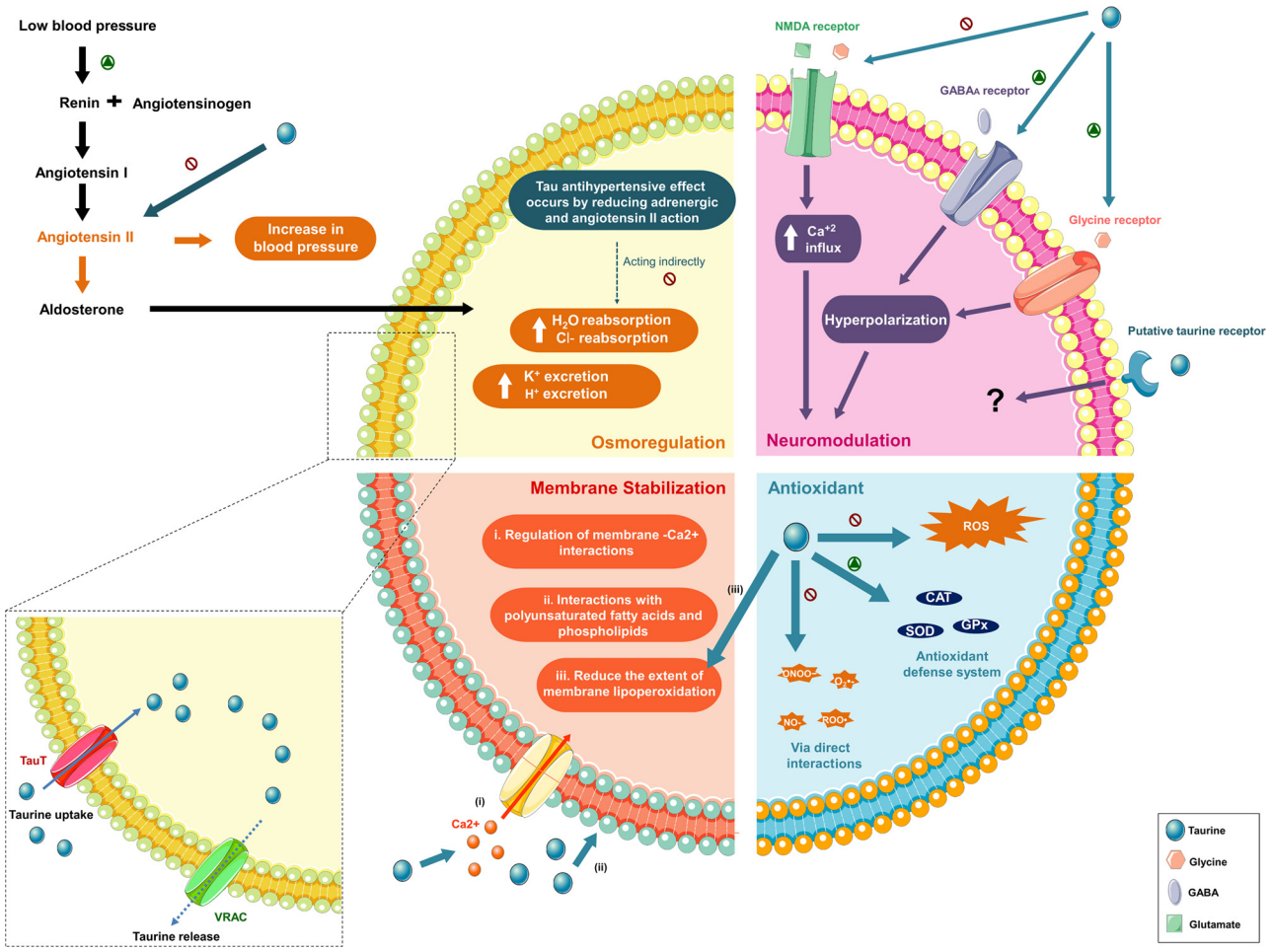

Fig. 1. Mechanisms of taurine action *in-vivo* include its role in osmoregulation, neuromodulation, membrane stabilization and antioxidant defense. The cartoon illustrates taurine transporters **(TauT and VRAC)**, as well as the putative taurine receptor, and the potential modulatory effects of taurine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