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Taurine increases hippocampal neurogenesis in aging mice

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Abstract Aging is associated with increased inflammation and reduced hippocampal neurogenesis, which may in turn contribute to cognitive impairment. Taurine is a free amino acid found in numerous diets, with anti-inflammatory properties. Although abundant in the young brain, the decrease in taurine concentration with age may underlie reduced neurogenesis. Here, we assessed the effect of taurine on hippocampal neurogenesis in middle-aged mice. We found that taurine increased cell proliferation in the dentate gyrus through the activation of quiescent stem cells, resulting in increased number of stem cells and intermediate neural progenitors. Taurine had a direct effect on stem/progenitor cells proliferation, as observed *in vitro*, and also reduced activated microglia. Furthermore, taurine increased the survival of newborn neurons, resulting in a net increase in adult neurogenesis. Together, these results show that taurine increases several steps of adult neurogenesis and support a beneficial role of taurine on hippocampal neurogenesis in the context of brain aging.
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Introduction

Neurogenesis persists during adulthood in the dentate gyrus (DG) of the hippocampus in most mammals (Altman & Das, 1965). Adult neural stem cells reside in the subgranular zone of the DG, where they give rise to intermediate progenitor cells. These progenitors proliferate rapidly to give rise to neurons, which migrate into the granule cell layer (Kronenberg et al., 2003). With their increased plasticity (Schmidt-Hieber et al., 2004), new neurons enhance synaptic plasticity in the hippocampus and participate to the mechanisms of learning and memory as well as mood control (Kheirbek et al., 2012). The age-dependent reduction in adult neurogenesis (Gebara et al., 2013; Kuhn et al., 1996; Encinas & Sierra, 2012) is associated with decreased learning performances (Gil-Mohapel et al., 2013), which can be restored by increasing adult neurogenesis with voluntary exercise (van Praag et al., 2005). Thus, manipulations aimed at increasing adult neurogenesis represent a promising approach for alleviating disease- or age-related cognitive impairment (Bolognin et al., 2014) as well as mood disorders (Drew & Hen, 2007). In this context, nutritional supplements acting on adult neurogenesis have been proposed as a beneficial approach to prevent or reduce age-related cognitive loss (van Praag et al., 2007).

Taurine is a free sulfur amino acid that is not incorporated in proteins. It is synthesized from methionine and cysteine by the rate-limiting enzyme cysteinesulfinic acid decarboxylase (CSD) that is found in the liver, the kidney and the brain,

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where it is localized in glial cells (Ripps & Shen, 2012). In the liver, CSD activity is increased by protein-rich diet (Bella et al., 1999) whereas in the brain, glutamate increases CSD activity (Wu et al., 1998). Taurine is also found in high concentrations in numerous diets such as meat and seafood (Huxtable, 1992) and crosses the blood brain barrier using a specific beta amino acid transporter TAUT (TAUrine Transporter (Benrabh et al., 1995)). Taurine is 3–4 times more abundant in the developing than in the mature brain (Miller et al., 2000) and its concentration decreases with aging (Banay-Schwartz et al., 1989), suggesting that taurine plays a role during brain development. Consistent with this, dietary taurine deficiency during gestation leads to impaired development of the cerebellum and the visual cortex of newborn cats (Sturman et al., 1985). Intriguingly, taurine also seems to play a role in the adult and aging brain: Chronic administration of taurine in aged mice (El Idrissi, 2008; Neuwirth et al., 2013) or in a mouse model of Alzheimer's disease (Kim et al., 2014) increases hippocampus-dependent learning and retention and reduces anxiety and depression (Chen et al., 2004). The mechanisms by which taurine increases learning performances are unclear, but recent work showed that taurine increases the proliferation of adult neural stem/progenitor cells from the subventricular zone *in vitro* (Ramos-Mandujano et al., 2014; Hernandez-Benitez et al., 2012), suggesting that the effect of taurine may be mediated by an increase in adult neurogenesis. However, these studies did not address whether taurine increased net hippocampal neurogenesis *in vivo*.

Here, we directly assessed the effect of taurine on the age-related decline of adult hippocampal neurogenesis. To this aim, we tested the effect of taurine injections on 10-month-old mice, an age at which adult neurogenesis has reached its minimal activity (Kuhn et al., 1996; Gil-Mohapel et al., 2013). Using the incorporation of the proliferation marker 5-bromo-2-deoxyuridine (BrdU), combined with the genetic and immunohistochemical identification of adult hippocampal stem cells, intermediate progenitors, newborn mature and immature neurons, we examined the effect of taurine on several steps of the formation of new neurons in the aging hippocampus.

Methods

Ethics statement

This study was carried out in strict accordance with the recommendations in the Guidance for the Care and Use of Laboratory Animals of the National Institutes of Health. All experimental protocols were approved by the Swiss animal experimentation authorities (Service de la consommation et des affaires vétérinaires, Chemin des Boveresses 155, 1066 Epalinges, Switzerland). Every effort was made to minimize the number of animals used and their suffering.

Animals and taurine administration

Animals used for the study were male mice of 2, 4, 6, 8 and 10 months of age at the beginning of the experiments. C57Bl/6j mice were purchased from Janvier (le Genest Saint Isle, France), nestin-GFP mice were a kind gift from the laboratory of K. Mori (PRESTO, Kyoto, Japan) (Yamaguchi et al., 2000). These mice express the green fluorescent protein (GFP) under the stem cell-specific promoter nestin. All animals were housed in a 12 h light/12 h dark cycle with free access to food and water and controlled temperature (22 °C) conditions. Taurine was prepared fresh every day and diluted in water containing 0.9% NaCl. 10-month-old mice were injected intraperitoneally every day for 40 consecutive days either with 0.2 ml of taurine (265 mg/kg, Sigma-Aldrich) or with 0.2 ml of vehicle (0.9% NaCl in water) for control animals.

BrdU administration

Mice were injected intraperitoneally with 5-bromo-2-deoxyuridine (Sigma-Aldrich, Buchs, Switzerland) at a concentration of 100 mg/kg in saline, 3 times per day at 2-h intervals, for 3 days. For proliferation studies, taurine was injected for 40 days and BrdU injection started 24 h after the last taurine injection. Mice were then sacrificed 24 h after the last BrdU injection. For survival studies, BrdU was injected for 3 days and 24 h after the last BrdU injection, taurine was injected for 40 days. 24 h after the last taurine injection, mice were sacrificed and analyzed (Chen et al., 2004).

Tissue collection and preparation

At the end of the experiment, mice received a lethal dose of pentobarbital (10 ml/kg, Sigma-Aldrich, Buchs, Switzerland) and were perfusion-fixed with 50 ml of 0.9% saline followed by 100 ml of 4% paraformaldehyde (Sigma-Aldrich, Switzerland) dissolved in phosphate buffer saline (PBS 0.1 M, pH 7.4). Brains were then collected, postfixed overnight at 4 °C, cryoprotected 24 h in 30% sucrose and rapidly frozen. Coronal frozen sections of a thickness of 40 μm were cut with a microtome-cryostat (Leica MC 3050S) and slices were kept in cryoprotectant (30% ethylene glycol and 25% glycerin in 1× PBS) at −20 °C until processed for immunostaining.

Immunohistochemistry

Immunochemistry was performed as previously described (Gebara et al., 2013). Briefly, sections were washed 3 times in PBS 0.1 M. BrdU detection required formic acid pretreatment (formamide 50% in 2× SSC buffer; 2× SSC is 0.3 M NaCl and 0.03 M sodium citrate, pH 7.0) at 65 °C for 2 h followed by DNA denaturation for 30 min in 2 M HCl for 30 min at 37 °C and rinsed in 0.1 M borate buffer pH 8.5 for 10 min. Then, slices were incubated in blocking solution containing 0.3% Triton-X100 and 15% normal serum normal goat serum (Gibco, 16210-064) or normal donkey serum (Sigma Aldrich, D-9663), depending on the secondary antibody in PBS 0.1 M. Slices were then incubated 40 h at 4 °C with the following primary antibodies: mouse monoclonal anti-BrdU (48 h, 1:250, Chemicon International, Dietikon, Switzerland), goat anti-DCX (1:500, Santa Cruz Biotechnology, sc-8066), rabbit anti-Ki-67 (48 h, 1:200, Abcam, ab15580), rabbit anti-Tbr2 (1:200, Abcam, ab23345), goat anti-Iba1 (1:200, Abcam, ab5076), mouse anti-MHC-II (1:200, Abcam, ab23990) rabbit anti-GFAP (1:500, Invitrogen, 180063) mouse anti-Neu-N (Chemicon International 1:1000). The sections were then incubated for 2 h in either of the secondary antibodies: goat anti-mouse Alexa-594 (1:250, Invitrogen), goat anti-mouse Alexa-660

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