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Taurine attenuates inflammatory response following cerebral ischemia and reperfusion

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Abstract

Taurine is a kind of endogenous free amino acid in tissue and a potent antioxidant agent its function may in part be to adjust calcium homeostasis in cells, anti-oxidative stress, anti-inflammatory and cell protector but little is known about the expression or the role of Taurine in the central nervous system. Stroke is the major cause of death and disability worldwide. Here, we investigated the role of Taurine in ischemic stroke as a potential neuroprotective using rat model of transient cerebral ischemia. Transient cerebral ischemia was induced by MCAO were performed on male Sprague-Dawley rats. TTC staining used to measurement of infarct volume in the brain and ELISA kits to assay cytokines. Our data suggested that Taurine reduced cerebral infarct size, decreased pro-inflammatory cytokines expression and produced lower level of ICAM-1. These results suggest that Taurine can be exerting significantly protective effect against brain ischemic injury through inhibiting pro-inflammatory cytokines and ICAM-1.

Keywords: Strock; Taurine; Proinflammatroy cytokines; ICAM-1; Cerebral I/R

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Introduction

Stroke is one of the world's leading causes of death and disability [1]. The World Health Organization (WHO) reported that 5.71 million people died of stroke in 2004 with an estimated acceleration to 7.8 million by 2030 [2]. In keeping with this estimated trajectory of stroke, it was also reported that within the next decade there will be a 12% global rise in stroke morbidity [4]. The two types of stroke are ischemic stroke and hemorrhagic stroke. Of the two approximately 85% are ischemic [3].

Ischemic stroke (cerebral ischemia) is due to a partial or complete reduction in blood flow to the brain. The ischemia may be global due to cardiac arrest or focal due to a blockage in a specific blood vessel. Brain regions most susceptible to damage are hippocampal CA1 and neocortical layers 3, 5, and 6 [4].

Cerebral hypoxia (a reduction of cerebral oxygen) generally accompanies an ischemic insult but may also occur without the loss of blood flow as in the case of respiratory arrest, near-drowning or carbon monoxide poisoning [5]. Insufficient oxygen and glucose supply in cerebral

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ischemia leads to unsustainable cellular homeostasis which initiates cell injury. Cellular injury progresses as a result of excitotoxicity, ionic imbalance, oxidative and nitrosative stresses, endoplasmic reticulum (ER) stress and mitochondrial disturbances, ultimately resulting in programmed cell death and necrosis [6]. Pathologically the ischemic infarct is observed as a central core, a region where cells undergo anoxic depolarization and never repolarize.

Cells in the core eventually become necrotic [7] immediately surrounding the core (perifocal region) is the ischemic penumbra, a region where cells receive some perfusion via collateral circulation and may repolarize but they are still highly vulnerable to injury [8].

Cells in the penumbra are subject to apoptosis but may be rescued by neuroprotective measures. If the ischemic process is not arrested the ischemic core will recruit the perifocal penumbra by a process called “spreading depression”; which is unarrested massive depolarization [9]. Manifestation of cerebral ischemia involves neurological deficit in cognition, motor and sensory functions, the severity of which reflects the location and size of the damaged area.

Localized reduction of brain blood flow can result in cerebral ischemia, and prolonged ischemia causes brain infarction, which in turn could result in death [10]. There are two kinds of stroke—ischemic strokes, which are caused by blood clots, and hemorrhagic strokes. Statistics pertaining to demise of individuals following ischemic cardiovascular stroke in 2008 was 7.3 million, with 6.2 million individuals dying from stroke or other cerebrovascular disease in 2008. Stroke or cerebrovascular diseases account for about 4.9% (about 450000 people) of total deaths in low-income countries, thus making it the sixth most common cause of death [11].

Thrombolytic therapy, which is deliquescing of blood clot, has been reported to be the optimum therapy for ischemic stroke. Effectiveness of this therapy lies in it being executed within the first 6 hours (the golden hours) following onset of stroke symptoms. Nevertheless, many patients miss the golden hours and are treated with antiplatelet aggregation drugs such as aspirin. Antiplatelet aggregations drugs have the tendency of decreasing risk of reattack; however, they neither allay nor reverse damage caused by stroke [12].

Due to the multiple pathophysiological mechanisms observed in ischemic stroke/cerebral ischemia, current treatments remain mostly ineffective apart from thrombolytic therapy which uses thrombolytic recombinant tissue plasminogen activators (rt-PA) [7] such as alteplase. This therapy allows only a 3–4.5 h window for effective treatment. It therefore becomes critical to develop other compounds that are multipotential in addressing the diverse pathological mechanisms in ischemic stroke/cerebral ischemia [13].

Taurine (2-amino-ethanesulfonic acid) is a sulphur containing, free amino acid, that is abundantly found in mammals [11]. Unlike other amino acids the presence of a sulphur group instead of a carboxyl group prevents it from being incorporated into proteins. It is mostly found in excitable tissues such as the brain, retina, cardiac muscle and skeletal muscle [14] and it is synthesized by methionine and cysteine metabolism with cysteine sulphinic acid decarboxylase (CSAD) being the rate-limiting enzyme [15].

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Apart from being synthesized endogenously, taurine may also be obtained from meat, dairy products, poultry, fish and shellfish [16]. While it was first discovered as a component of ox (*Bos tauru*; from which its name is derived) bile in 1827, it had taken over a century before insights into its physiological functions were made. Early concepts of its physiological functions were provided in a study by Curtis and Watkins [17].

They demonstrated that taurine could be a neurotransmitter which was later supported by Davison and Kaczmarck [18]. There is growing evidence of its physiological importance. Hayes and colleagues [29] reported that cats fed a taurine deficient diet developed central retinal degeneration. The importance of taurine in retinal function was also supported by several authors. Taurine is also a key player in: cardiovascular and muscular skeletal functions [33,34,35], regulating the release of pancreatic insulin and renal function [19].

Interestingly, taurine's role in brain development involves the differentiation and migration of cerebellar, pyramidal and visual cortical cells in cats and monkeys [20] as well as playing a role in both embryonic and adult neurogenesis [21]. These lines of evidence highlight a few of its physiological functions, for review [8].

Taurine also exhibits its potential to be effective against many diseases as observed in animal models of Type 1 and Type 2 diabetes, atherosclerosis and neurological disorders such as Alzheimer's, Parkinson's and Huntington's diseases. Its depletion has also been reported in cardiomyopathy [22].

Methods and Material

Animals

All animal procedures and protocols were performed in accordance with the Guide for the Care and Use of Laboratory Animals (NIH publication, 85-23, revised 1996) and were reviewed and approved by the Ethics Committee for the Use of Experimental Animals in Scientific Associate, Global eLearning Academy, Geneva, Switzerland. All male adult Sprague-Dawley (SD) rats (Zhejiang University Laboratory Animal Breeding and Research Center, Hangzhou, China) were housed at a constant temperature (25°C) and humidity (50–60%) under a regular 12 h light/dark schedule, with free access to food and water before and after ischemic induction. Seventy-five adult male Sprague-Dawley rats (weighing 250–300 g) were randomly assigned to 5 groups: normal control, sham group, middle cerebral artery occlusion (MCAO,), MCAO with Taurine (50 mg/kg) was administered intravenously 1 h after ischemia, and MCAO with vehicle (0.5 ml DMSO IP) 12 hours before ischemia. Both DMSO and Taurine were purchased from Sigma-Aldrich Co., USA.

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Induction of Cerebral Ischemic Reperfusion Injury

Methods of cerebral ischemic reperfusion injury were from previous research [23]. Rats were anesthetized with chloral hydrate (400 mg/kg) intraperitoneally. Under anesthesia, right common carotid arteries (CCA), external carotid artery (ECA), and internal carotid artery (ICA) were exposed via a ventral midline incision of the neck. After carefully isolating CCA and separating from the adjacent vagus nerve, CCA and ECA were ligatured with two surgical wires. An incision was made distal to the CCA ligation. Then, a piece of 26/0 monofilament nylon suture with its tip slightly rounded by heat was inserted through the right CCA incision and advanced a distance of 18 mm from the carotid bifurcation toward the origin of right middle cerebral artery, thus occluding blood flow to cortex and striatum. After 150 minutes, reperfusion was accomplished by careful withdrawal of nylon suture; CCA was ligatured distal to the incision, with muscular tissue and skin sewed up. Finally, animals were put into their respective cages.

Immunohistochemistry

24 hours following reperfusion, animals were deeply anesthetized with 4% chloral hydrate and then perfused transcardially with 500 ml of 0.9% saline, followed by 4% paraformaldehyde in 0.01 M PBS. Brains were removed, postfixed in a 4% paraformaldehyde solution, and transferred to a 30% sucrose solution prior to processing for immunostaining. Brains were then frozen and sectioned coronally. Sections were incubated for 15 minutes with 3% hydrogen peroxide in methanol to block endogenous peroxidases and then blocked for 1 hour with 0.3% Triton X-100/10% normal goat serum in 0.01 M PBS. Then, sections were incubated with primary antibody anti-iNOS, TNF-α, COX-2, caspase-3, and Bcl-2 (rabbit, 1 : 200, Thermo Fisher Scientific, Waltham, MA) overnight at 4°C. After a thorough washing in PBS, sections were incubated with HRP-conjugated goat anti-rabbit IgG (1 : 200; Santa Cruz Biotechnology, CA) for 1 hour and then visualized with 3,3-diaminobenzidine (DAB, Sigma-Aldrich Co., USA). Positive cells in each section were counted at 200x magnification.

Statistical analysis

Student's *t*-test was used to analyze data for significant differences. Values of $P < 0.05$ were regarded as significant.

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Results

Taurine Curtails Infarct Volume

In evaluating Taurine neuroprotectiveness, infarct volume was measured at 24 hours following reperfusion. Brains of rats were stained with 2% TTC to obtain infarct volume. Unstained areas (negative TTC stains) that appeared white were defined as infarct regions whereas normal regions appeared red (Figure 1(a)). Infarct volume (mm^3) was calculated as 2 mm (thickness of the slice) × sum of the infarction area (mm^2) in all slices using computerized planimetry (PC-based image tool software). As evidenced in Figure 1(b), infarct volume of the Taurine group was significantly decreased in comparison to the MCAO group (versus Taurine -treated group). No cerebral infarction was observed in the sham group. Infarct volume suggests Taurine plays a neuroprotective role in brain infarction.

Figure 1.

Unstained areas (negative TTC stains) were defined as infarct regions, while normal regions appeared red. (b) Bar graph represents the infarct volume from TTC staining in various groups.

Taurine Mitigates Neuronal Apoptosis

TUNEL-positive cell represents apoptotic cell. As illustrated in Figure 2(a), at 24 hours following reperfusion, number of apoptotic cells in penumbral area and infarct zone was observed. TUNEL method can identify DNA fragmentation of apoptotic cells. As depicted in Figure 2(b), in comparison to sham rats, number of TUNEL-positive cells was significantly increased in both MCAO groups (, versus sham group). In the Taurine -treated group, number of TUNEL-positive cells was significantly decreased relative to both MCAO groups (, versus Taurine -treated group). These results suggest Taurine could effectively obviate apoptotic cells following onset of stroke.

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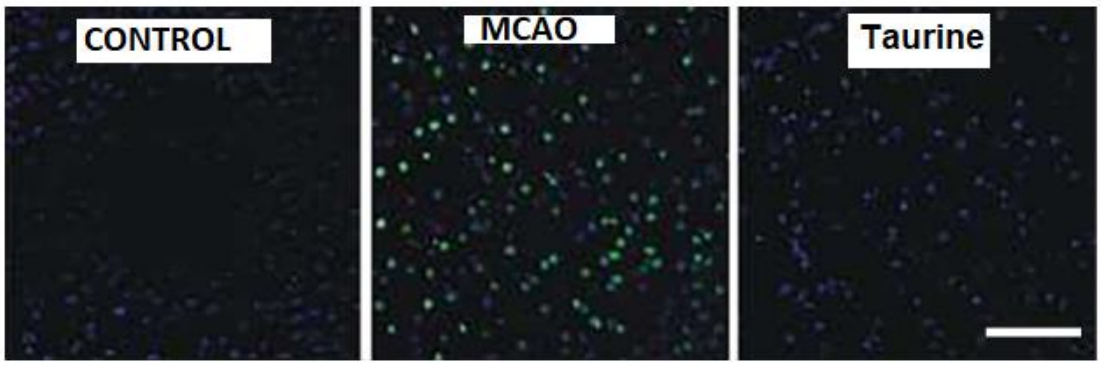

Figure 2.

Representative feature of TUNEL-positive cells in the ischemia area. (b) Bar graph reflected the TUNEL-positive staining score in each group.

Immunohistochemistry

Inflammatory cytokine expression in an MCAO rat model was detected via immunohistochemistry analysis in penumbral and stroke area at 24 hours after reperfusion. Positive staining cells were brown in color (Figure 3). Bcl-2, TNF-*α*, caspase-3, cyclooxygenase-2 (COX-2), and iNOS expressions in rat cortex were delineated, and the integral optical density (IOD) was measured with Image-Pro Plus 6.0 software. In comparison to MCAO group, Taurine suppressed the expressions of apoptotic cytokines, caspase-3, TNF-*α*, and iNOS (versus Taurine -treated group); however, expressions of antiapoptotic cytokines, Bcl-2, and COX-2 were stimulated (versus the Taurine -treated group) (Figure 3). Cytokine expressions between MCAO and DMSO groups were not statistically different.

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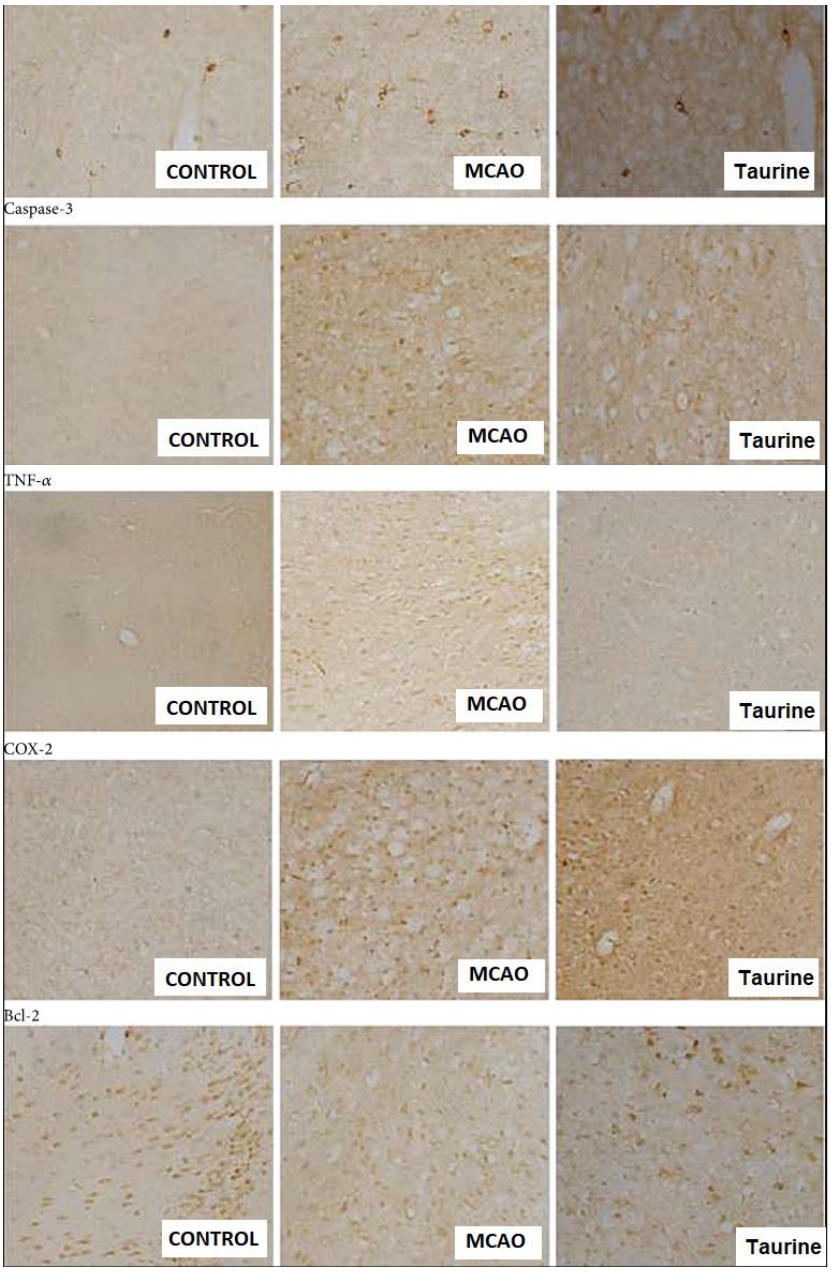

Figure 3.

Immunohistochemistry staining shown in penumbral and stroke areas at 24 h after reperfusion. Taurine downregulated the expression levels of caspase-3, TNF-*α*, and iNOS, but upregulated the levels of Bcl-2 and COX-2, when compared with the MCAO group.

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Discussion

Other functions of taurine, such as anti-oxidative, anti-inflammatory or osmoregulatory could also contribute to its neuroprotective mechanism [22] against ischemic stroke. In the presence of high mitochondrial calcium, the physiological production of reactive oxygen species [(ROS: such as superoxide anion (O_2^-), hydrogen peroxide (H_2O_2) and hydroxyl radical (·OH)] and nitric oxide NO, becomes pathological due to an imbalance of their production versus their degradation [194]. This pathological condition is commonly referred to as oxidative stress and it is observed in ischemic stroke [23].

The excessive intra-mitochondrial calcium $[Ca]_m$ is able to generate excessive ROS by one or all of such methods. Firstly, $[Ca]_m$ stimulates the tricarboxylic Acid (TCA) cycle, which enhances electron flow into the electron transport respiratory chain, increasing the mitochondrion's work and simultaneously increase the respiratory chain electron leakage to the acceptor O_2, generating ROS [6].

Secondly, $[Ca]_m$ disrupts the electron transport respiratory chain by either affecting conformational changes [24] in the respiratory complexes, exemplified by changes in complex IV (Wikstrom and Saari [25] or by activating the Ca^{2+}-dependent production of nitric oxide (via nitric oxide synthase), which inhibits complex I directly [11] and complex III in conjunction with calcium [26] of the respiratory chain.

The release of cytochrome *c* from the mitochondria inhibits complex IV [27]. This bottle neck in the respiratory chain diverts the flow of electrons from the chain to O_2. Thirdly, $[Ca]_m$ inactivates ROS scavengers, such as glutathione peroxidase (GPx) [28] resulting in a decrease in antioxidant capacity in the mitochondria. It is to be noted as well that the loss of GPx via an opened MPTP further reduces mitochondrial GPx [4]. Recci and colleagues [29] attributed the loss of mitochondrial respiratory chain integrity to a decline in the synthesis of the encoded proteins in the respiratory complexes.

Several lines of evidence have shown taurine to be protective against oxidative injury [9]. Taurine reduces ROS not by directly scavenging ROS [30] but instead by potentiating or rescuing endogenous anti-oxidants, as reported by many of these studies. Interestingly, Jong and colleagues reported that taurine's anti-oxidative effect is due to the maintenance of the mitochondrial respiratory chain integrity by taurine [31].

By using β-alanine, an inhibitor of taurine-linked reactions [32] they showed a reduction in complex I and complex III activity of the mitochondrial respiratory chain with a simultaneous reduction in oxygen consumption and an increase in mitochondrial oxidative stress (enhanced superoxide production, oxidation of glutathione and inactivation of aconitase, an oxidant sensitive enzyme). The reduction in complex 1 activity correlates with a reduction in the synthesis of mitochondrial proteins, ND5 and ND6; proteins that are apart of complex 1 protein assembly and are also encoded by taurine-conjugated mt $tRNA^{Leu(UUR)}$. The encoding function

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of mt $tRNA^{Leu(UUR)}$ was impaired by the taurine competitor, β-alanine. The reductions of oxidants reduce cellular damage such as membrane lipid peroxidation.

An inflammatory reaction occurs in response to brain ischemic stroke due to the infiltration of neutrophils, macrophages, activated microglia and inflammatory mediators such as various cytokines, adhesion molecules, and chemokines [33]. The transcription factor, nuclear factor-κB (NF-κB), enhances the production of inflammatory mediators by transcribing inflammatory genes. NF-κB's action is potentiated by poly-ADP-ribose polymerase (PARP) which is reported to act as its co-activator [8]. Inflammation was reduced by taurine (50 mg/kg b.wt.) in a rat model of transient focal ischemia [34]. These investigators observed that the up-regulation of PARP and NF-κB in the ischemic core and penumbra was reversed by taurine and that the levels of the inflammatory cytokines, tumor necrosis factor-α and interleukin-1β, were significantly reduced [35].

Edema is one of the resulting conditions after a brain ischemic insult. This is caused by an accumulation of intracellular Na^+ and Cl^- which instigates osmotic water influx [22]. Swelling then potentiates taurine's release; initially release is exocytosis and Ca^{2+}-dependent, subsequently through the reverse mode of the Na^+/Cl^--dependent TauT [11], as the ischemic insult prolong, release is through volume-sensitive chloride channels [2], and finally by diffusing across a permeabilized plasma membrane [5].

This regulates the cell's volume, preventing cell death by necrotic swelling. It was shown that taurine significantly reduced cell swelling in rat brain cortical slices after exposure to oxygen-glucose deprivation and reoxygenation [36].

In spite of the plethora of convincing demonstrations of the neuroprotective effect of taurine in ischemic stroke there are conflicting reports showing the failure of taurine to protect against this type of brain insult. Shuaib, reported that taurine (100 mg/kg, i.p.) did not statistically reduce infarct volume [37].

This contradictory report could be due to differences in experimental conditions, animal model, and route of administration or more interestingly, by a dose-dependent biphasic response of taurine in which a low concentration of taurine (1 mM) elicits hyperpolarization but at a higher concentration (10 mM), hyperpolarization is followed by slow depolarization.

Taurine's biphasic effect in an ischemic insult was clearly seen in an *in vivo* model of hypoxia-induced convulsion where taurine suppresses convulsion in a dose-dependent manner but at a high dose of 100 mg/kg no protection was observed [38]. We have also demonstrated the biphasic effect of taurine in excitatory amino acid-induced neurotoxicity in primary neuronal cultures. The biphasic response of taurine cautions investigators about the dose to be administered in their experiments which should be empirically determined, especially when using different experimental models [39].

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Conclusion

Taurine is synthesized within brain cells and exhibits a plethora of physiological functions [19]. It has a multiple of neuroprotective mechanisms in the CNS such as: regulating cellular osmolarity. In ischemic stroke, a pathological brain condition, taurine is released in the extracellular space resulting in a decrease in the concentration of intracellular taurine. The decrease in intracellular: extracellular taurine ratio attenuates the protective role of taurine and could potentiate neuronal damage during ischemia.

Taurine protects the endoplasmic reticulum from being stress, evidential by the reduction of ER stress markers such as CHOP and caspase-12 in taurine-treated experimental models.

Competing interests

The authors declare that they have no competing interests.

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