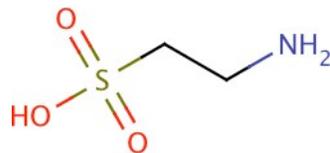


CINAPS Compound Dossier

Taurine

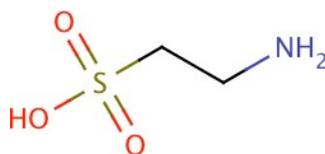


2/8/2008

I. Compound Information

Common name Taurine

Structure



PubChem ID

1123

MF

C2 H7 N O3 S

MW

125.15

CASRN

107-35-7

Polar surface area

88.77

logP

-1.87

IUPAC name

2-Aminoethane-1-sulfonic acid

Other names

2-Aminoethanesulfonic acid

Drug class

Cytoprotective osmoregulator, thermoregulator, and neuromodulator.

Notes

Development status

Marketed drug and "nutraceutical."

II. Rationale

IIa. Scientific Rationale / Mechanism

The physiological actions of taurine (2-aminoethanesulphonic acid) are reviewed in **Huxtable, 1992**. Taurine is a sulphur-containing β -amino acid found in high (millimolar) concentrations in excitable tissues such as brain and heart. Its suggested roles include osmoregulator, thermoregulator, neuromodulator, and potential neurotransmitter. This amino acid has also been shown to be released in large concentrations during ischaemia and excitotoxin-induced neuronal damage (**O'Byrne, 2000**).

Due to the hydrophilic structure, taurine poorly penetrates the lipid bilayer and the extracellular pool is likely regulated by specific mechanisms. The uptake of taurine is mediated by the well characterized taurine transporter TAUT. TAUT action can be reversed by changes in membrane ion gradient thus causing taurine efflux. The mechanisms regulating taurine release are less well understood and include release from neural tissue following depolarizing stimuli (**Molchanova, 2006**).

Extracellular taurine inhibits neuronal discharges (**Huxtable, 1989**). Its postsynaptic inhibitory effects are attributed to activation of a Cl^- conductance via GABAA and glycine receptors (**Haas, 1973; Hussy, 1997; Sergeeva, 2001**). Recently, it has been shown that, apart from inhibition, external taurine is able to induce an NMDA receptor-independent, long-lasting potentiation of synaptic transmission in the CA1 area of the hippocampus (**Galarreta, 1996**) and in the neostriatum (**Chepkova, 2002**). Taurine has been shown to activate Cl^- influx through GABAA receptors in mouse cerebellar granule cells. Consistent with this GABAA agonism *in vitro*, subcutaneous injection of taurine (43 mg/kg) in mice reduces kainic acid-induced seizure severity, suggesting GABAA activity *in vivo*. However, long term taurine administration through drinking water (0.05%, 4 weeks) induces a state of brain excitability characterized by increased susceptibility to kainic acid-induced seizures, increased glutamate and GABA in the brain, and reduced hippocampal GABAA receptor expression. This excitability induced by taurine is compatible with normal brain function and is sub-threshold to induce seizures (**El Idrissi, 2006**).

In rat cerebellar granule cells, taurine protected neurons from kainic acid induced apoptosis but not Sin-1 (3-morpholinopyridone hydrochloride) induced necrosis. Taurine did not reduce the increase in reactive oxygen species in this study (**Boldyrev, 1999**).

Taurine, which is present in millimolar concentrations in most mammalian tissues, has been reported to have a cytoprotective role. Its extracellular levels are increased in kainate- and N-methyl-D-aspartate-induced excitotoxicity in hippocampal slices (**Magnusson, 1991**) and in cases of induced ischaemia (**Saransaari, 1997; Torp, 1991**). It has been shown to protect cultured lens (**Devamanoharan, 1998**) cerebellar granular (**Boldyrev, 1999**), and kidney (**Michalk, 1996**) cells against oxidative stress (**Hayes, 2001**). In cultured cerebellar granule cells, enhanced taurine release is induced by hypoxia, ischemia, hypoglycemia, oxidative stress, and free radicals (**Saransaari, 1999**).

Taurine protects cultured neurons from glutamate-induced injury by reducing or preventing glutamate-induced increases in intracellular calcium concentrations. This is through the extracellular pool of taurine. Taurine does not inhibit glutamate binding to its receptor (**Chen, 2001**).

IIb. Consistency

As summarized in Section IIa, taurine has consistently demonstrated neuroprotective effects in several *in vivo* studies.

III. Efficacy (animal models of Parkinson's disease)

IIIa. Animal Models: Rodent

Both 1mM and 20mM taurine protect from MPP⁺ induced neurotoxicity in in vitro rat brain slices. Studies with taurine analogs and specific GABA agonists and antagonists suggest that this protective effect is mediated through a GABA_A agonism of taurine (O'Byrne, 2000).

Behavioral studies have suggested that taurine did not protect against the effects of direct intracerebral injection of 6-hydroxydopamine (Hashimoto, 1988). However, taurine administered in drinking water to male rats for 4 days prior and 3 days after injection of 6-hydroxydopamine into the medial forebrain bundle significantly decreased the loss of tyrosine hydroxylase positive cells (Ward, 2006). Hyper- and hypo-osmolar pulses in the rat substantia nigra have shown a sensitive and proportional response of the extrasynaptic pool of taurine to the extracellular osmolarity in the substantia nigra (SN), a response facilitated by ATP and glutamate release. These data are the first evidence suggesting an osmoregulatory role for taurine in the SN, a center where its only known function is inhibitory neurotransmission. Bearing in mind the neuroprotective capability of taurine, the osmotic modulation of this taurine pool could be relevant for SN cell survival in PD (Morales, 2007).

IIIb. Animal Models: Non-human primates

n/a

IV. Efficacy (Clinical and Epidemiological Evidence)

IVa. Clinical studies

n/a

IVb. Epidemiological evidence

Although no studies have been published to date, the fact that taurine is a major component (≥ 1 g per serving) of popular soft drinks such as “Red Bull” may be of epidemiological significance.

V. Relevance to other neurodegenerative diseases

In models of focal cerebral ischemia induced by middle cerebral artery occlusion in rats, both pre- (200 mg/kg) and post-treatment of taurine decreased the neurology deficit score, infarct volume and brain water content. Taurine post-treatment (67, 200 and 600 mg/kg) showed a dose-dependent neuroprotective effect. Taurine (200 mg/kg) significantly decreased neuronal loss in the cerebral cortex and hippocampus, and reduced the expression of caspase-3 as well. The neuroprotective effect of taurine was partly blunted by strychnine or bicuculline alone, and almost completely blocked by coapplication of both antagonists of glycine and GABAA receptors. It is suggested that taurine exerts a neuroprotective role on the brain when administered before or after MCAO. Such effect is possibly mediated by the activation of both GABAA receptors and strychnine-sensitive glycine receptors (**Wang, 2007**). In another study (**Zhou, 2006**), taurine administration prior to middle cerebral artery occlusion increased cerebral blood perfusion and reduced cell apoptosis and infarct volume. Taurine mediated protection from MCAO exhibits a dose-response from 1 mg/kg to 50 mg/kg when administered intravenously 1hr. post ischemia and analyzed 4 and 24 hrs. after MCAO (**Sun, 2007**).

In a rat model of Huntington's disease (HD) phenotype induced using the mycotoxin 3-nitropropionic acid (3-NP), administration of 3-NP caused a reduction in prepulse inhibition (PPI) of acoustic startle response, locomotor hyper- and/or hypoactivity, bilateral striatal lesions, brain oxidative stress, and decreased striatal gamma-aminobutyric acid (GABA) levels. Taurine is a semi-essential beta-amino acid that has been demonstrated to have both antioxidant and GABAA agonistic activity. In this study, treatment with taurine (200 mg/kg daily for 3 days) prior to 3-NP administration reversed both reduced PPI response and locomotor hypoactivity caused by 3-NP injection. Taurine pretreatment also caused about 2-fold increase in GABA concentration compared to 3-NP-treated animals. In addition, taurine demonstrated antioxidant activity against oxidative stress induced by 3-NP administration as evidenced by the reduced striatal malondialdehyde (MDA) and elevated striatal glutathione (GSH) levels. Histochemical examination of striatal tissue showed that prior administration of taurine ahead of 3-NP challenge significantly increased succinate dehydrogenase (SDH) activity compared to 3-NP-treated animals. Histopathological examination further affirmed the neuroprotective effect of taurine in 3-NP-induced HD in rats. Taken together, one may conclude that taurine has neuroprotective role in the current HD paradigm due, at least partly, to its indirect antioxidant effect and GABA agonistic action (**Tadros, 2005**).

VI. Pharmacokinetics

VIa. General ADME

In male and female adult rats at dosages of 30 or 300 mg/kg, a single oral dose of ^{14}C -taurine was rapidly absorbed, distributed to tissues and excreted unchanged in urine. Elimination of radioactivity from intracellular pools was slow. Pre-treatment of animals for 14 days with unlabelled taurine did not significantly affect the fate of ^{14}C -taurine. At the higher dose there was more extensive excretion combined with a lower percentage of the dose in the carcass, indicating the possibility of saturation of the tubular reabsorption mechanism for taurine. Daily administration of unlabelled taurine for 14 days did not result in an increase in total taurine in the brain. The data indicate that exogenous taurine rapidly equilibrates with endogenous body pools and that any excess is rapidly eliminated by the kidneys (Sved, 2007).

A large number of taurine derivatives have been reported in the literature with partial to marked clinical activity. This is indirect evidence of the pharmacologically significant bioavailability of taurine and its derivatives. For example, taurine derivatives such as taltrimide, acamprosate and taumustine, are already in the market as anti-convulsant, anti-alcoholism, and anti-cancer agents. The list of biological actions attributed to taurine is long and still growing, to mention just a few, osmoregulatory activity, bile salts synthesis, maintaining cellular functions, and cardiovascular actions. The importance of taurine is not limited to the above and its use as a therapeutic is increasing. However, amino acid therapy has its own limitations, e.g. restricted permeability, uncertain pharmacokinetics, hydrophilic nature, use of higher doses, and short duration. To overcome these shortcomings, many structural bioisosteres of taurine in the form of derivatives, homologues, analogues, & structural isomers have been evaluated. Many of these derivatives have shown encouraging results, either studied alone or combined with taurine. Taurine analogs are also cited in patents as anti-convulsant, anti-cancer, anti-alcoholism, and anti-microbial therapeutics (Gupta, 2005).

VIb. CNS Penetration

A high affinity, sodium and chloride dependent carrier for taurine (TAUT) is present at the luminal side of the endothelial cells. Taurine transport could be fitted by a model with saturable components. The kinetic constants in the parietal cortex were 1.4×10^{-4} /mol/s/g for the apparent V_{max} and 0.078 mM for the apparent K_m (Benrabh, 1995).

VIc. Calculated logBB

-1.46

VII. Safety, Tolerability, and Drug Interaction Potential

VIIa. Safety and Tolerability

Some indication of the general safety and tolerability of taurine is the fact that taurine is currently a component of infant formula, cat and dog food, eye drops, ear drops, energy drinks, anti-aging and anti-diabetes compositions and has been claimed as a component in human-use medications in a large number of patents (Gupta, 2005).

VIIb. Drug Interaction Potential

n/a

VIII. Bibliography

- Benrabh, 1995** Benrabh H.; Bourre J.M.; Lefauconnier J.M., *Taurine transport at the blood-brain barrier: an in vivo brain perfusion study*, Brain Res, **1995**, 692(1-2), 57-65.
-
- Boldyrev, 1999** Boldyrev A.A.; Johnson P.; Wei Y.; Tan Y.; Carpenter D.O., *Carnosine and taurine protect rat cerebellar granular cells from free radical damage*, Neurosci Lett, **1999**, 263(2-3), 169-72.
-
- Chen, 2001** Chen W.Q.; Jin H.; Nguyen M.; Carr J.; Lee Y.J.; Hsu C.C.; Faiman M.D.; Schloss J.V.; Wu J.Y., *Role of taurine in regulation of intracellular calcium level and neuroprotective function in cultured neurons*, J Neurosci Res, **2001**, 66(4), 612-9.
-
- Chepkova, 2002** Chepkova A.N.; Doreulee N.; Yanovsky Y.; Mukhopadhyay D.; Haas H.L.; Sergeeva O.A., *Long-lasting enhancement of corticostriatal neurotransmission by taurine*, Eur J Neurosci, **2002**, 16(8), 1523-30.
-
- Devamanoharan, 1998** Devamanoharan P.S.; Ali A.H.; Varma S.D., *Oxidative stress to rat lens in vitro: protection by taurine*, Free Radic Res, **1998**, 29(3), 189-95.
-
- El Idrissi, 2006** El Idrissi A., *Taurine and brain excitability*, Adv Exp Med Biol, **2006**, 583, 315-22.
-
- Galarreta, 1996** Galarreta M.; Bustamante J.; Martin Del Rio R.; Solis J.M., *Taurine induces a long-lasting increase of synaptic efficacy and axon excitability in the hippocampus*, J Neurosci, **1996**, 16(1), 92-102.
-
- Gupta, 2005** Gupta R.C.; Win T.; Bittner S., *Taurine analogues; a new class of therapeutics: retrospect and prospects*, Curr Med Chem, **2005**, 12(17), 2021-39.
-
- Haas, 1973** Haas H.L.; Hosli L., *The depression of brain stem neurones by taurine and its interaction with strychnine and bicuculline*, Brain Res, **1973**, 52, 399-402.
-

VIII. Bibliography (cont.)

- Hashimoto, 1988** Hashimoto-Kitsukawa S.; Okuyama S.; Aihara H., *Enhancing effect of taurine in the rat caudate spindle. II. Effect of bilateral 6-hydroxydopamine lesions of the nigro-striatal dopamine system*, Pharmacol Biochem Behav, **1988**, 31(2), 417-23.
-
- Hayes, 2001** Hayes J.; Tipton K.F.; Bianchi L.; Corte L.D., *Complexities in the neurotoxic actions of 6-hydroxydopamine in relation to the cytoprotective properties of taurine*, Brain Res Bull, **2001**, 55(2), 239-45.
-
- Hussy, 1997** Hussy N.; Deleuze C.; Pantaloni A.; Desarmenien M.G.; Moos F., *Agonist action of taurine on glycine receptors in rat supraoptic magnocellular neurones: possible role in osmoregulation*, J Physiol, **1997**, 502 (Pt 3), 609-21.
-
- Huxtable, 1989** Huxtable R.J., *Taurine in the central nervous system and the mammalian actions of taurine*, Prog Neurobiol, **1989**, 32(6), 471-533.
-
- Huxtable, 1992** Huxtable R.J., *Physiological actions of taurine*, Physiol Rev, **1992**, 72(1), 101-63.
-
- Magnusson, 1991** Magnusson K.R.; Koerner J.F.; Larson A.A.; Smullin D.H.; Skilling S.R.; Beitz A.J., *NMDA-, kainate- and quisqualate-stimulated release of taurine from electrophysiologically monitored rat hippocampal slices*, Brain Res, **1991**, 549(1), 1-8.
-
- Michalk, 1996** Michalk D.V.; Wingenfeld P.; Licht C.; Ugur T.; Siar L.F., *The mechanisms of taurine mediated protection against cell damage induced by hypoxia and reoxygenation*, Adv Exp Med Biol, **1996**, 403, 223-32.
-
- Molchanova, 2006** Molchanova S.M.; Oja S.S.; Saransaari P., *Properties of basal taurine release in the rat striatum in vivo*, Adv Exp Med Biol, **2006**, 583, 365-75.
-
- Morales, 2007** Morales I.; Dopico J.G.; Sabate M.; Gonzalez-Hernandez T.; Rodriguez M., *Substantia nigra osmoregulation: taurine and ATP involvement*, Am J Physiol Cell Physiol, **2007**, 292(5), C1934-41.
-

VIII. Bibliography (cont.)

- O'Byrne, 2000** O'byrne M.B.; Tipton K.F., *Taurine-induced attenuation of MPP+ neurotoxicity in vitro: a possible role for the GABA(A) subclass of GABA receptors*, J Neurochem, **2000**, 74(5), 2087-93.
-
- Saransaari, 1997** Saransaari P.; Oja S.S., *Enhanced taurine release in cell-damaging conditions in the developing and ageing mouse hippocampus*, Neuroscience, **1997**, 79(3), 847-54.
-
- Saransaari, 1999** Saransaari P.; Oja S.S., *Enhanced taurine release in cultured cerebellar granule cells in cell-damaging conditions*, Amino Acids, **1999**, 17(4), 323-34.
-
- Sergeeva, 2001** Sergeeva O.A.; Haas H.L., *Expression and function of glycine receptors in striatal cholinergic interneurons from rat and mouse*, Neuroscience, **2001**, 104(4), 1043-55.
-
- Sun, 2007** Sun M.; Xu C., *Neuroprotective Mechanism of Taurine due to Up-regulating Calpastatin and Down-regulating Calpain and Caspase-3 during Focal Cerebral Ischemia*, Cell Mol Neurobiol, **2007**, , .
-
- Sved, 2007** Sved D.W.; Godsey J.L.; Ledyard S.L.; Mahoney A.P.; Stetson P.L.; Ho S.; Myers N.R.; Resnis P.; Renwick A.G., *Absorption, tissue distribution, metabolism and elimination of taurine given orally to rats*, Amino Acids, **2007**, 32(4), 459-66.
-
- Tadros, 2005** Tadros M.G.; Khalifa A.E.; Abdel-Naim A.B.; Arafa H.M., *Neuroprotective effect of taurine in 3-nitropropionic acid-induced experimental animal model of Huntington's disease phenotype*, Pharmacol Biochem Behav, **2005**, 82(3), 574-82.
-
- Torp, 1991** Torp R.; Andine P.; Hagberg H.; Karagulle T.; Blackstad T.W.; Ottersen O.P., *Cellular and subcellular redistribution of glutamate-, glutamine- and taurine-like immunoreactivities during forebrain ischemia: a semiquantitative electron microscopic study in rat hippocampus*, Neuroscience, **1991**, 41(2-3), 433-47.
-
- Wang, 2007** Wang G.H.; Jiang Z.L.; Fan X.J.; Zhang L.; Li X.; Ke K.F., *Neuroprotective effect of taurine against focal cerebral ischemia in rats possibly mediated by activation of both GABAA and glycine receptors*, Neuropharmacology, **2007**, 52(5), 1199-209.
-

VIII. Bibliography (cont.)

Ward, 2006

Ward R.; Cirkovic-Velichovia T.; Ledequé F.; Tirizitis G.; Dubars G.; Datla K.; Dexter D.; Heushling P.; Crichton R., *Neuroprotection by taurine and taurine analogues*, Adv Exp Med Biol, **2006**, 583, 299-306.

Zhou, 2006

Zhou F.; Guo J.; Yang R.; Gu J.; Jin H.; Wu G.; Cheng J., *Effects of taurine on cerebral blood flow perfusion, cell apoptosis, and infarct volume in acute cerebral ischemic rats*, Adv Exp Med Biol, **2006**, 583, 353-8.
