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The use of taurine analogues to investigate taurine functions and their potential therapeutic applications

Review Article

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Summary. Despite the multitude of evidence for the beneficial effects of taurine supplementation in a variety of disease, the underlying modifying action of taurine with respect to either molecular or biochemical mechanisms is almost totally unknown. We have assessed the development of taurine analogues, particularly where there has been substitution at the suphonate or amine group. Such substitutions allow the investigator to probe the relationship between structure and function of the taurine molecule. In addition such studies should help to ascertain taurine's point of interaction with the effector molecule. These results will prepare the way for the development of the second generation of taurine analogues.

Keywords: Taurine analogues – Neurotransmitter – Neuromodulation – Antioxidant

Experimental and clinical use of taurine and its analogues

Over the last decade there has been considerable interest in the possible nutritional and therapeutic benefits of dietary supplementation with taurine. Such benefits have been reported to include improvement of brain function in infants (Benson and Masor, 1994), since taurine appears to play a vital role in the differentiation of neural stem cells. In addition, taurine supplementation can reduce the risk of a number of diseases, including diabetes (Wu et al., 1999), inflammatory bowel disease, (Son et al., 1998), ischaemia (McCarty, 1990) and cardiovascular disease (Kendler et al., 1997). It has also been reported to diminish alcoholic craving after detoxification (Wilde and Wagstaff, 1997). Furthermore, recent studies have also indicated that dietary supplementation with taurine may be beneficial in the prevention of neurodegeneration in the elderly (Wallace and Dawson, 1990).

This account will consider the properties of taurine in terms of these effects, with particular reference to the possible applications of taurine analogues. Such analogues may not only be used to help in understanding its physiological functions, but also to provide therapeutic or prophylactic compounds that supplement or enhance the beneficial actions of taurine.

Uptake and transport of taurine

A problem associated with its use as a dietary supplement is that, taurine is a hydrophilic compound that is poorly absorbed; it does not diffuse readily across membranes Thus, extremely high doses, typically greater than 3 g/day, are required for supplements to achieve any clinical efficacy. Taurine transporters are present on many cell types such that intracellular taurine concentrations are generally maintained at a significantly higher concentration than extracellular levels. In the brain, the physiological level in the extracellular space has been reported to be between 8 and 20 μM (Jacobson and Hamberger, 1985; Lerma et al.,

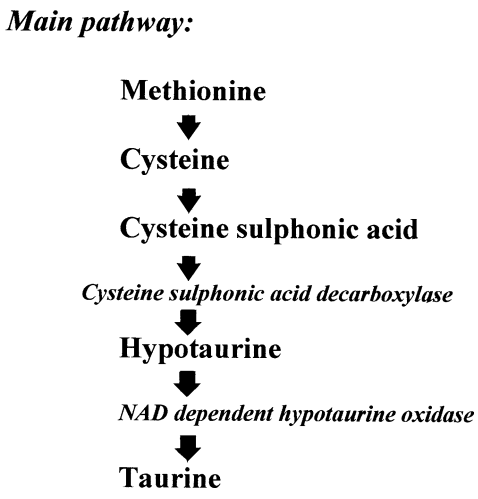


Fig. 1. Taurine biosynthesis

1986), which may correspond to an intracellular : extracellular concentration ratio as high as 600 : 1 (Jacobson and Hamburger, 1984; Pasantes-Morales, 1986). Under normal circumstances it appears that local synthesis of taurine, from methionine and cysteine, via the enzyme cysteine sulfinic acid decarboxylase (CSDI) (see Fig. 1), may be the major source of intracellular taurine.

Thus, if one wishes to develop taurine analogues for dietary use, their required properties should include improved lipophilicity, in order to enhance absorption, thereby reducing the dose required. Alternatively, the use of pro-drugs, which could diffuse across membranes before releasing their taurine moiety within the cell, could be a profitable avenue to explore. In this context, compounds such as β-sultan, Fig. 2, which hydrolyses slowly in water to yield taurine (Page M, personal communication), might be an interesting model compound, although the taurine transporter may extrude a proportion of such excesses taurine in order to maintain intracellular : extracellular ratio of taurine constant.

It is therefore surprising that there are few studies which have studied pharmacokinetics of taurine's distribution after its intraveneous injection, IV. Infusion

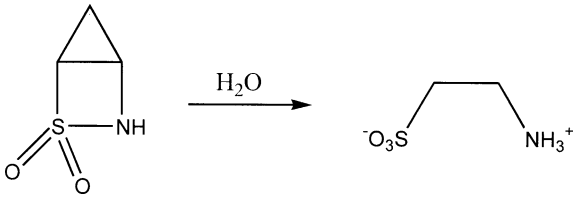


Fig. 2. β-Sultan hydrolyses slowly in water to yield taurine

of taurine improves glucose tolerance in diabetic rats while its intracranial administration has a neuromodulating effect, enhancing the rat caudate spindle in sham-operated rats possibly by decreasing the activity of the nigro-striatal DA system at the pre- and post-synaptic sites (Hashimoto et al., 1988). Some taurine analogues have been given intravenously; acamprosate to ascertain its mechanism of action in healthy volunteers (Bolo et al., 1998), (possibly via a central glutamatergic effect) and tauromustine which delayed cancer growth in rats which had been subcutaneously implanted wiht carcinomas (Roos et al., 1991).

Activities and functions of taurine

Taurine appears to have a wide diversity of functions that may contribute to its beneficial actions. These include modulation of intracellular calcium homeostasis, membrane stabilisation, osmoregulation, reactive-radical scavenging, neuroprotection and neurotransmission (see Huxtable 1992 and 2000 for reviews). The extent to which these different activities may contribute to its different therapeutic actions remains an enigma. Clearly, the development of taurine analogues for therapeutic or prophylactic use requires knowledge of such factors, so that the properties that are beneficial in specific systems can be optimised. Taurine analogues that possess only some of these properties can be of value in helping to understand the molecular properties that contribute to its specific actions in different systems. A variety of taurine analogues have been synthesised, but in many cases these have not been investigated systematically in terms of structure-function relations in different systems.

Taurine has been shown to modulate several calcium-ion and zinc-ion dependent physiological processes *in vitro*, which may be due to the formation of taurine complexes with these metal ions (Huxtable, 1992). It also alleviates effects arising from exposure to some toxic metal ions. For example, the glutathione levels in the lenticular system are reduced by exposure to lead but return to normal values following treatment with taurine (Neal et al., 1999). *In vitro* taurine also reduces the toxic effects of copper (Hwang et al., 1998) and plays a protective role against neurodegeneration caused by heavy metals (Aschner, 1997). Metal complexes of taurine have been detected in molluses from habitats polluted with cadmium, zinc and copper (Howard and Nickless, 1977).

Conversely, exposure to various metal ions has adverse effects on taurine levels. Lead significantly decreases taurine concentrations in plasma (McGowan and Donaldson, 1987) and nickel diminishes the protection of membranes afforded by taurine (Herrero et al., 1993). Despite the fact that some of the aforementioned effects may be due to the formation of metal ion complexes, relatively little work has been carried out to date on such taurine complexes. A cobalt(III)-taurine complex has been characterised *in vitro* (Ford and Nolan, 1980) and the properties of solutions of copper (II) – dipeptide – taurine complexes have been studied at physiological pH (O'Brien et al., 1999). Nickel (II) – methionine/ethionine – taurine complexes (Mittal et al., 1978), and $U0_2^{2+}$ – taurine complexes at low pH (Maslowska and Chruscinnski, 1984) have also been studied.

Some specific aspects of taurine function where taurine analogues may help to elucidate its effects

a) Formation of N-chlorotaurine (taurine chloramine)

There have been many claims that taurine can act as an antioxidant, i.e. a scavenger of reactive oxygen-containing free radicals (see Chahine and Feng, 1998). However its structure clearly is not that of an acceptor of electrons; indeed it is a considerably poorer antioxidant than its precursor cysteine. However it is a modulator of the "respiratory burst" in cells such as neutrophils. The primary amine group of taurine is strongly nucleophilic, such that it will react readily with hypocholorous acid (HOCl), (which is formed from H_2O_2 and chloride ions in a reaction catalysed by myeloperoxidase), during the respiratory burst, to form *N*-chlorotaurine (see Cunningham et al., 1998).

Since HOCl is highly toxic, *in vivo*, *N*-chlorotaurine may protect the cell from damage whilst maintaining its bactericidal activity. *N*-Chlorotaurine is converted to sulphoacetaldehyde, in a reaction that can occur spontaneously but is also enzyme catalysed, and then to isethionic acid (hydroxyethanesulphonic) in the tissues (Cunningham et al., 1998) (see Fig. 3). This appears to be the only route of taurine catabolism in most mammalian systems and this pathway together with conjugation with compounds such as cholate, to form taurocholate, may constitute the only ways of metabolic taurine loss.

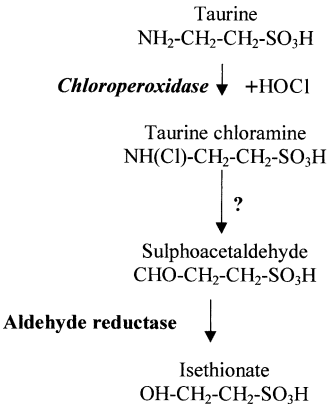


Fig. 3. Taurine catabolism

Substitution at the amino group of taurine will reduce its ability to react with HOCl. Hence *in vitro* *N*-methyltaurine, *N*,*N*-dimethytaurine and *N*,*N*,*N*,-trimethytaurine taurine are unable to react with hypochlorous acid.

$NH(CH_3)$-CH_2-CH_2-SO_3H
N-methyl-taurine
$N(CH_3)_2$-CH_2-CH_2-SO_3H
N,N-dimethyl-taurine
$^{+}N(CH_3)_3$-CH_2-CH_2-SO_3^{-}
N,N,N, trimethyltaurine

Administration of taurine chloramine to activated macrophages *in vitro*, inhibited the generation of nitric oxide, prostaglandin E2, tumour necrosis factor and interleukin 6, thereby modulating the inflammatory response (Marcinkiewicz et al., 1995). *In vitro* administration of taurine to neutrophils also diminishes the respiratory burst (Cunningham et al., 1998). In contrast, when macrophages, which do not contain myeloperoxidase, are loaded with taurine *in vivo* and then activated with lipopolysaccharides, an enhanced inflammatory response was evident; as reflected by an increased synthesis of inducible nitric oxide synthase (Fico and Ward, unpublished results). This may relate to the fact that catalase activity is inhibited by taurine (Ward et al., 2001), so that excess hydrogen peroxide generated during the respiratory burst cannot be removed. This could, in turn, lead to the activation of the transcription factor NFKappaB (see Marangolo et al., 2001). Thus, the development of taurine analogues that suppress the inflammatory response, without compromising other taurine functions, may be advantageous in the treatment of inflammatory diseases.

b) Taurine as a neurotransmitter or neuromodulator

Taurine is one of the most abundant free amino acids in the brain (see Huxtable et al., 1989) where, *inter alia*, it has been suggested to act as a neurotransmitter (Barbeau et al., 1975; Davison and Kaczmarek, 1971; Oja et al., 1978). In the rat hippocampus, immunocytochemical studies have shown the taurine synthetic enzyme CSDI to be localised in many pyramidal basket interneurons. This, together with electrophysiological observation of a hyperpolarising effect elicited by taurine, suggests that taurine may be used as a neurotransmitter by some of these interneurons (Taber et al., 1986). Taurine appears to fulfil many of the criteria of a neurotransmitter in the basal ganglia. High levels of taurine and its synthetic enzyme CSDI, as well as a high affinity uptake system are present in both neostriatum and substantia nigra (SN) (Bianchi et al., 1996). Furthermore, taurine is present in a subpopulation of striatonigral GABAergic neurons and behaves similarly to GABA at their terminals in the SN when the neostriatum is stimulated by kainic acid *in vivo* (KA) (Bianchi et al., 1998; Hayes et al., 2001). However, locally in the striatum most of the KA-induced release of taurine was independent of non-NMDA receptor stimulation and the propagation of action potentials, suggesting the involvement of a different mechanism from that responsible for the local release of GABA induced by KA (Bianchi et al., 1998). This difference may reflect different responses of the taurine and GABA, possibly related to the excitotoxic effects of KA in this brain area (Bianchi et al., 1998). Indeed, a proportion of the release of taurine induced by KA and quisqualate in the hippocampus, either *in vitro* (Magnusson et al., 1991) or *in vivo* (Menéndez et al., 1990), has been suggested to result from an osmoregulatory process, in that taurine is mobilised to counteract the toxic cellular oedema elicited by these excitatory agonists. However, the other component of KA-evoked release and almost all the taurine release induced by NMDA were independent of cell swelling, indicating taurine to have a function that is independent from its osmoregulatory role (Menéndez et al., 1990).

Recently, taurine has also been reported to induce a long-lasting potentiation (LLP) of excitatory synaptic potentials, owing to the enhancement of both synaptic efficacy and axon excitability in the CA1 area of rat hippocampal slices (del Olmo et al., 2000). This behaviour suggests taurine to be involved in the maintenance of LTP. Unfortunately, such a role in the plastic phenomena underlying LTP, has not been assessed further because of the lack of specific antagonists (see del Olmo et al., 2000). The development of specific analogues as agonists, which were free from actions at the GABA receptor (see Section c below) would be particularly valuable for such work and might also lead to the development of nootropic drugs.

Although taurine fulfils many of the criteria of a neurotransmitter, a specific taurine receptor has not yet been unequivocally characterised. The inhibitory action of taurine has been reported to be exerted by activating $GABA_A$ receptors (Bureau and Olsen, 1993; Taber et al., 1986; Zhu and Vicini, 1997; Ye et al., 1997) or glycine receptors (Horikoshi et al., 1988; Ye et al., 1997). However, a putative taurine receptor has been described by Wu et al. (1992) and Sgaragli et al. (1994; 1996) who studied the interactions of taurine and some of its analogues with a hypothetical receptor in rabbit brain that mediates the hypothermic effect of taurine. Some of the analogues tested behaved similarly to taurine, whereas others had the opposite effect, with *N*-methyl-taurine behaving similarly to taurine at lower concentrations but being antagonistic at higher concentrations. Such behaviour might be explained by postulating the existence of a receptor possessing two recognition sites, one negatively and the other positively charged, interacting with the amino and the sulphonic group of taurine, respectively. The interaction of the sulphonate group with the receptor appeared to depend on its tetrahedral shape, as the activity was maintained following replacement of the sulphur atom with As or P, but was lost in β-alanine, which has a planar carboxylate group (Sgaragli et al., 1996). The development of further analogues as more potent agonist or antagonist of such effects, as well as for direct interaction studies, should help in further understanding the receptors that recognise and respond to taurine.

c) Taurine and GABA

In vitro taurine increased chloride-ion conductance and hyperpolarised excitable membranes in a manner similar to that of GABA. Thus, taurine might be expected to mimic GABA in exerting a depressive effect on neuronal firing. However, both the GABA receptor antagonist bicuculline and the glycine receptor strychnine were shown to abolish the taurine-induced depression of neuronal firing in the medulla of

the cat (Haas and Hosli, 1973). This suggests that, although taurine and GABA may have some similar effects, their sites of action differ. Taurine has been shown to interact with both the $GABA_A$ and $GABA_B$ receptors *in vitro* (Kontro et al., 1990). However, the effects obtained appear to vary widely between different brain regions (For example see Huxtable, 1989; Bureau and Olsen, 1993). Studies on the effects of taurine on slices from the CA1 region of rat hippocampus have indicated the effects to be predominately through activation of dendritic $GABA_A$ receptors (del Olmo et al., 2000). However, taurine, as well as GABA may act as chemoattractants for neurons during embryonic cortical migration in the rat, through mechanisms that involve $GABA_B$ receptors (Behar et al., 2001). Taurine is a non-competitive inhibitor of the binding of GABA to rat brain membranes, indicating that it does not bind at the same site as GABA, although it is able to displace GABA agonists, such as muscimol (Huxtable, 1992).

Taurine is about 1000-times less potent than GABA in displacing muscimol from $GABA_A$ receptors *in vitro*. Marangolo et al. (1997) reported that 100 μM GABA inhibited the specific binding of [^{3}H]-muscimol (4 nM) to brain membranes by approximately 97%, whereas taurine (100 mM) inhibited the binding by 60%. The K_i value for this displacement by taurine was calculated to be 58.8 $\pm$ 8.8 mM. The displacement of the ligand of [^{35}S]-t-butylbicyclophosphorothionate (2 nM) from brain synaptic membranes by both taurine and GABA was shown to vary between different brain regions with mean IC_{50} values, from 3 regions, of 6.3 μM and 1.2 mM being obtained for the inhibition of binding by GABA and taurine, respectively (Chen et al., 1995). Similarly, Rabe et al. (2001) reported regional variations in the displacement of the $GABA_A$ receptor ligand [^{35}S]-t-butylbicyclophosphorothionate (6 nM) from rat brain sections by GABA and taurine. The mean values from 26 different regions showed 3 μM GABA to displace some 45% of the ligand whereas 5 mM taurine resulted in 52% displacement. The relatively low affinity of taurine for the $GABA_A$ receptors has been reported to result in its unbinding before desensitizing. In patch-clamp studies this behaviour is characterised by a rapid response and recovery, without the additional slow exponential decay that would result from desensitization and decreased reopening of Cl^- channels (Zhu and Vicini, 1997).

The effects of a variety of taurine analogues have been compared, with those of unlabelled taurine, as inhibitors of radioactively-labelled taurine in an *in vitro* glioma cell-culture model. The only compounds that inhibited ^{3}H taurine uptake by C6 glioma cells were β-alanine, guanidoinoethanesulphonic acid, GES, GABA and *N*-methyltaurine (Marangolo et al., 1997).

NH_3-CH_2-CH_2-COOH
β-alanine
NH_2-CH_2-CH_2-CH_2-COOH
γ-aminobutyric acid, GABA
NH = C(NH_2)-NH-CH_2-CH_2-SO_3H
Guanidoinoethanesulphonic acid

Further studies also showed that the only taurine analogue to inhibit GABA transport into glioma cells was *N*-methyl taurine (Marangolo et al., 1997).

GABAergic transmission is terminated when GABA is cleared from the synaptic cleft by its rapid sodium- and chloride-dependent uptake through GABA transporters. Genes for four high affinity GABA transporters have been cloned, GAT1, GAT2, GAT3 and BGT1. It has been suggested that the high-affinity taurine uptake system into neurons and astrocytes share properties with the GABA uptake system (Liu et al., 1993). High-affinity and low-affinity transport systems for both taurine and GABA have been demonstrated to occur in synaptosomes and glial cells (Debler et al., 1987; Henn, 1976). Furthermore a taurine transporter, named TAUT, cloned from rat brain is homologous with high affinity GABA transporters (Peterson and Miller, 1995) Potent inhibitors of TAUT are taurine, β-alanine, hypotaurine and GES (Marangolo et al., 1997).

NH_2-CH_2-CH_2-SO_2H
Hypotaurine

In addition, β-alanine and hypotaurine have been shown to have high affinity for two of the GABA transporters, GAT2 and GAT3 *in vitro* (Ramanthan et al., 1997). In contrast, taurine has a low affinity for the GABA transporters (Zhang and Liu, 1998). In experiments with rat brain synaptosomes β-alanine and GES were shown to inhibit taurine uptake *in vitro* whereas GABA and *N*-methyltaurine inhibited only weakly (Marangolo et al., 1997).

Taurine has been shown to be a competitive inhibitor of the binding of ^{3}H muscimol (a GABA receptor agonist) to $GABA_A$ receptors. Testing of the effects of taurine and its analogues, each at the same concentration, on ^{3}H muscimol binding to rat synaptic mem-

branes *in vitro* showed that inhibition of binding by GABA was 97%, by taurine was 60%, whereas TAG and GES caused 50 and 46% inhibition, respectively. *N*-methyltaurine, *N*,*N*,-dimenthyl taurine and *N*,*N*,*N*-trimethyl taurine reduced the binding of ^{3}H muscimol by 32%, 40% and 25% respectively (Marangolo et al., 1997).

d) Taurine and calcium ion homeostasis

Taurine has been shown to affect Ca^{2+} transport in many tissues, including heart, brain and retina. The high-affinity (15–20 μm) uptake system for Ca^{2+} from cytosol has been shown to be stimulated by taurine in several membrane systems, including cardiac sarcolemma, retinal rod outer segments, disk membrane and brain synaptosomes (Sebring and Huxtable, 1985; Kuo and Miki, 1980; Izumi et al., 1977). In heart, the normalising action of taurine on both low and high levels of intracellular Ca^{2+} has been attributed to direct modulation of Ca^{2+} channels and/or indirect effects operating via Ca^{2+}-Na^{+}-exchange (Satoh and Sperelakis, 1993). Furthermore, administration of taurine into the lateral ventricle increased Ca^{2+} levels in cerebrospinal fluid from conscious rabbits and this was correlated with a decline of body temperature in these animals (Palmi et al., 1985; Sgaragli et al., 1994). It has been suggested that taurine might act intracellularly to sequester Ca^{2+} that is released from mitochondria and other intracellular stores (Kass et al., 1988). However, taurine is a poor calcium ion chelator (Irving et al., 1982).

Furthermore, Chen et al. (2001) have shown that inhibition of taurine uptake by guanidoinoethanesulfonic acid did not affect its ability to antagonise glutamate-induced elevation of intracellular free Ca^{2+}. They suggested that the action of taurine might involve inhibition of the reverse mode of the Na^{+}/Ca^{2+} exchangers.

Taurine has been shown to enhance Ca^{2+} uptake by mitochondria *in vitro* in an apparently saturable process, with a K_m value of about 2.63 mM, suggesting that a specific binding process is involved (Palmi et al., 1998, 1999). The taurine analogue *N*,*N*-dimethyltaurine also stimulated calcium ion uptake, but only at much higher concentrations, whereas, isethionic acid, 3-aminopropanesulphonic acid and 2-aminoethylphosphonic were without effect. In contrast 2-aminoethylarsonate was a weak inhibitor of mitochondrial Ca^{2+} uptake but inhibited the stimulatory effect of taurine in an apparently competitive fashion (K_i = 0.05 mM) (Palmi et al., 1999, 2000).

NH_2-CH_2-CH_2-PO_3H_2
2-aminoethylphosphonic acid
NH_2-CH_2-CH_2-AsO_3H_2
2-aminoethylarsonaic acid
$NH_2CH_2CH_2CH_2SO_3H$
Aminopropanesulphonic acid
HO-CH_2-CH_2-SO_3H
Isethionic acid

Thus it appears that taurine may have a specific role in modulating mitochondrial Ca^{2+} homeostasis. This could explain the beneficial effect of this amino acid in pathological conditions, such as oxidative stress and excitotoxicity, where an increased intracellular Ca^{2+} concentration and a reduced capacity for mitochondrial respiration might potentially contribute to irreversible injury and cell death. Furthermore taurine stimulates mitochondrial oxidation (Palmi et al., 1996; El Idrissi and Trenkner 1999) and has also been reported to influence protein phosphorylation (Militante et al., 2000) but no clear relationship between these two processes has yet been established.

The 1,4-dihydroisonicotinoyl acid derivative of taurine (tauropirone; Fig. 4) been shown to increase the activity of blood platelet Ca/Mg-ATPase and to decrease platelet aggregation (Table 1). Taurine has a similar effect on aggregation but only at significantly higher (approximately 30-fold) concentrations (Poikans et al., 1994).

e) Taurine and neuroprotection

Large increases in extracellular taurine have been shown to be associated with kainate-and *N*-methyl-D-aspartate (NMDA)-induced excitotoxicity in hippocampal slices (Pazdernik et al., 1990; Magnusson et al.,

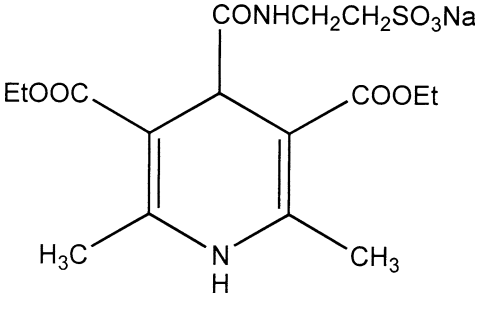


Fig. 4. Chemical structure of tauropirone

Table 1. The Anti-aggregation activity of 2,6-dimethyl-1,4-dihydroisonicotinic acid derivatives and their effect on Ca^{2+}/Mg^{2+}-ATPase from human blood platelets

Compound	Conc (mM)	Primary aggregation (% of controls)	Activity Ca^{2+}/Mg^{2+}-ATPase (% of controls)
4a	1.0	100	100
4b	0.5	49 ± 12	147 ± 10
4c	1.5	50 ± 8	–
4d	1.0	100	100
5	2.0	72 ± 9	100
Taurine	15.0	60 ± 6	133 ± 8

From Poikans et al. (1994)

1991). Similar increases have been reported in cases of induced ischaemia (Torp et al., 1991). Such data have been interpreted in terms of taurine having a protective role in the brain, particularly in cases of toxic insult. Taurine has been reported to protect cultured rat astrocytes from reperfusion injury (Raschke et al., 1995) and to have protective effects against glutamate-induced neuronal injury in cultured neurons (Chen et al., 2001). In contrast, the taurine analogues guanidinoethanesulphonic acid, GES, *N*,*N*,-dimethyltaurine and *N*,*N*,*N*,-trimethyltaurine as well as taurine itself, at concentrations of 1, 5 or 20 mM, were ineffective at protecting mouse cerebellar granule cells against the toxicity of 100 μM glutamate (Marangolo, 1999).

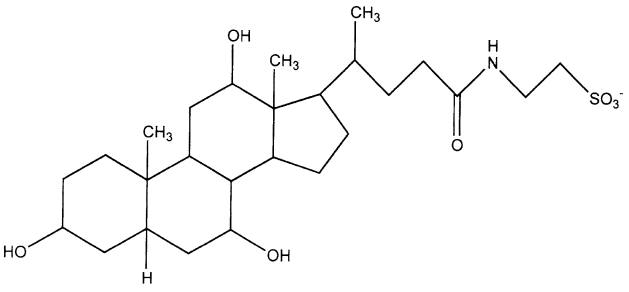
Primary neuronal cultures of mouse cerebellar granule cells, which contain neurons expressing both NMDA and non-NMDA glutamate receptors (Cull-Candy et al., 1988; Pemberton et al., 1998; Bhave et al., 1999), have been used as model for the analysis of excitotoxicity (see Carroll et al., 1998; Lim and Ho, 1998). Tauropirone (see Fig. 4) was found to protect cultured rat cerebellum granular cells from glutamate-induced toxicity (Klimavichus, Tizivatis and Duburs, unpublished results). It was suggested that an essential role of the 1,4-dihydropyridone ring in tauropirone is to act as a carrier molecule, to enhance penetration of the blood brain barrier. However, this dihydropyridone derivative is negatively charged and its incorporation into the model phospholipid membranes of liposomes is low.

The neurotoxin 1-methyl-4-phenylpyridinium (MPP^+), which is the oxidised metabolite of 1-methyl-4-phenyl-1,2,3,6- tetrahydropyridine (MPTP), causes degeneration of dopamine neurons of the substantia nigra pars compacta *in vivo*, although at higher concentrations it becomes more generally neurotoxic. The mechanism of toxicity appears to be biphasic. An acute effect on ATP levels has been observed in several cell types as MPP^+ is accumulated by mitochondria and reversibly inhibits the activity of complex 1 of the mitochondrial respiratory chain (see Tipton and Singer, 1993). The interactions with the mitochondrial electron transport system also result in the formation of reactive oxygen-containing radicals which contribute to the neurotoxicity (see Bates et al., 1995).

Studies in rat brain coronal slices showed taurine, at concentrations of 1 and 20 mM to protect against the toxicity of 25 mM MPP^+. Neither phosphonotaurine or GES, at either 1 or 20 mM, gave any significant protection against MPP^+ toxicity but *N*,*N*,*N*-trimethyltaurine (1 mM) protected to a similar extent as taurine itself. Since phosphonotaurine is not transported into nerves or glial cells, an extracellular osmoregulatory action appears unlikely to underlie the neuroprotection afforded by taurine. The analogue GES has been shown to inhibit uptake of taurine into both synaptosomes and glial cells (see Huxtable, 1981). However, GES was not neuroprotective and neither did it affect the neuroprotection afforded by taurine. These results would indicate that taurine does not have to enter the cell to exert its effects.

N,*N*,*N*-trimethyltaurine is not taken up into cells and, as discussed above, is unable to react with HOCl to form a chloramine. However, whereas GES and phosphonotaurine do not bind to GABA receptors (Rebel et al., 1994; Marangolo et al., 1997), *N*,*N*,*N*-trimethyltaurine has been shown to bind to $GABA_A$ receptors in synaptic membrane preparations (Marangolo et al., 1997). These results suggest that taurine exerts its neuroprotective effects in this system by interacting with $GABA_A$ receptors. This was confirmed by the results of studies on the effects of the GABA-receptor ligands muscimol and bicuculline. The agonist muscimol behaved similarly to taurine, whereas the taurine and antagonist bicuculline mutually opposed each other (O'Byrne and Tipton, 2000).

Taurine has been shown to protect cultured lens (Devamanoharan et al., 1988), cerebellar granular cells (Boldyrev et al., 1999) and kidney (Michalk et al., 1996) cells *in vitro* against oxidative stress. The neurotoxin 6-hydroxydopamine destroys catecholaminergic nerves in sympathetically innervated tissues (see Thoenen and Tranzer, 1968) by a mechanism that is generally believed to involve the direct generation of reactive-oxygen radicals (see Cadet and Brannock,



Taurocholoic acid

$HOOC\text{-}CH(NH_2)\text{-}CH_2\text{-}SO_3H$

Cysteic acid

$NH_3\text{-}\ CH_2SH\text{-}CH\text{-}COO\text{-}$

Cysteine

$HOH_2C\text{-}C(CH_3)_2\text{-}CHOH\text{-}CO\text{-}NH\text{-}CH_2\text{-}CH2\text{-}COO\text{-}$

Pantothenate

Fig. 5. Taurine analogues which alter ethanol-induced behaviour and metabolism

1998). The concentrations of taurine in rat basal ganglia and ralphe nuclei were found to be increased 3 days after treatment wiht the 6-hydroxydopamine (Molina-Holgado et al., 1993). However, behavioural (Hashimoto-Kitsukawa et al., 1998) and microdialysis studies (Hayes et al., 2001) have indicated taurine to be ineffective in protecting against the neurotoxicity of this compound (Hayes et al., 2001).

f) Taurine and alcohol

The modulating effects of taurine and its analogues *in vivo* upon ethanol consumption and ethanol induced behavioural changes has been recognised for over twenty years. For example, taurocholoic acid decreases ethanol preference, whereas cysteic acid (Messiha, 1979), cysteine, (Harada et al., 1982), taurine (Ward et al., 2001) and D-pantethine (Watanabe et al., 1986) diminish circulating ethanol concentrations (Fig. 5). The beneficial effects of taurine during ethanol withdrawal may, at least in part, result from its anticonvulsant effects as an agonist of GABA receptors (see Section c and e). Homotaurine, an agonist of GABA receptors, reduces ethanol consumption in rats which spontaneously drink ethanol cells (Boismare et al., 1984).

$(CH_3CONHCH_2CH_2CH_2SO_3)_2Ca$,
Acamprosate

The drug Acamprosate, has been shown to be clinical effective in the treatment of alcohol-craving in detoxified alcoholic subjects. As yet, the structure of Acamprosate has not been determined and it is uncertain whether it is a Ca^{2+} chelate with two molecules of *N*-acetylhomotaurine or a simple calcium salt. Its absorption across the gastrointestinal tract, either by passive diffusion or mediated transport is low, (only 11% of the administered daily dose of 1–2 g is absorbed). It has been suggested that the acetylation and calcium may facilitate its passage across the blood brain barrier (Nalpas et al., 1990). It does not appear to be metabolised, 50% of the ingested dose is excreted in the urine while the remainder may be excreted via the biliary tract. It takes 5–7 days of oral dosage (1–2 g daily) before steady-state plasma concentrations of 370–650 μg/l are attained (Ward et al., 2000).

The pharmacological effect of Acamprosate appears to be related to its actions upon central neuromediator systems, and both GABA and glutamate/NMDA pathways have been implicated. Acamprosate inhibits neuronal excitability by antagonising the actions of the excitatory transmitter; reducing the depolarisation-dependent entry of Ca^{2+} into the cell. The reduced glutamatergic transmission involves either inhibition of glutamate release from the presynaptic neurone or reduction of glutamate receptor activation in the alcoholic environment. Acamprosate appears to be neuroprotective during withdrawal, as shown by a diminished release of lactate dehydrogenase from rat cortical neuronal cultures that had been with-drawn from ethanol for 3 days. This may result from the inhibition of glutamatergic transmission, since Acamprosate caused a dose-dependent decrease in $^{45}Ca^{2+}$ uptake in these alcohol-withdrawn cells and also in control cells (Mayer et al., 1999, Fig. 6).

Despite its efficacy in the treatment of detoxified alcoholic abusers, a second generation of taurine analogues, which show greater uptake by the GI tract, would be valuable to decrease the administered doses.

g) Taurine and muscle contraction

Taurine is present at relatively high concentrations in the muscles of man: human type I skeletal muscle contains 39.2 mmol/kg^{-1} dry weight whereas the taurine content of Type IIa and IIb muscle fibres is ap-

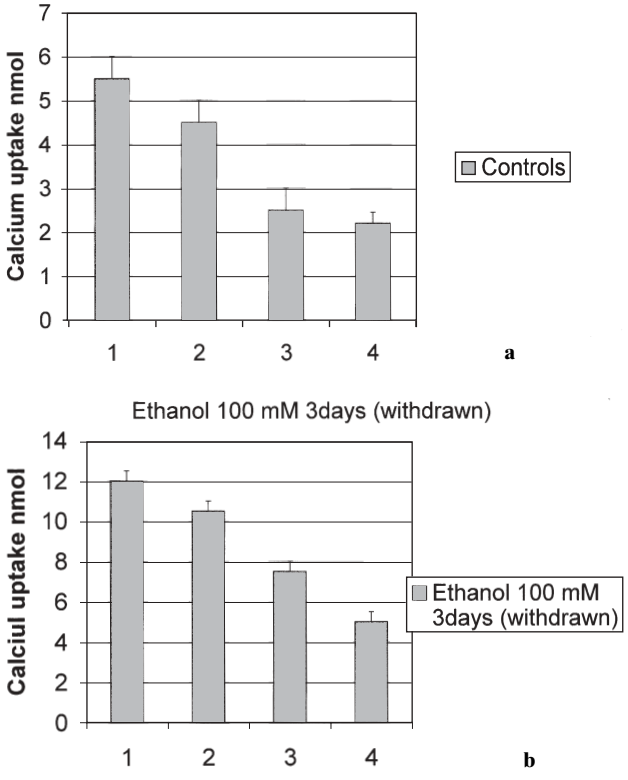


Fig. 6. Release of $^{45}Ca^{2+}$ from cerebellar granular cells after incubation with glutamate in (**a**) controls and (**b**) alcoholised conditions. Key *1* = glutamate; *2* = +Ac 10 μM; *3* = +Ac 1 μM; *4* = +Ac 100 μM. (*Ac*, after acamprosate) (Adapted from Mayer et al., 1999)

proximately 4 times lower i.e. 9.6 mmol/kg^{-1} dry weight (Harris et al., 1998). The high concentration of taurine would suggest an important role for this sulphonated amino acid in muscle function. Taurine applied *in vitro*, at millimolar concentrations, increases the macroscopic conductance of skeletal muscle membranes to Cl^- and stabilises the sarcolemma (Conte Camerino et al., 1987). However, intracellular taurine may also have a physiological role in modulating the excitatory-contraction coupling mechanism independently of a Cl^- channel effect, probably by controlling calcium availability. This could involve an interaction between taurine and the Ca^{2+} transporters present in the sarcoplasmic reticulum (De Luca et al., 1996). Taurine, in the millimolar concentration range, increases the rate of calcium uptake by skeletal-muscle sarcoplasmic reticulum (Huxtable and Bressler, 1973). In contrast, the taurine derivative tauropirone was without effect on calcium fluxes across the sarcoplasmic reticulum membrane *in vitro* (Rubtsov et al., 1989). Taurine may also play an osmoregulatory role in muscle function, since it is able to compensate for changes in osmolarity by its movement, together with other osmolytes, out of the cell during periods of hypo-osmolarity with the reverse occurring in hyper-osmolar conditions (Huxtable, 1992). The muscle appears to be a tissue where various properties of taurine are exhibited and may, thus, represent an valuable model in which to test new taurine analogues. Our recent studies (Ward et al., 1999; Cuisinier et al., 2001) have shown a relationship between elevated serum taurine levels and exercise performance, (referred to as the intensity), rather than the duration of the exercise in human athletes possibly indicating its release from muscle fibres.

h) Conclusions

In general the levels of taurine necessary for beneficial effects in model systems are high. For example, Chahine and Feng (1998) used 10 mM taurine in their studies of the protective effects of taurine against reperfusion-induced arrhythmia in isolated ischaemic rat heart, Matsuda et al. (1996) used 3–30 mM taurine in a study of the protective effect of taurine against reperfusion injury in cultured rat astrocytes and Raschke et al. (1995) showed 15 mM taurine protected isolated guinea pig heart from neutrophil-induced reperfusion injury. Such high levels are consistent with the reported taurine concentrations in many tissues (for review see Huxtable, 1992). This is consistent with its known properties, such as its affinity for the $GABA_A$ receptor, its HOCl-scavenging activity and its osmotic action. The studies of the protective effects of taurine against MPP^+ toxicity suggested that a taurine concentration of 20 mM was somewhat less effective than one of 1 mM (O'Byrne et al., 2000). Wu et al. (1990) also suggested that there might be a biphasic response to taurine and Schurr et al. (1987) reported taurine concentrations up to 2 mM afforded increasing protection of rat hippocampal slices against the effects of hypoxia whereas 5 mM taurine was without effect.

There is no recommended dietary intake level for taurine. Although there is, to our knowledge, no evidence that high levels of taurine are toxic, it remains to be established whether its beneficial effects might be lost if very high levels are administered for therapeutic or prophylactic purposes.

A discussion of all aspects of the potential therapeutic benefits that have been suggested for taurine is outside the scope of this review, which has concentrated on areas where taurine analogues have been

involved. Such studies have shown the effects of a wide number of different taurine analogues on a number of biological functions where taurine has been implicated. This may reflect the multifactorial nature of the functions of taurine within the tissues. However it has been difficult to relate changes in biological function with chemical structure. It is hoped that within the next few years a comprehensive study of these taurine analogues will be achieved which will have two major results; a prediction of which taurine analogues will show beneficial biological function in defined systems and a lower administered dose will be achieved with the design of drugs which show higher lipophilicity.

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