Amino Acids (2002) 23: 345–357
DOI 10.1007/s00726-002-0203-1

Amino
Acids
Printed in Austria

Interactions between taurine and ethanol in the central nervous system

Review Article

M. F. Olive

Ernest Gallo Clinic and Research Center, Department of Neurology, University of California at San Francisco, Emeryville, California, U.S.A.

Received November 21, 2001
Accepted January 4, 2002
Published online August 20, 2002;

Summary. This purpose of this review will be to summarize the interactions between the endogenous amino acid taurine and ethyl alcohol (ethanol) in the central nervous system (CNS). Taurine is one of the most abundant amino acids in the CNS and plays an integral role in physiological processes such as osmoregulation, neuroprotection and neuromodulation. Both taurine and ethanol exert positive allosteric modulatory effects on neuronal ligand-gated chloride channels (i.e., $GABA_A$ and glycine receptors) as well as inhibitory effects on other ligand- and voltage-gated cation channels (i.e., NMDA and Ca^{2+} channels). Behavioral evidence suggests that taurine can alter the locomotor stimulatory, sedating, and motivational effects of ethanol in a strongly dose-dependent manner. Microdialysis studies have revealed that ethanol elevates extracellular levels of taurine in numerous brain regions, although the functional consequences of this phenomenon are currently unknown. Finally, taurine and several related molecules including the homotaurine derivative acamprosate (calcium acetylhomotaurinate) can reduce ethanol self-administration and relapse to drinking in both animals and humans. Taken together, these data suggest that the endogenous taurine system may be an important modulator of effects of ethanol on the nervous system, and may represent a novel therapeutic avenue for the development of medications to treat alcohol abuse and alcoholism.

Keywords: Taurine – Ethanol – Locomotor activity – Sedation – self-administration – Acamprosate – Central nervous system (CNS)

Introduction

Taurine in a sulfonated β-amino acid that is highly abundant in excitable tissues, including the heart and brain. In addition to functioning as a neuroprotectant, antioxidant, osmoregulator and Ca^{2+} modulator (reviewed elsewhere by Huxtable, 1989, 1992; Oja and Saransaari, 1996; Saransaari and Oja, 2000), taurine may function as an inhibitory neuromodulator and neurotransmitter in the central nervous system (Kuriyama, 1980; McBride and Frederickson, 1980; Oja and Kontro, 1990; Oja and Saransaari, 1996). Synthesized from cysteine by the enzyme cysteine sulfinic acid decarboxylase (CSAD), high levels of taurine are found in the cerebral cortex, basal ganglia, hippocampus, hypothalamus and cerebellum (Palkovits et al., 1986). Taurine and CSAD can be found in both neuronal and glial structures (Madsen et al., 1985; Yoshida et al., 1986, 1987; Ida et al., 1987). In neurons, taurine immunoreactivity can be found in presynaptic terminals, consistent with its putative role as a neurotransmitter, but also in neuronal dendrites and cell bodies (Taber et al., 1986; Almarghini et al., 1991).

Similar to taurine, ethanol also exerts a wide range of physiological effects on the nervous system, including neuromodulation, inhibition of neurotransmission, and alterations in Ca^{2+} homeostasis (for reviews see Carlen et al., 1993; Crews et al., 1996; Fadda and Rossetti, 1998; Harris, 1999; Little, 1999). This review will highlight studies demonstrating biochemical and behavioral interactions between taurine and ethanol in the central nervous system, as well as studies on the ability of taurine and related molecules to alter voluntary ethanol consumption in animals and humans.

Similarities in the neurochemical actions of taurine and ethanol

Taurine is the most abundant neuroactive amino acid in the brain extracellular fluid (Jacobson and

Hamberger, 1984; Jacobson et al., 1985; Huxtable, 1989). Microdialysis studies have demonstrated extracellular taurine levels to be in the low to mid-micromolar range in various brain regions, while extracellular concentrations of gamma-aminobutyric acid (GABA) and glutamate are approximately an order of magnitude lower (Huxtable, 1989). However, because microdialysis sampling is an indirect measure of synaptic overflow, effective taurine concentrations at the synaptic cleft are likely to be in the low millimolar range. Interestingly, low millimolar concentrations of ethanol are also necessary to produce physiological effects in the nervous system (Crews et al., 1996; Little, 1999). Thus, taurine and ethanol appear to be relatively unique in requiring high effective concentrations in the nervous system as compared to other endogenous and exogenous neuroactive substances.

Taurine is structurally similar to the classical inhibitory neurotransmitter gamma-aminobutyric acid (GABA) (Fig. 1). Not surprisingly, taurine can mimic the effects of GABA in enhancing chloride ion flux across neuronal membranes from numerous brain regions. These effects can be reversed by the classical $GABA_A$ receptor antagonists bicuculline or picrotoxin, indicating an action of taurine on the $GABA_A$ receptor chloride ionophore complex (Table 1). Further evidence that taurine exerts some of its effects through $GABA_A$ receptors comes from binding studies in which taurine was shown to displace the binding of both direct and allosteric agonists of the $GABA_A$ receptor complex (Williams et al., 1980; Iwata et al., 1984; Medina and De Robertis, 1984; Malminen and Kontro, 1986, 1989; Quinn, 1990; Quinn and Miller, 1992; Quinn and Harris, 1995). Taurine has also been shown to bind to the $GABA_B$ receptor (Kontro and Oja, 1990; Kontro et al., 1990), although no functional consequences of this binding have been observed (see del Olmo et al., 2000).

Numerous studies have demonstrated that the inhibitory effects on taurine on neurons are also blocked by the glycine receptor antagonist strychnine, indicating that taurine can also potentiate glycine receptor function (Table 1). In addition, a few studies have shown that some of electrophysiological effects of taurine, but not GABA or glycine, are blocked by the putative taurine antagonist TAG (6-aminomethyl-3-methyl-4H,1,2,4-benzothiadiazine-1,1-dioxide HCl) (Yarbrough et al., 1981; Girard et al., 1982; Okamoto et al., 1983b). Thus, in addition to being a relatively nonspecific agonist for inhibitory amino acid receptors, taurine may act on a separate and yet undefined taurine receptor in the nervous system (Kudo et al., 1988; Wu et al., 1990). A handful of studies have also demonstrated that taurine can inhibit neuronal calcium channel function and responses to the excitatory amino acid N-methyl-D-aspartate (NMDA) (Table 1).

Table 1. Neuropharmacological actions of taurine in the CNS*

Action	References
Potentiation of $GABA_A$ receptor function	Haas and Hösli, 1973 Okamoto and Sakai, 1980 Taber et al., 1986 Bureau and Olsen, 1991 del Olmo et al., 2000
Potentiation of glycine receptor function	Curtis et al., 1968a,b Haas and Hösli, 1973 Okamoto and Sakai, 1980 Mayer, 1981 Kurachi et al., 1983 Kurachi and Aihara, 1985 Taber et al., 1986 Lewis et al., 1991 Häusser et al., 1992
Inhibition of excitatory amino acid receptor function	Kurachi et al., 1983 Lehmann et al., 1984 Kurachi and Aihara, 1985
Inhibition of neuronal calcium channel function	Okamoto et al., 1983a,c

* Note: studies examining taurine effects in transfected cell lines or peripheral nervous system preparations are reviewed elsewhere (Huxtable, 1989, 1992)

Thus, taurine appears to exert its inhibitory effects on neuronal activity and neurotransmission by potentiating $GABA_A$ and glycine receptor function and inhibiting excitatory amino acid receptor and Ca^{2+} channel function. Interestingly, the most well-characterized pharmacological effects of ethanol on the nervous system are strikingly similar to that of taurine: potentiation of ligand-gated chloride channel function and inhibition of excitatory amino acid receptor and calcium channel function (reviewed elsewhere by Crews et al., 1996; Little, 1999). On the basis of these observations, one might expect taurine and ethanol to exert markedly synergistic effects on central nervous system function. While there is some evidence of such synergism, there is also evidence that taurine and related molecules can actually antagonize certain behavioral effects of the ethanol as well as ethanol self-administration behavior.

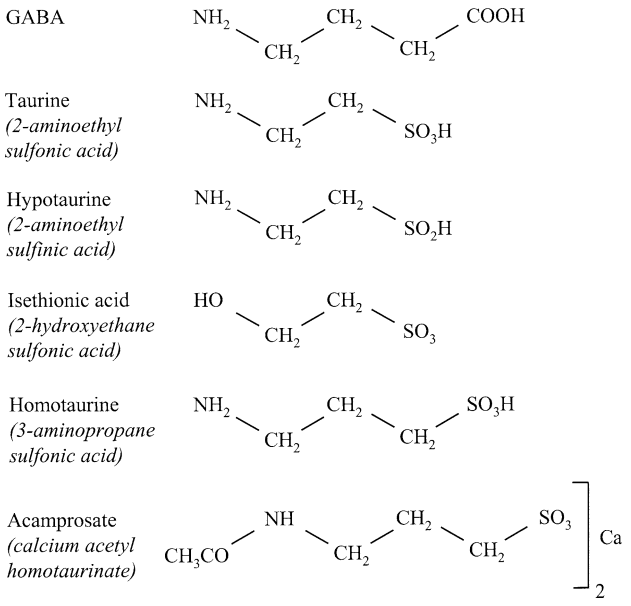

Fig. 1. Chemical structures of GABA, taurine, the taurine precursor hypotaurine, the taurine metabolite isethionic acid, the $GABA_A$ agonist homotaurine and the anti-craving compound acamprosate. Note that acamprosate is an acetylated form of homotaurine and is dimerized as a calcium salt

Modulation of extracellular taurine levels in the brain by ethanol

An early study demonstrated that chronic, but not acute, administration of ethanol to rats decreased whole brain taurine concentrations, which returned to basal level following ethanol withdrawal (Iwata et al., 1980). However, the subsequent development of the microdialysis technique has allowed researchers to examine the effects of acute and chronic ethanol administration and consumption on extracellular levels of taurine in discrete brain regions. Acute administration of ethanol (1–2 g/kg i.p.) has been shown to elicit a 50–100% increase extracellular levels of taurine in the nucleus accumbens of rats (Dahchour et al., 1994, 1996) and mice (Olive et al., 2000b). These findings have also been replicated in the nucleus accumbens after acute administration of the ethanol metabolite acetaldehyde (20–100 mg/kg i.p., Ward et al., 1997). Ethanol does not alter extracellular levels of glutamate or GABA in this region (Dahchour et al., 1996), and rats do not appear to develop tolerance to this effect after repeated treatment with 1–2 g/kg i.p. ethanol (Dahchour et al., 1996). Elevations in extracellular taurine levels by acute ethanol administration (1 and 3 g/kg i.p.) have also been observed in the amygdala (Quertemont et al., 1998, 1999), hippocampus (Dahchour and De Witte, 2000) and frontal cortex (Dahchour and De Witte, 2000).

Recent studies have provided evidence for genetic influences in ethanol-stimulated taurine release in the CNS. For example, rats genetically bred for high alcohol sensitivity (HAS) show a transient 50% increase in extracellular taurine levels in the nucleus accumbens following acute injection of ethanol (2 g/kg i.p.), whereas low alcohol sensitive (LAS) rats do not exhibit such an increase in extracellular taurine levels until 2 hrs following the injection (Dahchour et al., 2000). Similarly, whereas Sardinian non-alcohol-preferring (sNP) rats exhibit a transient 50% increase in extracellular taurine levels in the nucleus accumbens following acute injection of ethanol (2 g/kg i.p.), Sardinian alcohol-preferring rats (sP) only demonstrate a 25% increase in extracellular taurine levels in this region. Finally, work from our laboratory had demonstrated that mice lacking the epsilon isoform of protein kinase C (PKCε), which have been characterized as behaviorally and biochemically "supersensitive" to ethanol and other positive allosteric modulators of the $GABA_A$ receptor complex (Hodge et al., 1999), display elevated basal extracellular levels of taurine in the nucleus accumbens and an absence of ethanol-stimulated increases in dialysate taurine levels (Olive et al., 2000b). Interestingly, these mice also fail to exhibit an ethanol-stimulated dopamine release in the nucleus accumbens (Olive et al., 2000b), a phenomenon thought to play a role in the rewarding and reinforcing effects of ethanol. Taken together, these data suggest that genetic contributions to ethanol sensitivity and preference may alter interactions between taurine and ethanol in the CNS.

Microdialysis experiments have also revealed a role for taurine in the neurochemical changes that occur during ethanol withdrawal. During acute withdrawal from chronic alcohol intoxication, CNS neurons become hyperexcitable and the organism becomes prone to convulsions (Saitz, 1998; Littleton, 1998; Gonzalez, 1998). This phenomenon is believed to be mediated, at least in part, by an up-regulation of NMDA receptor number and function (Grant et al., 1990; Gulya et al., 1991; Hoffman and Tabakoff, 1991; Whittington et al., 1995; Tsai and Coyle, 1998) and increased glutamate release (Rossetti and Carboni, 1995; Rossetti et al., 1999; Ward et al., 1999). In a study by Dahchour and colleagues (Dahchour and De Witte, 2000), rats were made dependent on ethanol by vapor

inhalation for 4 weeks and subsequently underwent microdialysis monitoring for 12 hrs during the acute withdrawal phase. These investigators found that taurine treatment (45 mg/kg i.p.) 5 hr into the withdrawal phase completely suppressed withdrawal induced increases in extracellular glutamate levels in the nucleus accumbens. Along these lines, data from our laboratory suggest that increasing extracellular taurine levels in the nucleus accumbens suppresses basal glutamate release as well (Olive et al., 2000a). Thus, taurine appears to have an inhibitory effect on excitatory amino acid neurotransmission, which may counteract the neuronal hyperexcitability observed during ethanol withdrawal.

The precise neurobiological significance and mechanisms underlying ethanol-induced increases in CNS extracellular taurine levels are currently unknown. Some investigators have speculated that taurine may be released in response to ethanol to compensate for osmotic changes caused by ethanol in the brain extracellular fluid (Dahchour et al., 1996; Quertemont et al., 1999). However, increases in extracellular taurine levels in the amygdala have also been reported to occur after acute saline treatment in combination with the presentation of a conditioned ethanol-associated olfactory stimulus (Quertemont et al., 1998). Thus, ethanol-induced increases in extracellular taurine may not be solely related to osmoregulatory processes, but may play a role in the environmental adaptations to ethanol exposure.

It is also possible that ethanol-induced taurine release may mediate several of the physiological effects of ethanol on the nervous system. As outlined above, both taurine and ethanol potentiate inhibitory amino acid receptor function and inhibit excitatory amino acids receptor and Ca^{2+} channel function. Thus, ethanol-induced release of taurine from intracellular stores may, in fact, potentiate the effects of ethanol itself on neuronal excitability. Since the release of taurine into the extracellular environment results in decreased intracellular taurine levels, this phenomenon may also have profound effects on cellular functioning. For example, both ethanol and taurine are known to modulate intracellular calcium homeostasis and protein phosphorylation (reviewed elsewhere by Carlen et al., 1993; Catlin et al., 1999; Crews et al., 1996; Gandhi and Ross, 1989; Huxtable, 1992; Lombardini, 1994; Pandey, 1998; Stubbs and Slater, 1999). Thus, the lowering of intracellular taurine levels by ethanol may mediate some of the effects of ethanol on various intracellular signaling mechanisms. Finally, both ethanol and taurine are known to interact with lipid membranes (Buck and Harris, 1991; Gustavsson, 1990; Huxtable, 1992), and it is possible that ethanol-induced increases in extracellular taurine may mediate some of the effects of ethanol on neuronal membrane composition, stability and fluidity.

Effects of taurine on ethanol-induced locomotor activity and sedation

Acute intraperitoneal administration of low doses of ethanol (1–2.5 g/kg) to mice results in increased locomotor activity during the first hour after injection (Frye and Breese, 1981). This effect is also observed after oral administration of ethanol, and is not due to peritoneal irritation (Frye and Breese, 1981). The locomotor effects of ethanol are mediated, at least in part, by activation of the central catecholaminergic and cholinergic systems (Mason et al., 1979; Milton et al., 1995; Strombom and Liedman, 1982; Lewis and June, 1990; Blomqvist et al., 1992). Interestingly, the locomotor effect of ethanol appears to be mostly absent in rats (Frye and Breese, 1981), indicating species-specificity of these effects.

Several studies over the past two decades have demonstrated a significant interaction between taurine and the acute behavioral actions of ethanol in rodents. Aragon and colleagues demonstrated that acute administration of taurine (30–45 mg/kg i.p.) inhibited the locomotor activity produced by a 1 g/kg dose of ethanol, whereas taurine administration (30–60 mg/kg i.p.) enhanced the locomotor stimulant effect of a higher (2 g/kg i.p.) dose of ethanol (Aragon et al., 1992). Thus, taurine appears to modulate ethanol-stimulated locomotor activity in a manner that is dependent on the dose of ethanol administered. The inhibitory effects of taurine on ethanol-stimulated locomotor activity may be a result of taurine acting on central GABAergic systems (Cott et al., 1976).

Other molecules in the metabolic pathways of taurine have also been shown to modulate ethanol-stimulated locomotor activity (see Fig. 1). Both the taurine precursor hypotaurine (Font et al., 2001) and the taurine metabolite isethionic acid (Miquel et al., 1999) have also been shown to enhance ethanol-induced locomotor activity at higher (2.4–2.5 g/kg i.p.) but not lower (1–1.6 g/kg i.p.) doses of ethanol. The effects of hypotaurine on ethanol-induced locomotor activity appeared to be centrally mediated, as they are

antagonized by β-alanine, a competitive inhibitor of the blood-to-brain transport mechanism of hypotaurine (Font et al., 2001). The effects of taurine and hypotaurine on ethanol-stimulated locomotor activity appear to be specific for ethanol, as neither compound demonstrated an effect on the locomotor-stimulant effects of D-amphetamine (Aragon et al., 1992), caffeine (Font et al., 2001) or cocaine (Font et al., 2001).

Higher doses of ethanol (>3 g/kg i.p.) produce sedation and loss-of-righting reflex in rodents (Frye and Breese, 1981). Since high doses of taurine are also sedating (Barbeau et al., 1975), although not potent enough alone to induce a loss-of-righting reflex (Ferko, 1987), it is not surprising that taurine prolongs ethanol-induced sedation when given intracerebroventricularly (Mattucci-Schiavone and Ferko, 1985; McBroom et al., 1986; Ferko, 1987; Ferko and Bobyock, 1988). However, other investigators have demonstrated that acute administration of taurine actually attenuates the sedating effects of ethanol when given peripherally (Iida and Hikichi, 1976; Boggan et al., 1978; McBroom et al., 1986). The fact that taurine prolongs ethanol-induced sedation when given directly into the brain but reduces it when administered systemically suggests that taurine may exert some of its effects on ethanol-induced sedation via peripheral mechanisms. In addition, although exogenously administered taurine is transported across the blood-brain barrier (Benrabh et al., 1995; Tamai et al., 1995), the differential effects of taurine on ethanol-induced sedation may also be due to the differential pharmacokinetic/pharmacodynamics and absorption of taurine into the CNS following intraventricular vs. peripheral administration (see McBroom et al., 1986).

Effects of taurine on the motivational effects of ethanol

Ethanol is generally considered to have both rewarding and aversive motivational properties. These properties can be measured by the conditioned place preference (CPP) paradigm, in which repeated pairings of drug administration with a unique physical environment results in a preference for that environment in a drug-free state (Cunningham et al., 2000). A CPP for ethanol is, however, is strongly dose-dependent, with CPP being established only with doses between 0.8 and 2.0 g/kg i.p., whereas higher doses tend to induce an aversion for the ethanol-paired environment (van der Kooy et al., 1983; Asin et al., 1985; Reid et al., 1985; Bozarth, 1990; Quertemont et al., 1998; Cunningham et al., 2000; Quertemont and De Witte, 2001; Cunningham and Henderson, 2000). The ethanol metabolite acetaldehyde can also produce CPP (Smith et al., 1984; Quertemont and De Witte, 2001). Ethanol CPP appears to be enhanced with repeated exposure to ethanol, indicating that tolerance to the initial aversive effects of ethanol may develop, unmasking its appetitive and rewarding effects (Cunningham, 1981; Gauvin and Holloway, 1992; Holloway et al., 1992; Cunningham et al., 2000). The development of a CPP for ethanol can be further modified by the introduction of additional sensory stimuli, such as olfactory cues. In a recent study (Quertemont et al., 1998), supplementation of rats with taurine in the drinking water (625 mg/100 ml) resulted in an ethanol CPP when an olfactory stimulus (vinegar odor) was paired ethanol at a dose of 0.3 g/kg i.p., a dose that normally does not produce ethanol CPP. Conversely, taurine-supplemented rats displayed a reduced aversion to the olfactory stimulus paired with a higher (2.0 g/kg) dose of ethanol. These data indicate that the ability of taurine to modify the rewarding/motivational and aversive properties of ethanol are highly dependent on the dose of ethanol administered.

The aversive properties of ethanol can also be measured by another paradigm known as conditioned taste aversion (CTA) (Hunt and Amit, 1987; Cunningham et al., 2000). In this procedure, ethanol injections are repeatedly paired with a novel food or taste stimulus. Unexpectedly, addictive substances, including ethanol, often produce a conditioned aversion to the novel food or taste stimulus, suggesting that certain drugs of abuse produce aversive motivational effects (Hunt and Amit, 1987). Aragon and colleagues (Aragon and Amit, 1993) demonstrated that simultaneous administration of taurine (45 mg/kg i.p.) enhanced CTA produced by 0.8 mg/kg ethanol i.p., blocked CTA produced by 1.2 g/kg ethanol i.p., and had no effect on CTA produced by 1.6 g/kg ethanol i.p. Thus, taurine can also modulate the aversive properties of ethanol in a manner strongly dependent on the dose of ethanol administered.

One might speculate that any effects of taurine of ethanol-induced locomotion, sedation or place/taste preference could be attributable to the ability of taurine to modulate ethanol metabolism and elimination rates. While several studies have shown that taurine,

but not hypotaurine, can indeed modulate alcohol dehydrogenase activity and oxidation of acetaldehyde (Watanabe et al., 1985; Theofanopoulos and Lau-Cam, 1998; Font et al., 2001; Ward et al., 2001), these experiments utilized chronic treatments at doses of taurine that were much larger (>300 mg/kg) than those used in the aforementioned behavioral experiments. Thus, it is likely that the ability of taurine and related molecules to alter ethanol-induced behaviors are mediated by pharmacological interactions in the CNS.

Effects of taurine and related molecules on ethanol self-administration

Preclinical studies examining the neuropharmacological basis of ethanol-seeking behavior normally employ one of two methods of ethanol self-administration: operant self-administration and the two-bottle choice paradigm. In operant self-administration procedures, rodents are placed in an operant chamber and trained to press a lever (or perform some other simple motor task) which results in the presentation of a small quantity of an ethanol-containing solution (usually 8–12% v/v). In the two bottle-choice procedure, rodents are given concurrent access to two (or sometimes more) bottles on the home cage, each of which contains either water or an ethanol-containing solution. In both procedures, outbred strains of rodents normally tend to avoid ethanol-containing solution due to its aversive taste. However, this initial taste aversion can be overcome by either forced ethanol exposure (i.e., several days with access to an ethanol-containing solution as the only source of fluids), or the introduction of sucrose or saccharin into the ethanol solution, which is subsequently "faded out" over a period of several weeks (Samson, 1986). In two bottle choice experiments in which pharmacological manipulations or challenges are introduced, the length of the period of concurrent access to the two solutions is often restricted to only a few hours per day. This "limited access" paradigm has been shown to: (1) produce greater ethanol intake than continuous (i.e., 24 h) access paradigms (Holloway et al., 1984; Marcucella et al., 1984; Linseman, 1987); (2) produce patterns of ethanol consumption that can be more accurately separated from consumption related to feeding behavior seen in continuous access paradigms (Samson et al., 1991); (3) is more characteristic of "binge" pattern drinking seen in human alcoholics (Mendelson and Mello, 1966; Epstein et al., 1995); and (4) confines the drinking behavior of the animal to a time period in which the majority of the drug administered has not be metabolized and excreted from the body.

Our laboratory recently used the two bottle choice paradigm to assess the effects of acute administration of taurine and the taurine precursor hypotaurine on ethanol consumption in rats (Olive and Hodge, 2001). These compounds were administered i.p. 15 min prior to a 1 hr fluid access session with water and 10% v/v ethanol being concurrently available. Baseline fluid consumption (determined as an average of daily intake values for 2 weeks prior to any drug administration) was 1.35 ± 0.08 g/kg/l hr for ethanol and 12.36 ± 0.44 mls/l hr for water. As seen in Fig. 2, taurine administration reduced acute ethanol consumption by approximately 25 to 40% at doses of 50, 100 and 200 mg/kg. However, a 17% reduction in water intake was also observed at the 200 mg/kg dose of taurine, indicating non-specific effects on fluid consumption at this dose. The taurine precursor hypotaurine reduced ethanol intake by approximately 15–25% at doses of 50 and 100 mg/kg without altering water intake (Fig. 2).

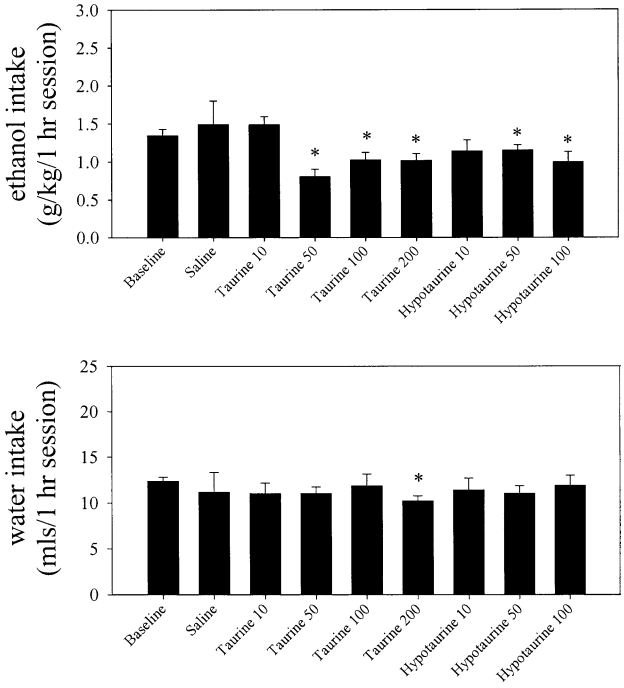

Fig. 2. Effects of acute administration of taurine and hypotaurine on voluntary ethanol (top panel) and water (bottom panel) consumption in rats (n = 13) using the two bottle choice paradigm. Drugs and doses (in mg/kg) are given on the x-axis. Drugs were administered i.p. 15 min prior to a 1 hr access period to both water and 10% v/v ethanol. * $p < 0.05$ vs. baseline using Student's t-test

Taken together, these data indicate that acute administration of taurine and related compounds can modestly reduce voluntary ethanol consumption in rats. These effects are likely mediated by the CNS, as exogenously administered taurine is rapidly transported across the blood-brain barrier (Benrabh et al., 1995; Tamai et al., 1995). However, the neurochemical mechanisms underlying this reduction in ethanol intake by taurine are unclear. One possibility is that taurine may attenuate the acute reinforcing effects of ethanol. Alternatively, since taurine and ethanol share similar neuropharmacological mechanisms of action (i.e., potentiation of ligand-gated chloride channel function and inhibition of calcium channel and excitatory amino acid receptor function), it is possible that the combination of taurine and ethanol produces a synergistic-like effects on the CNS, thus reducing the amount of ethanol needed to achieve the desired pharmacological effect. Such synergism is likely very dose-dependent, and studies on interactions between the doses of taurine administered and the amount of ethanol consumed by the animals should further clarify this possibility.

Acamprosate – a mysterious anti-craving homotaurine derivative

In the mid-1980's, a handful of studies began to emerge demonstrating that the homotaurine derivative acamprosate (calcium acetylhomotaurinate, see Fig. 1) reduced voluntary ethanol consumption in rodents (Boismare et al., 1984; Le Magnen et al., 1987; Gewiss et al., 1991). Around the same time, several studies in human subjects demonstrated that acamprosate was efficacious in reducing the relapse to relapse to alcohol drinking following detoxification (Lhuintre et al., 1985, 1990). This discovery of acamprosate as an "anti-craving" compound (Spanagel and Zieglgansberger, 1997) represented a significant landmark in the development of novel medications to treat alcohol abuse and alcoholism. While the present review will focus mostly on basic science studies of acamprosate, the reader may find reviews on clinical studies on acamprosate elsewhere (Wilde and Wagstaff, 1997; Johnson and Ait-Daoud, 2000; Kranzler, 2000; Mason, 2001).

Acute administration of acamprosate appears to suppress ethanol intake in non-dependent animals only at higher doses (i.e., 400 mg/kg i.p.), with lower doses being ineffective (Le Magnen et al., 1987; Gewiss et al., 1991; Heyser et al., 1998; Stromberg et al., 2001). However, repeated administration of lower doses (100–200 mg/kg) appears to more efficacious in attenuating acute ethanol consumption in both dependent and non-dependent animals (Le Magnen et al., 1987; Gewiss et al., 1991; Naassila et al., 1998; Czachowski et al., 2001). This may be due to the fact that acamprosate does not reach steady state plasma levels until after 5–7 days of treatment (Saivin et al., 1998). As with humans, acamprosate also reduces relapse to ethanol consumption during prolonged periods of abstinence in rodents (Spanagel et al., 1996; Hölter et al., 1997; Heyser et al., 1998; Spanagel and Hölter, 2000). There are also several reports that acamprosate reduces ethanol withdrawal-induced hypermotility (Gewiss et al., 1991; Dahchour and De Witte, 1999; Spanagel et al., 1996), place avoidance (Cole et al., 2000), withdrawal-induced glutamate release in the nucleus accumbens (Dahchour et al., 1998; Dahchour and De Witte, 2000) as well as withdrawal-induced c-fos expression in the hippocampus and cerebellum (Putzke et al., 1996). Thus, acamprosate not only reduces ethanol intake but several aspects of the ethanol withdrawal syndrome as well.

There is also evidence that acamprosate can interact with the behavioral effects of opiate drugs. Acamprosate has been reported to reduce sensitization to the locomotor effects of morphine (Spanagel et al., 1998) and attenuate the conditioned place aversion produced by naloxone-precipitated morphine withdrawal (Kratzer and Schmidt, 1998). However, acamprosate does not modify basal or stress-induced relapse to heroin self-administration (Spanagel et al., 1998) or morphine drug discrimination (Pascucci et al., 1999). Thus, acamprosate may be of limited use in the treatment of opiate dependence.

The mechanisms by which acamprosate exerts its anti-craving effects are largely unknown. Acamprosate does not alter blood ethanol levels (Gewiss et al., 1991; Daoust et al., 1992; Saivin et al., 1998), ethanol-induced cortical hypervasculatization (Gewiss et al., 1991), or ethanol-induced hypothermia, motor impairment or taste aversion (Le Magnen et al., 1987). Acamprosate does not act as a "substitute" for ethanol in drug discrimination studies (Spanagel et al., 1996; Grant and Woolverton, 1989) and is not sedating (Littleton, 1995). Although acamprosate has poor bioavailability following peripheral administration, it reduces ethanol intake when given intracerebro-

ventricularly (Naassila et al., 2000), indicating a CNS site of action.

Since acamprosate is derived from the $GABA_A$ agonist homotaurine (Fig. 1), one might expect acamprosate to have agonist properties at $GABA_A$ receptors as well. Indeed, early studies showed that acamprosate enhanced the accumulation of GABA in brain synaptosomes (Chabenat et al., 1988; Daoust et al., 1992), and its alcohol intake-reducing effects were reversed by the $GABA_A$ antagonist bicuculline (Boismare et al., 1984; Daoust et al., 1987). A subsequent report indicated that acamprosate could possible enhance GABAergic transmission by blockade of presynaptic inhibitory $GABA_B$ autoreceptors (Berton et al., 1998). However, several studies have failed to demonstrate that acamprosate directly enhances $GABA_A$-mediated inhibitory postsynaptic potentials or chloride influx (Zeise et al., 1993; Berton et al., 1998). Thus, the ability of acamprosate to function as a GABA agonist remains in question.

There is more convincing evidence that acamprosate interacts with excitatory amino acid receptors, notably the NMDA receptor. Several studies have demonstrated that acamprosate binds to the polyamine site on the NMDA receptor complex (al Qatari et al., 1998; Naassila et al., 1998; Popp and Lovinger, 2000). However, the functional consequences of acamprosate binding to the NMDA receptor complex have been contradictory. For example, acamprosate has been reported to enhance NMDA-mediated glutamatergic neurotransmission in the nucleus accumbens (Berton et al., 1998) and hippocampus (Madamba et al., 1996). Yet others have reported that acamprosate weakly antagonizes NMDA receptor function in hippocampal (Rammes et al., 2001), cortical (Zeise et al., 1990, 1993) or mesencephalic neurons (Allgaier et al., 2000). Still others reported no effect of acamprosate on NMDA-mediated currents in striatal or cerebellar neurons (Popp and Lovinger, 2000). These differences may attributable to the differential subunit composition of NMDA receptors across these brain regions. Nonetheless, repeated administration of acamprosate has been shown to up-regulate the expression of NMDA receptor subunits in various brain regions similar to that observed following non-competitive NMDA receptor antagonist administration (Rammes et al., 2001). In addition, acamprosate can reduce glutamate-induced neurotoxicity during ethanol withdrawal (al Qatari et al., 2001), and one study indicated that acamprosate can reduce glutamatergic neurotransmission in human subjects (Bolo et al., 1998). Thus, while there is more convincing evidence that acamprosate interacts with NMDA rather than GABAergic neurotransmission, the precise mode of action of this compound still awaits definitive clarification.

Other recent reports indicate that acamprosate inhibits Ca^{2+} channel function in cultured mesencephalic neurons (Allgaier et al., 2000), suggesting a third possible mode of action. Lastly, De Witte and colleagues have proposed that acamprosate may act via a taurinergic mechanism (Dahchour and De Witte, 2000). For instance, acute injections of high dose of acamprosate (1 g/kg) elevate extracellular taurine levels in the rat nucleus accumbens (Dahchour et al., 1995; Dahchour and De Witte, 2000). Acamprosate can also displace the binding of radiolabelled taurine, but glutamate or GABA, to cultured neurons in vitro (Wu et al., 2001), although this study used concentrations of acamprosate (1 mM) that were found to be neurotoxic. Taurine can also inhibit the intestinal transport of acamprosate (Mas-Serrano et al., 2000). Taken together, these few studies suggest that acamprosate may indeed interact with cellular receptors or membrane transporters of taurine. Further studies on precisely how acamprosate interacts with endogenous taurine systems may help shed light on the elusive neuropharmacological actions of this anti-craving compound.

Conclusions

This review has highlighted literature indicating that taurine and ethanol can interact at numerous levels in the CNS, from the biochemical to the behavioral. However, more research on these interactions are needed to further clarify several issues, including (1) the precise mechanisms and functional consequences of ethanol-induced increases in extracellular taurine levels, (2) the neural circuitry and neurotransmitters involved in the modulation of motivational and behavioral effects of ethanol by taurine, and (3) the neuropharmacological mechanism by which acamprosate may reduce ethanol intake and relapse to drinking during abstinence. Such studies will ultimately shed light on how acute and chronic ethanol consumption alters the neurochemistry of the brain, and how taurinergic systems in the brain might be targeted for pharmacological management of alcohol abuse and alcoholism.

Acknowledgements

This work was supported by funds from the State of California for medical research on alcohol and substance abuse through the University of California at San Francisco. The author wishes to thank Drs. C. W. Hodge and P. H. Janak for their support and helpful discussions.

References

al Qatari M, Bouchenafa O, Littleton J (1998) Mechanism of action of acamprosate. Part II. Ethanol dependence modifies effects of acamprosate on NMDA receptor binding in membranes from rat cerebral cortex. Alcohol Clin Exp Res 22: 810–814

al Qatari M, Khan S, Harris B, Littleton J (2001) Acamprosate is neuroprotective against glutamate-induced excitotoxicity when enhanced by ethanol withdrawal in neocortical cultures of fetal rat brain. Alcohol Clin Exp Res 25: 1276–1283

Allgaier C, Franke H, Sobottka H, Scheibler P (2000) Acamprosate inhibits Ca^{2+} influx mediated by NMDA receptors and voltage-sensitive Ca^{2+} channels in cultured rat mesencephalic neurones. Naunyn-Schmied Arch Pharmacol 362: 440–443

Almarghini K, Remy A, Tappaz M (1991) Immunocytochemistry of the taurine biosynthesis enzyme, cysteine sulfinate decarboxylase, in the cerebellum: evidence for a glial localization. Neuroscience 43: 111–119

Aragon CM, Amit Z (1993) Taurine and ethanol-induced conditioned taste aversion. Pharmacol Biochem Behav 44: 236–263

Aragon CM, Trudeau LE, Amit Z (1992) Effect of taurine on ethanol-induced changes in open-field locomotor activity. Psychopharmacology 107: 337–340

Asin KE, Wirtshafter D, Tabakoff B (1985) Failure to establish a conditioned place preference with ethanol in rats. Pharmacol Biochem Behav 22: 169–173

Barbeau A, Inoue N, Tsukada Y, Butterworth RF (1975) The neuropharmacology of taurine. Life Sci 17: 669–677

Benrabh H, Bourre JM, Lefauconnier JM (1995) Taurine transport at the blood-brain barrier: an in vivo brain perfusion study. Brain Res 692: 57–65

Berton F, Francesconi WG, Madamba SG, Zieglgänsberger W, Siggins GRF (1998) Acamprosate enhances N-methyl-D-apartate receptor-mediated neurotransmission but inhibits presynaptic GABA(B) receptors in nucleus accumbens neurons. Alcohol Clin Exp Res 22: 183–191

Blomqvist O, Soderpalm B, Engel JA (1992) Ethanol-induced locomotor activity: involvement of central nicotinic acetylcholine receptors? Brain Res Bull 29: 173–178

Boggan WO, Medberry C, Hopkins DH (1978) Effect of taurine on some pharmacological properties of ethanol. Pharmacol Biochem Behav 9: 469–472

Boismare F, Daoust M, Moore N, Saligaut C, Lhuintre JP, Chretien P, Durlach J (1984) A homotaurine derivative reduces the voluntary intake of ethanol by rats: are cerebral GABA receptors involved? Pharmacol Biochem Behav 21: 787–789

Bolo N, Nédélec JF, Muzet M, De Witte P, Dahchour A, Durbin P, Macher JP (1998) Central effects of acamprosate: part 2. Acamprosate modifies the brain in-vivo proton magnetic resonance spectrum in healthy young male volunteers. Psychiatry Res 82: 115–127

Bozarth MA (1990) Evidence for the rewarding effects of ethanol using the conditioned place preference method. Pharmacol Biochem Behav 35: 485–487

Buck KJ, Harris RA (1991) Neuroadaptive responses to chronic ethanol. Alcohol Clin Exp Res 15: 460–470

Bureau MH, Olsen RW (1991) Taurine acts on a subclass of $GABA_A$ receptors in mammalian brain in vitro. Eur J Pharmacol 207: 9–16

Carlen PL, Jahromi SS, Valiante TA, Velumian AA, Weiner JL, Zhang L (1993) The role of calcium homeostasis and calcium currents in ethanol actions on central mammalian neurons. Alcohol Alcohol [Suppl 2]: 395–401

Catlin MC, Guizzetti M, Costa LG (1999) Effects of ethanol on calcium homeostasis in the nervous system: implications for astrocytes. Mol Neurobiol 19: 1–24

Chabenat C, Chretien P, Daoust M, Moore N, Andre D, Lhuintre JP, Saligaut C, Boucly P, Boismare F (1988) Physicochemical, pharmacological and pharmacokinetic study of a new GABAergic compound, calcium acetylhomotaurinate. Meth Find Exp Clin Pharmacol 10: 311–317

Cole JC, Littleton JM, Little HJ (2000) Acamprosate, but not naltrexone, inhibits conditioned abstinence behaviour associated with repeated ethanol administration and exposure to a plus-maze. Psychopharmacology 147: 403–411

Cott J, Carlsson A, Engel J, Lindqvist M (1976) Suppression of ethanol-induced locomotor stimulation by GABA-like drugs. Naunyn-Schmied Arch Pharmacol 295: 203–209

Crews F, Morrow AL, Criswell H, Breese GR (1996) Effects of ethanol on ion channels. Int Rev Neurobiol 39: 283–367

Cunningham CL (1981) Spatial aversion conditioning with ethanol. Pharmacol Biochem Behav 14: 263–264

Cunningham CL, Henderson CM (2000) Ethanol-induced conditioned place aversion in mice. Behav Pharmacol 11: 591–602

Cunningham CL, Fidler TL, Hill KG (2000) Animal models of alcohol's motivational effects. Alcohol Res Health 24: 85–92

Curtis DR, Hosli L, Johnston GA (1968a) A pharmacological study of the depression of spinal neurones by glycine and related amino acids. Exp Brain Res 6: 1–18

Curtis DR, Hosli L, Johnston GA, Johnston IH (1968b) The hyperpolarization of spinal motoneurones by glycine and related amino acids. Exp Brain Res 5: 235–258

Czachowski CL, Legg BH, Samson HH (2001) Effects of acamprosate on ethanol-seeking and self-administration in the rat. Alcohol Clin Exp Res 25: 344–350

Dahchour A, De Witte P (1999) Acamprosate decreases the hypermotility during repeated ethanol withdrawal. Alcohol 18: 77–81

Dahchour A, De Witte P (2000a) Ethanol and amino acids in the central nervous system: assessment of the pharmacological actions of acamprosate. Prog Neurobiol 60: 343–362

Dahchour A, De Witte P (2000b) Taurine blocks the glutamate increase in the nucleus accumbens microdialysate of ethanol-dependent rats. Pharmacol Biochem Behav 65: 345–350

Dahchour A, Quertemont E, De Witte P (1994) Acute ethanol increases taurine but neither glutamate nor GABA in the nucleus accumbens of male rats: a microdialysis study. Alcohol Alcohol 29: 485–487

Dahchour A, Durbin P, De Witte P (1995) Ethanol and acamprosate increase the extracellular taurine in the nucleus accumbens: a microdialysis study. Alcohol Alcohol 30: 483

Dahchour A, Quertemont E, De Witte P (1996) Taurine increases in the nucleus accumbens microdialysate after acute ethanol administration to naive and chronically alcoholised rats. Brain Res 735: 9–19

Dahchour A, De Witte P, Bolo N, Nédélec JF, Muzet M, Durbin P, Macher JP (1998) Central effects of acamprosate: part 1. Acamprosate blocks the glutamate increase in the nucleus accumbens microdialysate in ethanol withdrawn rats. Psychiatry Res 82: 107–114

Dahchour A, Hoffman A, Deitrich R, De Witte P (2000) Effects of ethanol on extracellular amino acid levels in high- and low-alcohol sensitive rats: a microdialysis study. Alcohol Alcohol 35: 548–553

Daoust M, Lhuintre JP, Saligaut C, Moore N, Flipo JL, Boismare F (1987) Noradrenaline and GABA brain receptors are co-involved in the voluntary intake of ethanol by rats. Alcohol Alcohol [Suppl 1]: 319–322

Daoust M, Legrand E, Gewiss M, Heidbreder C, De Witte P, Tran G, Durbin P (1992) Acamprosate modulates synaptosomal GABA transmission in chronically alcoholised rats. Pharmacol Biochem Behav 41: 669–674

del Olmo N, Bustamante J, Martín del Río R, Solís JM (2000) Taurine activates $GABA_A$ but not $GABA_B$ receptors in rat hippocampal CA1 area. Brain Res 864: 298–307

Epstein EE, Kahler CW, McCrady BS, Lewis KD, Lewis S (1995) An empirical classification of drinking patterns among alcoholics: binge, episodic, sporadic, and steady. Addict Behav 20: 23–41

Fadda F, Rossetti ZL (1998) Chronic ethanol consumption: from neuroadaptation to neurodegeneration. Prog Neurobiol 56: 385–431

Ferko AP (1987) Ethanol-induced sleep time: interaction with taurine and a taurine antagonist. Pharmacol Biochem Behav 27: 235–238

Ferko AP, Bobyock E (1988) Effect of taurine on ethanol-induced sleep time in mice genetically bred for differences in ethanol sensitivity. Pharmacol Biochem Behav 31: 667–673

Font L, Miquel M, Aragon CMG (2001) Behavioral consequences of the hypotaurine-ethanol interaction. Pharmacol Biochem Behav 70: 333–339

Frye GD, Breese GR (1981) An evaluation of the locomotor stimulating action of ethanol in rats and mice. Psychopharmacology 75: 372–379

Gandhi CR, Ross DH (1989) Influence of ethanol on calcium, inositol phospholipids and intracellular signalling mechanisms. Experientia 45: 407–413

Gauvin DV, Holloway FA (1992) Historical factors in the development of ETOH-conditioned place preference. Alcohol 9: 1–7

Gewiss M, Heidbreder C, Opsomer L, Durbin P, De Witte P (1991) Acamprosate and diazepam differentially modulate alcohol-induced behavioural and cortical alterations in rats following chronic inhalation of ethanol vapour. Alcohol Alcohol 26: 129–137

Girard Y, Atkinson JG, Haubrich DR, Williams M, Yarbrough GG (1982) Aminomethyl-1,2,4-benzothiadiazines as potential analogues of gamma-aminobutyric acid. Unexpected discovery of a taurine antagonist. J Med Chem 25: 113–116

Gonzalez LP (1998) Electrophysiological changes after repeated alcohol withdrawal. Alcohol Health Res 22: 34–37

Grant KA, Woolverton WL (1989) Reinforcing and discriminative stimulus effects of Ca-acetyl homotaurine in animals. Pharmacol Biochem Behav 32: 607–611

Grant KA, Valverius P, Hudspith M, Tabakoff B (1990) Ethanol withdrawal seizures and the NMDA receptor complex. Eur J Pharmacol 176: 289–296

Gulya K, Grant KA, Valverius P, Hoffman PL, Tabakoff B (1991) Brain regional specificity and time-course of changes in the NMDA receptor-ionophore complex during ethanol withdrawal. Brain Res 547: 129–134

Gustavsson L (1990) Brain lipid changes after ethanol exposure. Ups J Med Sci [Suppl 48]: 245–266

Haas HL, Hösli L (1973) The depression of brain stem neurones by taurine and its interaction with strychnine and bicuculline. Brain Res 52: 399–402

Harris RA (1999) Ethanol actions on multiple ion channels: which are important? Alcohol Clin Exp Res 23: 1563–1570

Häusser MA, Yung WH, Lacey MG (1992) Taurine and glycine activate the same Cl-conductance in substantia nigra dopamine neurones. Brain Res 571: 103–108

Heyser CJ, Schulteis G, Durbin P, Koob GF (1998) Chronic acamprosate eliminates the alcohol deprivation effect while having limited effects on baseline responding for ethanol in rats. Neuropsychopharmacology 18: 125–133

Hodge CW, Mehmert KK, Kelley SP, McMahon T, Haywood A, Olive MF, Wang D, Sanchez-Perez AM, Messing RO (1999) Supersensitivity to allosteric $GABA_A$ receptor modulators and alcohol in mice lacking PKCε. Nature Neurosci 2: 997–1002

Hoffman PL, Tabakoff B (1991) The contribution of voltage-gated and NMDA receptor-gated calcium channels to ethanol withdrawal seizures. Alcohol Alcohol [Suppl 1]: 171–175

Holloway FA, King DA, Bedingfield JB, Gauvin DV (1992) Role of context in ethanol tolerance and subsequent hedonic effects. Alcohol 9: 109–116

Holloway FA, Bird DC, Devenport JA (1984) Periodic availability: factors affecting alcohol selection in rats. Alcohol 1: 19–25

Hölter SM, Landgraf R, Zieglgansberger W, Spanagel R (1997) Time course of acamprosate action on operant ethanol self-administration after ethanol deprivation. Alcohol Clin Exp Res 21: 862–868

Hunt T, Amit Z (1987) Conditioned taste aversion induced by self-administered drugs: paradox revisited. Neurosci Biobehav Rev 11: 107–130

Huxtable RJ (1989) Taurine in the central nervous system and the mammalian actions of taurine. Prog Neurobiol 32: 471–533

Huxtable RJ (1992) Physiological actions of taurine. Physiol Rev 72: 101–163

Ida S, Hikichi M (1976) Effect of taurine on ethanol-induced sleeping time in mice. J Stud Alcohol 37: 19–26

Ida S, Kuriyama K, Tomida Y, Kimura H (1987) Antisera against taurine: quantitative characterization of the antibody specificity and its application to immunohistochemical study in the rat brain. J Neurosci Res 18: 626–631

Iwata H, Matsuda T, Lee E, Yamagami S, Baba A (1980) Effect of ethanol on taurine concentration in the brain. Experientia 36: 332–333

Iwata H, Nakayama K, Matsuda T, Baba A (1984) Effect of taurine on a benzodiazepine-GABA-chloride ionophore receptor complex in rat brain membranes. Neurochem Res 9: 535–544

Jacobson I, Hamberger A (1984) Veratridine-induced release in vivo and in vitro of amino acids in the rabbit olfactory bulb. Brain Res 299: 103–112

Jacobson I, Sandberg M, Hamberger A (1985) Mass transfer in brain dialysis devices–a new method for the estimation of extracellular amino acids concentration. J Neurosci Meth 15: 263–268

Johnson BA, Ait-Daoud N (2000) Neuropharmacological treatments for alcoholism: scientific basis and clinical findings. Psychopharmacology 149: 327–344

Kontro P, Oja SS (1990) Interactions of taurine with GABAB binding sites in mouse brain. Neuropharmacology 29: 243–247

Kontro P, Korpi ER, Oja SS (1990) Taurine interacts with $GABA_A$ and $GABA_B$ receptors in the brain. Prog Clin Biol Res 351: 83–94

Kranzler HR (2000) Pharmacotherapy of alcoholism: gaps in knowledge and opportunities for research. Alcohol Alcohol 35: 537–547

Kratzer U, Schmidt WJ (1998) The anti-craving drug acamprosate inhibits the conditioned place aversion induced by naloxone-

precipitated morphine withdrawal in rats. Neurosci Lett 252: 53–56

Kudo Y, Akiyoshi E, Akagi H (1988) Identification of two taurine receptor subtypes on the primary afferent terminal of frog spinal cord. Br J Pharmacol 94: 1051–1056

Kurachi M, Aihara H (1985) The action of taurine on the response to glutamate in the motoneuron of the isolated frog spinal cord. Neuropharmacology 24: 775–781

Kurachi M, Yoshihara K, Aihara H (1983) Effect of taurine on depolarizations induced by L-glutamate and other excitatory amino acids in the isolated spinal cord of the frog. Jap J Pharmacol 33: 1247–1254

Kuriyama K (1980) Taurine as a neuromodulator. Fed Proc 39: 2680–2684

Lehmann A, Hegberg H, Hamberger A (1984) A role for taurine in the maintenance of homeostasis in the central nervous system during hyperexcitation? Neurosci Lett 52: 341–346

Le Magnen J, Tran G, Durlach J (1987a) Lack of effects of Ca-acetyl homotaurinate on chronic and acute toxicities of ethanol in rats. Alcohol 4: 103–108

Le Magnen J, Tran G, Durlach J, Martin C (1987b) Dose-dependent suppression of the high alcohol intake of chronically intoxicated rats by Ca-acetyl homotaurinate. Alcohol 4: 97–102

Lewis MJ, June HL (1990) Neurobehavioral studies of ethanol reward and activation. Alcohol 7: 213–219

Lewis CA, Ahmed Z, Faber DS (1991) A characterization of glycinergic receptors present in cultured rat medullary neurons. J Neurophysiol 66: 1291–1303

Lhuintre JP, Daoust M, Moore ND, Chretien P, Saligaut C, Tran G, Bosimare F, Hillemand B (1985) Ability of calcium bis acetyl homotaurine, a GABA agonist, to prevent relapse in weaned alcoholics. Lancet 1 (8496): 1014–1016

Lhuintre JP, Moore N, Tran G, Steru L, Langrenon S, Daoust M, Parot P, Ladure P, Libert C, Boismare F, et al (1990) Acamprosate appears to decrease alcohol intake in weaned alcoholics. Alcohol Alcohol 25: 613–622

Linseman MA (1987) Alcohol consumption in free-feeding rats: procedural, genetic and pharmacokinetic factors. Psychopharmacology 92: 254–261

Little HJ (1999) The contribution of electrophysiology to knowledge of the acute and chronic effects of ethanol. Pharmacol Ther 84: 333–353

Littleton J (1995) Acamprosate in alcohol dependence: how does it work? Addiction 90: 1179–1188

Littleton J (1998) Neurochemical mechanisms underlying alcohol withdrawal. Alcohol Health Res 22: 13–24

Lombardini JB (1994) The inhibitory effects of taurine on protein phosphorylation: comparison of various characteristics of the taurine-affected phosphoproteins present in rat retina, brain and heart. Adv Exp Med Biol 359: 9–17

Madamba SG, Schweitzer P, Zieglgänsberger W, Siggins GR (1996) Acamprosate (calcium acetylhomotaurinate) enhances the N-methyl-D-aspartate component of excitatory neurotransmission in rat hippocampal CA1 neurons in vitro. Alcohol Clin Exp Res 20: 651–658

Madsen S, Ottersen OP, Storm-Mathisen J (1985) Immunocytochemical visualization of taurine: neuronal localization in the rat cerebellum. Neurosci Lett 60: 255–260

Malminen O, Kontro P (1986) Modulation of the GABA-benzodiazepine receptor complex by taurine in rat brain membranes. Neurochem Res 11: 85–94

Malminen O, Kontro P (1989) Gamma-aminobutyric acid and benzodiazepine receptors in cultured cerebellar granule cells: effects of taurine and its lipophilic derivatives. Neuropharmacology 28: 907–912

Marcucella H, Munro I, MacDonall JS (1984) Patterns of ethanol consumption as a function of the schedule of ethanol access. J Pharmacol Exp Ther 230: 658–664

Mason BJ (2001) Treatment of alcohol-dependent outpatients with acamprosate: a clinical review. J Clin Psychiatry 62 [Suppl 20]: 42–48

Mason ST, Corcoran ME, Fibiger HC (1979) Noradrenergic processes involved in the locomotor effects of ethanol. Eur J Pharmacol 54: 383–387

Mas-Serrano P, Granero L, Martin-Algarra RV, Guerri C, Polache A (2000) Kinetic study of acamprosate absorption in rat small intestine. Alcohol Alcohol 35: 324–330

Mattucci-Schiavone L, Ferko AP (1985) Acute effects of taurine and a taurine antagonist on ethanol-induced central nervous system depression. Eur J Pharmacol 113: 275–278

Mayer ML (1981) Inhibitory actions of amino acids in the preoptic-anterior hypothalamus of the rat. Exp Brain Res 43: 154–158

McBride WJ, Frederickson RC (1980) Taurine as a possible inhibitory transmitter in the cerebellum. Fed Proc 39: 2701–2705

McBroom MJ, Elkhawad AO, Dlouha H (1986) Taurine and ethanol-induced sleeping time in mice: route and time course effects. Gen Pharmacol 17: 97–100

Medina JH, De Robertis E (1984) Taurine modulation of the benzodiazepine-gamma-aminobutyric acid receptor complex in brain membranes. J Neurochem 42: 1212–1217

Mendelson JH, Mello NK (1966) Experimental analysis of drinking behavior of chronic alcoholics. Ann N Y Acad Sci 133: 828–845

Milton GV, Randall PK, Erickson CK (1995) Low-dose effect of ethanol on locomotor activity induced by activation of the mesolimbic system. Alcohol Clin Exp Res 19: 768–776

Miquel M, Correa M, Sanchis-Segura C, Aragon CMG (1999) The ethanol-induced open-field activity in rodents treated with isethionic acid acid, a central metabolite of taurine. Life Sci 64: 1613–1621

Naassila M, Legrand E, d'Alche-Birée F, Daoust M (1998) Cyamemazine decreases ethanol intake in rats and convulsions during ethanol withdrawal syndrome in mice. Psychopharmacology 140: 421–428

Naassila M, Hammoumi S, Legrand E, Durbin P, Daoust M (1998) Mechanism of action of acamprosate. Part I. Characterization of spermidine-sensitive acamprosate binding site in rat brain. Alcohol Clin Exp Res 22: 802–809

Naassila M, Beauge FJ, Sebire N, Daoust M (2000) Intracerebroventricular injection of antisense oligos to nNOS decreases rat ethanol intake. Pharmacol Biochem Behav 67: 629–636

Oja SS, Kontro P (1990) Neuromodulatory and trophic actions of taurine. Prog Clin Biol Res 351: 69–76

Oja SS, Saransaari P (1996) Taurine as osmoregulator and neuromodulator in the brain. Metabol Brain Dis 11: 153–164

Okamoto K, Sakai Y (1980) Localization of sensitive sites to taurine, gamma-aminobutyric acid, glycine and beta-alanine in the molecular layer of guinea-pig cerebellar slices. Br J Pharmacol 69: 407–413

Okamoto K, Kimura H, Sakai Y (1983a) Effects of taurine and GABA on Ca spikes and Na spikes in cerebellar purkinje cells in vitro: intrasomatic study. Brain Res 260: 249–259

Okamoto K, Kimura H, Sakai Y (1983b) Evidence for taurine as an inhibitory neurotransmitter in cerebellar stellate interneurons: selective antagonism by TAG (6-aminomethyl-3-methyl-4H,1,2,4-benzothiadiazine-1,1-dioxide). Brain Res 265: 163–168

Okamoto K, Kimura H, Sakai Y (1983c) Ionic mechanisms of the action of taurine on cerebellar Purkinje cell dendrites in vitro: intradendritic study. Brain Res 260: 261–269

Olive MF, Hodge CW (2001) Taurine-related compounds differentially alter ethanol consumption and ethanol-stimulated

dopamine release in rats: comparison with acamprosate. Alcohol Clin Exp Res 25: 17A

Olive MF, Mehmert KK, Hodge CW (2000a) Modulation of extracellular neurotransmitter levels in the nucleus accumbens by a taurine uptake inhibitor. Eur J Pharmacol 409: 291–294

Olive MF, Mehmert KK, Messing RO, Hodge CW (2000b) Reduced operant ethanol self-administration and in vivo mesolimbic dopamine responses to ethanol in PKCε deficient mice. Eur J Neurosci 12: 4131–4140

Palkovits M, Elekes I, Lang T, Patthy A (1986) Taurine levels in discrete brain nuclei of rats. J Neurochem 47: 1333–1335

Pandey SC (1998) Neuronal signaling systems and ethanol dependence. Mol Neurobiol 17: 1–15

Pascucci T, Cioli I, Pisetzky F, Dupre S, Spirito A, Nencini P (1999) Acamprosate does not antagonise the discriminative stimulus properties of amphetamine and morphine in rats. Pharmacol Res 40: 333–338

Popp RL, Lovinger DM (2000) Interaction of acamprosate with ethanol and spermine on NMDA receptors in primary cultured neurons. Eur J Pharmacol 394: 221–231

Putzke J, Spanagel R, Tolle TR, Zieglgansberger W (1996) Anticraving drug acamprosate reduces c-fos expression in rats undergoing ethanol withdrawal. Eur J Pharmacol 317: 39–48

Quertemont E, de Neuville J, De Witte P (1998a) Changes in the amygdala amino acid microdialysate after conditioning with a cue associated with ethanol. Psychopharmacology 139: 71–78

Quertemont E, Goffaux V, Vlaminck A-M, Wolf C, De Witte P (1998b) Oral taurine supplementation modulates ethanol-conditioned stimulus preference. Alcohol 16: 201–206

Quertemont E, Dahchour A, Ward RJ, De Witte P (1999) Ethanol induces taurine release in the amygdala: an in vivo microdialysis study. Addict Biol 4: 47–54

Quertemont E, De Witte P (2001) Conditioned stimulus preference after acetaldehyde but not ethanol injections. Pharmacol Biochem Behav 68: 449–454

Quinn MR (1990) Taurine allosterically modulates binding sites of the $GABA_A$ receptor. Prog Clin Biol Res 351: 121–127

Quinn MR, Harris CL (1995) Taurine allosterically inhibits binding of [35S]-t-butylbicyclophosphorothionate (TBPS) to rat brain synaptic membranes. Neuropharmacology 34: 1607–1613

Quinn MR, Miller CL (1992) Taurine allosterically modulates flunitrazepam binding to synaptic membranes. J Neurosci Res 33: 136–141

Rammes G, Mahal B, Putzke J, Parsons C, Spielmanns P, Pestel E, Spanagel R, Zieglgansberger W, Schadrack J (2001) The anticraving compound acamprosate acts as a weak NMDA-receptor antagonist, but modulates NMDA-receptor subunit expression similar to memantine and MK-801. Neuropharmacology 40: 749–760

Reid LD, Hunter GA, Beaman CM, Hubbell CL (1985) Toward understanding ethanol's capacity to be reinforcing: a conditioned place preference following injections of ethanol. Pharmacol Biochem Behav 22: 483–487

Rossetti ZL, Carboni S (1995) Ethanol withdrawal is associated with increased extracellular glutamate in the rat striatum. Eur J Pharmacol 283: 177–183

Rossetti ZL, Carboni S, Fadda F (1999) Glutamate-induced increase of extracellular glutamate through *N*-methyl-D-aspartate receptors in ethanol withdrawal. Neuroscience 93: 1135–1140

Saitz R (1998) Introduction to alcohol withdrawal. Alcohol Health Res 22: 5–12

Saivin S, Hulot T, Chabac S, Potgieter A, Durbin P, Houin G (1998) Clinical pharmacokinetics of acamprosate. Clin Pharmacokinetics 35: 331–345

Samson HH (1986) Initiation of ethanol reinforcement using a sucrose-substitution procedure in food- and water-sated rats. Alcohol Clin Exp Res 10: 436–442

Samson HH, Tolliver GA, Schwarz-Stevens K (1991) Ethanol self-administration in a nonrestricted access situation: effect of ethanol initiation. Alcohol 8: 43–53

Saransaari P, Oja SS (2000) Taurine and neural cell damage. Amino Acids 19: 509–526

Smith BR, Amit Z, Splawinsky J (1984) Conditioned place preference induced by intraventricular infusions of acetaldehyde. Alcohol 1: 193–195

Spanagel R, Hölter SM (2000) Pharmacological validation of a new animal model of alcoholism. J Neural Trans 107: 669–680

Spanagel R, Zieglgansberger W (1997) Anti-craving compounds for ethanol: new pharmacological tools to study addictive processes. Trends Pharmacol Sci 18: 54–59

Spanagel R, Hölter SM, Allingham K, Landgraf R, Zieglgänsberger W (1996a) Acamprosate and alcohol: I. Effects on alcohol intake following alcohol deprivation in the rat. Eur J Pharmacol 305: 39–44

Spanagel R, Putzke J, Stefferl A, Schobitz B, Zieglgansberger W (1996b) Acamprosate and alcohol: II. Effects on alcohol withdrawal in the rat. Eur J Pharmacol 305: 45–50

Spanagel R, Zieglgansberger W, Hundt W (1996c) Acamprosate and alcohol: III. Effects of alcohol discrimination in the rat. Eur J Pharmacol 305: 51–56

Spanagel R, Sillaber I, Zieglansberger W, Corrigall WA, Stewart J, Shaham Y (1998) Acamprosate suppresses the expression of morphine-induced sensitization in rats but does not affect heroin self-administration or relapse induced by heroin or stress. Psychopharmacology 139: 391–401

Stromberg MF, Mackler SA, Volpicelli JR, O'Brien CP (2001) Effect of acamprosate and naltrexone, along or in combinations, on ethanol consumption. Alcohol 23: 109–116

Strombom UH, Liedman B (1982) Role of dopaminergic neurotransmission in locomotor stimulation by dexamphetamine and ethanol. Psychopharmacology 78: 271–276

Stubbs CD, Slater SJ (1999) Ethanol and protein kinase C. Alcohol Clin Exp Res 23: 1552–1560

Taber KH, Lin CT, Liu JW, Thalmann RH, Wu JY (1986) Taurine in hippocampus: localization and postsynaptic action. Brain Res 386: 113–121

Tamai I, Senmaru M, Terasaki T, Tsuji A (1995) Na(+)- and Cl(−)-dependent transport of taurine at the blood-brain barrier. Biochem Pharmacol 50: 1783–1793

Theofanopoulos V, Lau-Cam CA (1998a) The effects of taurine and biogenetically related sulfur-containing compounds on the metabolism of and hypothermia by ethanol in the rat. Adv Exp Med Biol 442: 299–307

Theofanopoulos V, Lau-Cam CA (1998b) Modification by taurine of the metabolism and hypothermic effect of ethanol in the rat. Adv Exp Med Biol 442: 309–318

Tsai G, Coyle JT (1998) The role of glutamatergic neurotransmission in the pathophysiology of alcoholism. Annu Rev Med 49: 173–184

van der Kooy D, O'Shaughnessy M, Mucha RF, Kalant H (1983) Motivational properties of ethanol in naive rats as studied by place conditioning. Pharmacol Biochem Behav 19: 441–445

Ward RJ, Colantuoni C, Dahchour A, Quertemont E, De Witte P (1997) Acetaldehyde-induced changes in the monoamine and amino acid extracellular microdialysate content of the nucleus accumbens. Neuropharmacology 36: 225–232

Ward RJ, Marshall EJ, Ball D, Martinez J, De Witte P (1999) Homeostasis of taurine and glutamate plasma levels after acute

and chronic ethanol administration in man. Neurosci Res Comm 24: 41–49

Ward RJ, Kest W, Bruyeer P, Lallemand F, De Witte P (2001) Taurine modulates catalase, aldehyde dehydrogenase, and ethanol elimination rates in rat brain. Alcohol Alcohol 36: 39–43

Watanabe A, Hobara N, Nagashima H (1985) Lowering of liver acetaldehyde but not ethanol concentrations by pretreatment with taurine in ethanol-loaded rats. Experientia 41: 1421–1422

Whittington MA, Lambert JD, Little HJ (1995) Increased NMDA receptor and calcium channel activity underlying ethanol withdrawal hyperexcitability. Alcohol Alcohol 30: 105–114

Wilde MI, Wagstaff AJ (1997) Acamprosate: a review of its pharmacology and clinical potential in the management of alcohol dependence after detoxification. Drugs 53: 1038–1053

Williams M, Risley EA, Totaro JA (1980) Interactions of taurine and beta-alanine with central nervous system neurotransmitter receptors. Life Sci 26: 557–560

Wu JY, Liao CC, Lin CJ, Lee YH, Ho JY, Tsai WH (1990) Taurine receptor in the mammalian brain. Prog Clin Biol Res 351: 147–156

Wu JY, Jin H, Schloss TV, Faiman MD, Ningaraj NS, Foos T, Chen W (2001) Neurotoxic effect of acamprosate, n-acetylhomotaurine, in cultured neurons. J Biomed Sci 8: 96–103

Yarbrough GG, Singh DK, Taylor DA (1981) Neuropharmacological characterization of a taurine antagonist. J Pharmacol Exp Ther 219: 604–613

Yoshida M, Karasawa N, Ito M, Sakai M, Nagatsu I (1986) Demonstration of taurine-like immunoreactive structures in the rat brain. Neurosci Res 3: 356–363

Yoshida M, Teramura M, Karasawa N, Sakai M, Nagatsu I (1987) Immunohistochemistry of taurine and GABA in serial brain sections of the rat. Biogen Amines 4: 135–144

Zeise ML, Kasparow S, Capogna M, Zieglgänsberger W (1990) Calciumdiacetylhomotaurinate (CA-AOTA) decreases the action of excitatory amino acids in the rat neocortex in vitro. Prog Clin Biol Res 351: 237–242

Zeise ML, Kasparov S, Capogna M, Zieglgänsberger W (1993) Acamprosate (calciumacetylhomotaurinate) decreases postsynaptic potentials in the rat neocortex: possible involvement of excitatory amino acid receptors. Eur J Pharmacol 231: 47–52

Author's address: Dr. M. Foster Olive, Ernest Gallo Clinic and Research Center, Department of Neurology, University of California at San Francisco, 5858 Horton Street, Suite 200, Emeryville, California, U.S.A.,
Fax +1/510/985 3101, E-mail: folive@itsa.ucsf.edu