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The Interaction Between Ethanol and Cysteine on the Central Depressant Effects of Ethanol in Mice

ANDREW P. FERKO

Hahnemann University, School of Medicine, Department of Pharmacology
Broad and Vine Streets, Philadelphia, PA 19102

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FERKO, A. P. *The interaction between ethanol and cysteine on the central depressant effects of ethanol in mice.* PHARMACOL BIOCHEM BEHAV **36**(3) 619–624, 1990.—In this study male Swiss-Webster mice were used to examine the effects of cysteine (ICV), a precursor in the biosynthesis of taurine, on ethanol-induced loss of the righting reflex. The interaction of ethanol with gamma-aminobutyric acid (GABA) and isethionic acid, a metabolite of taurine, was also investigated on ethanol-induced central nervous system depression as measured by loss of the righting reflex experiments. Immediately after the animals regained the righting reflex following ethanol injection (IP) mice received an ICV injection of saline, cysteine (1, 15 or 25 μmol/kg), GABA (1, 15 or 25 μmol/kg) or isethionic acid (25 or 50 μmol/kg). Upon ICV administration of cysteine or GABA the mice again lost the righting reflex. This effect occurred immediately and in a dose-dependent manner. The compound, isethionic acid, failed to cause a second loss of the righting reflex following ethanol administration (IP). In the absence of ethanol cysteine or GABA (25 μmol/kg, ICV) did not produce a substantial loss of the righting reflex in mice. In another experiment mice were pretreated (IP) with L-2-oxothiazolide-4-carboxylate (OTC) 2 hr prior to ethanol administration (IP). OTC is a compound which can be converted to cysteine in the body. In the presence of ethanol OTC (15 mmol/kg) caused an enhancement of ethanol-induced central nervous system depression under certain conditions. When OTC (25 μmol/kg), however, was injected by the ICV route immediately after the animals regained the righting reflex following ethanol administration, OTC did not augment the central depressant properties of ethanol. This experiment indicated that OTC was inactive by itself and that it required a certain time period to be converted to cysteine in mice. In this investigation the results suggest that cysteine, a sulfur-containing amino acid, can enhance ethanol-induced depression as measured by the loss of the righting reflex and that cysteine may be involved in some manner with the central depressant properties of ethanol.

Ethanol Cysteine GABA Isethionic acid L-2-Oxothiazolidine-4-carboxylate (OTC) Sleep time Loss of righting reflex

TAURINE is present in the central nervous system in relatively high concentrations and can exert a depressant effect (4,34). It is suggested that taurine may function as a neurotransmitter (20, 21, 45) or in the modulation of transmission (6, 16, 20). The modulatory effect of taurine has been postulated on the GABA-benzodiazepine receptor chloride ionophore complex (6, 16, 30).

Several reports indicate that taurine enhances the central nervous system depressant properties of ethanol when this sulfur-containing amino acid is injected by the intracerebroventricular (ICV) route. In Sprague-Dawley rats taurine prolongs ethanol-induced loss of the righting reflex in a dose-dependent manner (28). When taurine is administered (ICV) to Swiss-Webster mice in the presence of ethanol, there is an enhancement of the depressant effect of ethanol as measured by loss of the righting reflex experiments (13). In addition, TAG, a taurine antagonist (6-aminomethyl-3-methyl-4H-1,2,4-benzothiadiazine-l-dioxide HCl), attenuates the effect of taurine to increase ethanol-induced loss of the righting reflex (13,28). In another experiment (12) the results indicate that Long-Sleep (LS) mice exhibit a longer return to the loss of the righting reflex in the presence of ethanol from taurine administration (ICV) than Short-Sleep (SS) mice.

In the central nervous system cysteine is a precursor in the biosynthesis of taurine. Previous work (32) indicates that cysteine (IP) can depress spontaneous locomotor activity in mice. Cysteine, however, fails to alter ethanol-induced loss of the righting reflex when it is administered by the IP route. It may be that cysteine does not readily enter the central nervous system at this dose (3). A recent investigation shows that L-2-oxothiazolidine-4-carboxylate (OTC) enters into the mouse and rat brain following IP injection and is converted into cysteine by the enzyme, 5-oxoprolinase (3). OTC appears to produce less toxic effects than cysteine when it is given by the IP route. It is the intent of this investigation to note if cysteine exhibits pharmacologic properties similar to taurine in the enhancement of ethanol-induced loss of the righting reflex.

In this study the interaction of ethanol with OTC and cysteine is examined. Various doses of OTC (IP, ICV) and cysteine (ICV) are given in the presence of ethanol (IP). Duration of the loss of the righting reflex is used as an index of central nervous depression. The hypothesis of this study is that cysteine (ICV) possesses central depressant properties which can enhance ethanol-induced loss of the righting reflex. In addition, the effects of the cysteine and ethanol interaction are compared with the effects of gamma-aminobutyric acid (GABA) on ethanol-induced loss of the righting

reflex when GABA is given by the ICV route. Previous works demonstrate that GABA agonists (IP) augment the ethanol-induced loss of the righting reflex (23,29).

METHOD

Male Swiss-Webster mice (25–30 g) were obtained from Charles River Laboratories (Wilmington, MA). The mice were housed for 1 week prior to experimentation at 21 ± 1°C with a light cycle from 6:00 a.m. to 6:00 p.m. The animals had free access to Purina Laboratory Chow (Ralston Purina Co., St. Louis, MO) and water. Ethanol solution (21% w/v) for injection was prepared from 95% ethanol in saline. L-Cysteine, L-2-oxothiazolidine-4-carboxylate (OTC), isethionic acid, and gamma-aminobutyric acid were purchased from Sigma Chemical Co. (St. Louis, MO). Drug solutions for injection (ICV) were prepared in saline (0.9% NaCl) and adjusted to pH 7.0 with NaOH solution (13,28). All other chemicals were obtained from commercial sources and were of analytical grade.

Loss of the Righting Reflex (LORR) Experiments With Ethanol (IP) and Cysteine (ICV), GABA (ICV) and Isethionic Acid (ICV)

Duration of the loss of the righting reflex was used as an index of ethanol-induced central nervous system depression and was measured as the interval between the loss of the righting reflex after ethanol injection (IP) and the gain of the righting reflex. The gain of the righting reflex required that the animal be able to re-right himself 3 times within 15 sec, after again being placed on his back. Duration of the loss of the righting also is referred to as sleep time or hypnosis (12, 13, 28). In addition, the onset of loss of the righting reflex (time between ethanol injection and loss of the righting reflex) was recorded.

The intent of these experiments was to ascertain if an ICV injection of cysteine, GABA or isethionic acid could enhance the degree of central nervous system depression and return the mice to a loss of the righting reflex when cysteine, GABA, or isethionic acid was given at the end of the ethanol-induced loss of the righting reflex. The procedure (35) for intracerebroventricular (ICV) injection involved cutting the scalp of an anesthetized mouse and injections (at a depth of 3 mm) 2 mm caudal and 2 mm lateral to bregma using a Hamilton microliter syringe with a 26-gauge needle of ⅜ inch. Drug solutions were administered slowly into the ventricle over a period of approximately 20 sec. The correct position of the injection was verified at autopsy by using trypan blue.

At the beginning of the experiment mice received an IP injection of ethanol (4.2 g/kg). Twenty minutes after the loss of the righting reflex a 26-gauge needle was used to enter the ventricle of the brain of the ethanol-anesthetized mouse but no saline or drug solution was given at this time, since this was a preparatory step for ICV drug administration (12,13). Immediately after the animals regained the righting reflex following ethanol injection mice received an ICV injection of saline, cysteine (1, 15 or 25 μmol/kg), GABA (1, 15 or 25 μmol/kg), or isethionic acid (25 or 50 μmol/kg) in a volume of 5 μl. The ethanol (ETOH) duration of loss of the righting reflex (LORR) was determined from the loss of the righting reflex to the gain of the righting reflex after ethanol administration (IP). A second period of the LORR was recorded and called the Return to LORR. The return to loss of the righting reflex was measured from the loss of the righting reflex to the gain of the righting reflex after drug or saline injection (ICV). Blood samples (20 μl) were obtained from the orbital sinus of mice when they regained the righting reflex after the injection (ICV) of saline or drug. An enzymatic method (24) was used to measure blood ethanol concentrations.

The next experiments were performed to note if cysteine or GABA by itself could cause a loss of the righting reflex in mice. Animals were administered saline (0.02 ml/g, IP) and then 20 min later the mice were lightly anesthetized with methoxyflurane. At this time an ICV preparatory injection was made as previously described (12, 13, 35). Forty minutes later the mice were heavily sedated with methoxyflurane (without the loss of the righting reflex) and injected (5 μl) with saline, cysteine (25 μmol/kg) or GABA (25 μmol/kg). The mice were observed for 2 hr after drug administration.

Experiments With Ethanol (IP) and L-2-Oxothiazolidine-4-Carboxylic Acid, OTC (IP and ICV)

These experiments were performed to determine if OTC administration could cause a loss of the righting reflex in the presence of ethanol. OTC is a compound that is biotransformed into cysteine (3). Saline (0.02 ml/g) or OTC (7.5 or 15.0 mmol/kg, IP) were given 2 hr prior to the administration of ethanol. These doses of OTC (in the mmol range) cause an increase in rodent brain cysteine levels (3). Two hr later ethanol was injected (4.2 g/kg, IP). The onset to the loss of the righting reflex and the duration of the loss of the righting reflex were recorded. Immediately after regaining the righting reflex following ethanol administration the mice were injected IP with saline or OTC (7.5 or 15.0 mmol/kg) to determine if a return to the loss of the righting reflex occurred in the mice. Blood samples for ethanol assay (20 μl) were obtained from the orbital sinus of mice when they regained the righting reflex after the administration of saline or OTC.

In the next experiment the interaction between ethanol (IP) and OTC (ICV) was examined to note if OTC can enhance the central depressant properties of ethanol when the compound was given by the intracerebroventricular route. Mice were injected with ethanol (4.2 g/kg, IP) and the onset to the loss of the righting reflex and the duration of the loss of the righting reflex were recorded. Saline or OTC (25 μmol/kg) was injected (ICV) in a volume of 5 μl immediately after regaining the righting reflex following ethanol administration to note if OTC produced a return to the loss of the righting reflex.

Statistical Analysis

Significant differences were determined by analysis of variance (ANOVA). All multiple comparisons with a control and comparisons among the experimental groups were done by ANOVA followed by Scheffe's test.

RESULTS

Table 1 indicates that cysteine causes a central depressant effect in the presence of ethanol. The ICV injection of cysteine after the animals have regained the righting reflex following ethanol administration produced a return to the loss of the righting reflex (LORR) which occurred in a dose-dependent manner. The percentage increase in the duration of LORR for cysteine at doses of 15 and 25 μmol/kg was 127 and 307% respectively, when these doses were compared with the lowest dose of cysteine administered to mice. As the cysteine (CYS) return to the LORR increased with the various doses of cysteine the blood ethanol concentrations which were obtained at the end of the return to the LORR period, were decreased. The effect of cysteine (ICV) to cause a loss of the righting reflex in the presence of ethanol was immediate in onset.

In the second experiment the interaction of ethanol with GABA, an inhibitory neurotransmitter in the central nervous system, was studied. In a similar manner to cysteine, GABA enhanced the central depressant properties of ethanol. When

TABLE 1

EFFECTS OF CYSTEINE (CYS, μmol/kg, ICV) TO PRODUCE A RETURN TO THE LOSS OF THE RIGHTING REFLEX (LORR) IMMEDIATELY AFTER REGAINING THE RIGHTING REFLEX FOLLOWING ETHANOL (ETOH, 4.2 g/kg, IP) INJECTION

Group	N	Onset to LORR (sec)	ETOH-LORR (min)	CYS-Return to LORR (min)†	Blood ETOH (mg/ml)
ETOH + Saline (controls)	10	99 ± 3*	53.6 ± 5.4	3.3 ± 1.2	3.53 ± 0.07
ETOH + CYS (1.0)	8	87 ± 4	59.9 ± 5.9	16.2 ± 2.3	3.26 ± 0.03
ETOH + CYS (15.0)	7	94 ± 5	54.7 ± 6.6	36.8 ± 7.5‡	3.19 ± 0.08
ETOH + CYS (25.0)	8	90 ± 5	50.6 ± 4.4	66.0 ± 10.8‡§¶	2.70 ± 0.22‡§¶

*Values are means ± S.E.M.

†CYS injected (ICV) immediately after regaining the righting reflex following ETOH administration.

‡Significantly different from controls ($p<0.01$).

§Significantly different from CYS (1.0) Group ($p<0.05$).

¶Significantly different from CYS (15) Group ($p<0.05$).

GABA was injected (ICV) immediately after regaining the righting reflex following ethanol (IP) administration, there occurred a return to the LORR (Table 2). The greatest effect of GABA was manifested by the 25 μmol/kg dose. The blood ethanol values, which were obtained at the end of the second period, decreased as the doses of GABA were increased. The onset of the return to the LORR was immediate following the ICV injection of GABA. Several mice exhibited respiratory depression and a degree of cyanosis that lasted from 1 to 3 min after the injection (ICV) of the largest dose of GABA.

Since cysteine, a precursor in the biosynthesis of taurine, was able to enhance the central depressant effects of ethanol, it was decided to determine if there was any interaction between ethanol and isethionic acid, a metabolic of taurine. Mice were injected with ethanol (4.0 g/kg, IP) and when they regained the righting reflex following ethanol administration, the mice were immediately injected (ICV) with saline (N = 11) or isethionic acid (25 or 50 μmol/kg; N = 7 and 6, respectively) in a volume of 5 μl. There were no significant differences in the return to the LORR data for the control group and the isethionic acid-treated groups (data not shown). These results indicated that isethionic acid did not enhance the central depressant properties of ethanol. Isethionic acid appears to be an inactive metabolite of taurine under these experimental conditions.

In another experiment cysteine or GABA was administered (ICV) in the absence of ethanol to assess if cysteine (25 μmol/kg) or GABA (25 μmol/kg) by itself could induce a loss of the righting reflex. Mice were given saline (0.02 ml/g, IP) and then 60 min later injected (ICV) with saline, cysteine, or GABA. The controls (saline), cysteine group (25 μmol/kg) and the GABA-treated mice (25 μmol/kg) had lost the righting reflex for 0.0 ± 0.0, 0.0 ± 0.0 and 8.0 ± 2.9 min, respectively. Each group contained 4–5 animals. From these data it appears that cysteine or GABA alone was not responsible for the results when either cysteine (Table 1) or GABA (Table 2) was injected (ICV) in the presence of ethanol. Besides the short period of the loss of the righting reflex produced by GABA injection the animals also experienced respiratory depression and some degree of cyanosis that lasted from 2 to 3 min after the administration of GABA. No differences in behavior were observed when cysteine or GABA-treated mice were compared with controls for 2 hr postinjection.

In the final experiments the interaction between ethanol and

TABLE 2

INTERACTION BETWEEN ETHANOL (ETOH, 4.2 g/kg, IP) AND GABA (μmol/kg, ICV) ON RETURN TO THE LOSS OF THE RIGHTING REFLEX (LORR)

Group	N	Onset to LORR (sec)	ETOH-LORR (min)	GABA-Return to LORR (min)†	Blood ETOH (mg/ml)
ETOH + Saline (controls)	11	97 ± 3*	56.3 ± 3.3	4.0 ± 1.5	3.43 ± 0.08
ETOH + GABA (1.0)	6	84 ± 5	60.0 ± 7.2	21.7 ± 4.3‡	3.27 ± 0.09
ETOH + GABA (15)	7	84 ± 3	52.3 ± 5.1	33.0 ± 3.4§	3.21 ± 0.07
ETOH + GABA (25)	8	89 ± 5	57.4 ± 9.1	39.0 ± 4.8§¶	3.09 ± 0.08‡

*Values are means ± S.E.M.

†GABA injected (ICV) immediately after regaining the righting reflex following ETOH administration.

‡Significantly different from controls ($p<0.05$).

§Significantly different from controls ($p<0.01$).

¶Significantly different from GABA (1.0) Group ($p<0.05$).

TABLE 3

INTERACTION BETWEEN ETHANOL (4.2 g/kg, IP) AND L-2-OXOTHIAZOLIDINE-4-CARBOXYLIC ACID (OTC, mmol/kg, IP) ON ETHANOL-INDUCED LOSS OF THE RIGHTING REFLEX (LORR)

Group	Treatment	N	Onset to LORR (sec)	ETOH-LORR (min)	OTC-Return to the LORR (min)§	Blood ETOH mg/ml
I	ETOH* + Saline	12	97 ± 4‡	62.7 ± 6.7	2.2 ± 1.0	3.29 ± 0.10
II	ETOH† + OTC (7.5)	3	97 ± 11	55.7 ± 7.2	0.0 ± 0.0	3.06 ± 0.16
III	ETOH† + OTC (15)	11	108 ± 5	78.5 ± 9.0	34.5 ± 10.0¶	2.94 ± 0.29
IV	ETOH* + OTC (15)	6	97 ± 2	59.7 ± 5.1	12.8 ± 4.1	2.84 ± 0.08

*Pretreated with saline 2 hr before ethanol injection.

†Pretreated with OTC dose 2 hr before ethanol injection.

‡Values are means ± S.E.M.

§Administered saline or OTC, IP, immediately after regaining righting reflex following ETOH administration.

¶Significantly different from ETOH + Saline Group ($p<0.05$).

L-2-oxothiazolidine-4-carboxylic acid (OTC) was examined. OTC is a compound that is converted to cysteine in the body (3). Animals were pretreated with saline (0.02 ml/g, IP) or OTC (7.5 or 15 mmol/kg, IP) 2 hr before ethanol (4.2 g/kg, IP) administration (Table 3). In addition when the animals regained the righting reflex after the injection of ethanol they were again injected with OTC (Groups II and III) to determine if a return to the LORR occurred. Although pretreatment with OTC (15 mmol/kg, IP) did lengthen the ETOH-LORR (Group III), this value was not significantly different from controls (Table 3). When a second injection of OTC (15 mmol/kg, IP) was given to the Group III (Table 3) immediately after the animals regained the righting reflex following ethanol administration, there resulted a significant return to the LORR. In Table 3 Group IV were given only OTC (15 mmol/kg, IP) when the animals regained the righting reflex following ethanol injection. A short return to the LORR was produced by OTC, but this value was not significantly different from control. The effect of OTC (15 mmol/kg, IP) in Group III may be due to the fact that OTC was given to this group in two separate doses which may have increased the formation of cysteine in the brain and enhanced the depressant effect of ethanol. A second explanation may be that OTC is an active compound by itself and when OTC reached the brain a return to the LORR was produced in the presence of ethanol. To test this hypothesis that OTC is an active compound which can augment the depressant effect of ethanol similar to cysteine, animals were given OTC by the ICV route.

TABLE 4

EFFECT OF L-2-OXOTHIAZOLIDINE-4-CARBOXYLIC ACID (OTC, 25 μmol/kg, ICV) ON THE CENTRAL DEPRESSANT PROPERTIES OF ETHANOL (ETOH, 4.2 g/kg, IP) AS MEASURED BY THE LOSS OF THE RIGHTING REFLEX (LORR)

Group	N	Onset to LORR (sec)	ETOH-LORR (min)	OTC-Return† to the LORR (min)
ETOH + Saline	8	91 ± 5*	65.0 ± 6.2	4.8 ± 1.6
ETOH + OTC	6	88 ± 4	63.2 ± 5.6	6.7 ± 1.6

*Values are means ± S.E.M.

†OTC was given (ICV) immediately after regaining righting reflex following ETOH administration.

Table 4 shows that OTC (25 μmol/kg, ICV) failed to cause a return to the LORR in the presence of ethanol. It appears that OTC does not possess similar properties to cysteine when both these compounds are used at the same dose and under similar experimental conditions.

DISCUSSION

The results of this investigation show that cysteine, a precursor in the biosynthesis of taurine, enhances the central depressant properties of ethanol. Cysteine (ICV) causes a dose-dependent effect in returning the animals to a second loss of the righting reflex (LORR) period following the initial administration of ethanol. The interaction between cysteine and ethanol is similar to previous reports on the effect of taurine (ICV) to produce a return to the loss of the righting reflex in the presence of ethanol in mice (12,13).

Earlier work indicates that cysteine (IP) decreases spontaneous locomotor activity in mice (32). Experiments on ethanol-induced the loss of the righting reflex, however, show that cysteine (50 mg/kg, IP) exerts little effect on the duration of the ethanol-induced loss of the righting reflex. The lack of effect on ethanol-induced loss of the righting reflex when cysteine is given by the IP route, may be related to the fact that peripheral administration of cysteine requires about 4 hr to reach its peak level in the brain (3). Intraperitoneal administration of taurine also fails to enhance the central depressant properties of ethanol (19,32). Information in the literature indicates that taurine does not readily enter the brain in significant amounts after acute peripheral administration (19,25). Intracerebroventricular injection of taurine, however, results in an enhancement of ethanol-induced loss of the righting reflex (12, 13, 28). In this study the doses of cysteine that are given ICV and the doses of taurine in previous ethanol work (12, 13, 28) are similar in range to ICV doses of taurine used in other investigations (14,37).

The results that were obtained in this study indicate that the effects of cysteine are drug-induced. The effects from cysteine injection (ICV) are not related to the osmotic effect of these concentrations. OTC (25 μmol/kg) and isethionic acid (25 and 50 μmol/kg) which were injected ICV into mice did not produce a return to the loss of the righting reflex following the initial administration of ethanol. In addition GABA, an inhibitory neurotransmitter in the brain, requires μmol/kg doses to produce a second loss of the righting reflex following ethanol administration (Table 2). It appears that μmol/kg dosage is required in this ICV injection technique to allow absorption and distribution of the drug

from the ventricle of the brain to eventually reach the target tissues in the central nervous system.

In Table 3 the compound OTC, which is biotransformed to cysteine in the brain (3), causes a return to the loss of the righting reflex in the presence of ethanol upon IP administration (Group III). It appears that the formation of cysteine from OTC is possibly responsible for the interaction between ethanol and OTC, since OTC produces no effect when it is administered by the ICV route immediately after the animals regain the righting reflex following ethanol administration (Table 4). The use of OTC in this study adds some support that cysteine can interact with ethanol to enhance the central depressant properties of ethanol. Another explanation of the effect of cysteine is that cysteine is converted to taurine in the brain and that taurine is the actual active compound. Although some cysteine may be biotransformed to taurine, it seems that cysteine is an active compound in itself, since the effect of cysteine occurs immediately after the ICV administration of the drug and allows no time for the synthesis of taurine (8) to take place.

Data from this investigation also does not indicate that cysteine is interfering with the biotransformation of ethanol, since lower blood ethanol levels are found in animals after the ethanol-cysteine interaction, particularly at the highest doses of cysteine which cause the longest return to the loss of the righting reflex (Table 1). Although the orbital sinus (venous blood) is used to obtain blood samples, it is known that blood samples from this location quite closely reflect the ethanol concentration in the brain (27,40). Animals exhibit a loss of the righting reflex following ethanol administration until the ethanol is biotransformed to some threshold level. This threshold level of ethanol concentration is characteristic for a given strain or species (39). Since cysteine does not appear to modify the pharmacokinetics of ethanol, it therefore may be that cysteine is altering some fundamental central nervous system sensitivity to ethanol (39).

The exact mechanism by which cysteine enhances the ethanol-induced loss of the righting reflex is unknown. Since hypothermia is present during the interaction between ethanol and cysteine, the possible involvement of a decrease in body temperature should be considered for this drug-drug interaction. Ethanol-induced hypothermia may alter cellular metabolism such as protein synthesis (17), levels of free fatty acid and corticosterone, and tyrosine concentration (36). Some other effects of ethanol that are not influenced by the presence of hypothermia include 1) ethanol-induced decrease of cerebellar cGMP (9), 2) reduction in the hyperglycemic response to ethanol (46), and 3) the metabolism of ethanol as reflected by the disappearance of ethanol from the blood (10,11).

It is known that changes in body temperature influence the central depressant effect of ethanol (1, 2, 26). As measured by the duration of the loss of the righting reflex, ethanol-induced central nervous system depression decreases as rectal temperature decreases from 38 to 32°C and at more severe hypothermia (28°C) there is observed, however, no alteration of the duration of the loss of the righting reflex as compared with controls (26). When animals exhibited a body temperature of 25°C, there resulted an increase in ethanol-induced depression at this excessive reduction in body temperature. These animals appeared to be moribund (26). In the present study the animals never approached this condition. Other researchers in their works also have shown that the sensitivity to ethanol is increased as body temperature is increased (7, 18, 36). Experimental evidence indicates that ethanol and the general anesthetic agents produce a disordering effect (increased membrane fluidity) in discrete microenvironments of cellular membranes (15, 22, 41). It is suggested that there is an augmentation of the ethanol-induced disordering effect in membranes in the presence of an increase in temperature and therefore an enhanced central depressant effect. A decrease in temperature reduces the sensitivity to ethanol in the central nervous system (22,41).

It appears that the central nervous system sensitivity to ethanol may be related to a combination of cellular events that are both dependent and nondependent on temperature (2). At present, however, the exact manner by which body temperature influences brain sensitivity to ethanol is unknown. Under the experimental conditions in this present study hypothermia occurs during the interaction between ethanol and cysteine, therefore, according to evidence in the literature the interaction between ethanol and cysteine should have decreased central nervous system depression and not increased it as the result show in the experiments (Table 1). It appears that the enhanced central nervous system depression for the ethanol-cysteine interaction is possibly related to other contributory factors rather than to hypothermia under our experimental design.

A possible avenue for future investigation is the role of cysteine in GABA receptor-mediated chloride transport. Recent reports indicate that some effects of ethanol in the central nervous system involve the GABAergic system with respect to chloride ion fluxes (42,43). In addition, it is suggested that taurine may modulate the GABA receptor complex-mediated chloride flux. There is evidence that ethanol stimulates the release of taurine from astroglial cells in a dose-dependent manner (38). The inhibitory action of taurine in the central nervous system is due to an increase in chloride ion influx into neuronal membranes (5,44). The augmentation of chloride ion fluxes may be related to an agonistic action of taurine on the chloride channel, however, the effect of taurine is less than that of GABA (33). Other investigators indicate that taurine probably is a neuromodulator of GABA mediated chloride ion fluxes (6, 16, 30, 31). Future experiments that involve taurine and cysteine with GABA and/or ethanol-mediated chloride transport in the central nervous system may provide some information about the interaction of these sulfur-containing amino acids with ethanol.

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