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Cysteine Sulfinic Acid Can Enhance the Central Depressant Effect of Ethanol in Mice

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FERKO, A. P. *Cysteine sulfinic acid can enhance the central depressant effect of ethanol in mice.* PHARMACOL BIOCHEM BEHAV **39**(3) 653–657, 1991.—The interaction between ethanol and cysteine sulfinic acid was examined in male Swiss-Webster mice. The loss of the righting reflex (LORR) was used as a measurement of central nervous system depression. In addition, the interaction between ethanol and cysteic acid, a metabolite of cysteine sulfinic acid, was studied. Immediately after the animals regained the righting reflex following ethanol injection (IP), mice were given an ICV injection of saline, cysteine sulfinic acid (1, 15 or 25 μmol/kg) or cysteic acid (1, 15, or 25 μmol/kg). There occurred a return to the LORR within 30 s after the ICV injection of drugs. The return to the LORR by the administration of the amino acids in the presence of ethanol occurred in a dose-dependent fashion. When cysteine sulfinic acid or cysteic acid (25 μmol/kg, ICV) was injected in the absence of ethanol, no loss of the righting reflex occurred. In other experiments, bicuculline methiodide was given ICV with cysteine sulfinic acid (25 μmol/kg), cysteic acid (25 μmol/kg), or GABA (25 μmol/kg) in the presence of ethanol. Bicuculline methiodide, a GABA antagonist, reduced the effects of the three amino acids to produce a return to the LORR in the presence of ethanol. These results indicate that cysteine sulfinic acid, an excitatory amino acid, and cysteic acid can enhance the central depressant properties of ethanol. Since bicuculline antagonized the effects of these two amino acids, a GABAergic mechanism may be involved in the interaction between ethanol and cysteine sulfinic acid or cysteic acid.

Ethanol Cysteine sulfinic acid Cysteic acid GABA Bicuculline Loss of the righting reflex
Central nervous system depression Sleep time

THIS study examines the effects of L-cysteine sulfinic acid on ethanol-induced central nervous system depression. Cysteine sulfinic acid is an intermediate in the biosynthesis of taurine (1,8). In the brain, taurine exhibits inhibitory properties (4,22) while cysteine sulfinic acid is considered to have excitatory effects (5,14). Several investigations show that taurine injected intracerebroventricularly (ICV) enhances the depressant properties of ethanol as measured by the loss of the righting reflex.

In Swiss-Webster mice, taurine produces a dose-response effect to enhance the depressant effect of ethanol (9). When the interaction between ethanol and taurine is studied in Long Sleep and Short Sleep mice, taurine causes a greater enhancement of the action of ethanol in Long Sleep than in Short Sleep mice (10). Taurine also augments the central depressant properties of ethanol in Sprague-Dawley rats (18). The effect of taurine, to increase the duration of the loss of the reflex, is inhibited by the administration of TAG, a taurine antagonist (6-aminomethyl-3-methyl-4H-1, 2, 4-benzo-thiadiazine-1-dioxide HCl) (9, 10, 18).

Cysteine sulfinic acid is widely distributed in the central nervous system (13). During depolarization of neuronal tissue, cysteine sulfinic acid is elaborated in a calcium-dependent manner (6,15). It is suggested that cysteine sulfinic acid may be a putative excitatory neurotransmitter (2). In in vitro experiments, cysteine sulfinic acid is reported to release the inhibitory neurotransmitter, GABA, from brain slices through a possible receptor mechanism (2,3). Since cysteine sulfinic acid can release GABA, it may be that this sulfur-containing amino acid alters the central depressant action of ethanol.

In this study, various doses of cysteine sulfinic acid and cysteic acid, a biotransformation product of cysteine sulfinic acid, are injected intracerebroventricularly (ICV) in the presence of ethanol. The hypothesis of this research project is that cysteine sulfinic acid enhances the central depressant properties of ethanol. The loss of the righting reflex is used to assess the degree of central nervous system depression induced by cysteine sulfinic acid and cysteic acid in the presence of ethanol. The interaction between ethanol and GABA is also examined when GABA is administered by the ICV route. Other investigations show that GABA and GABA agonists increase the ethanol-induced loss of the righting reflex (11, 16, 19).

METHOD

Male Swiss-Webster mice (25–30 g) were obtained from Charles River Laboratories (Wilmington, MA). Animals 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 mice 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 sulfinic acid, L-cysteic acid, gamma-aminobutyric acid and bicuculline methiodide were obtained 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 (9–

11). All other chemicals were purchased from commercial sources and were of analytical grade.

Loss of the Righting Reflex (LORR) Experiments With Ethanol (IP) and Cysteine Sulfinic Acid (ICV) and Cysteic Acid (ICV)

The duration of the LORR was used as an index of ethanol-induced central nervous system depression, and was measured as the interval between the LORR after ethanol injection (IP) and the gain of the righting reflex. The gain of the righting reflex required that the animal be able to reright itself 3 times within 15 s, after again being placed on his back. In addition, the onset of the LORR (time between ethanol injection and loss of the righting reflex) was recorded.

The procedure (23) for intracerebroventricular (ICV) injection involved cutting the scalp of an anesthetized mouse and injecting (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 3/8 inch. Drug solutions were administered slowly into the ventricle over a period of approximately 10 s. The correct position of the injection was verified at autopsy by using trypan blue.

The aim of these experiments was to determine if cysteine sulfinic acid or cysteic acid could enhance the degree of central nervous system depression and return the animals to a second loss of the righting reflex when cysteine sulfinic acid or cysteic acid was given at the end of the ethanol-induced loss of the righting reflex (LORR).

In the experiments, mice received an IP injection of ethanol (4.2 g/kg). Twenty minutes after the LORR, 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 (9–11). Immediately after the animals regained the righting reflex following ethanol administration, mice received an ICV injection of saline, cysteine sulfinic acid (1, 15 or 25 μmol/kg) or cysteic acid (1, 15 or 25 μmol/kg) in a volume of 5 μl. The ethanol (ETOH) duration of the LORR was determined from 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 the loss of the righting reflex was measured from 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 ICV injection of saline or drug. An enzymatic method (17) was used to measure blood ethanol concentrations.

The next experiments were done to determine if cysteine sulfinic acid or cysteic acid by itself could produce a loss of the righting reflex in mice. Mice were injected with saline (0.02 ml/kg, IP), and then 20 min later the animals were lightly anesthetized with methoxyflurane. At this time, an ICV preparatory injection was made as previously described (9, 11, 23). Forty minutes later, the mice were heavily sedated with methoxyflurane (without the LORR) and injected (5 μl) with saline, cysteine sulfinic acid or cysteic acid. The mice were observed for 2 h after drug administration.

The Antagonism of Cysteine Sulfinic Acid, Cysteic Acid, and GABA by Bicuculline Methiodide

These experiments were performed to note if bicuculline methiodide, a GABA antagonist, could reduce the effect of cysteine sulfinic acid and cysteic acid to produce a second LORR in the presence of ethanol. Animals were administered ethanol (4.2 g/kg, IP), and 20 min later a preparatory ICV injection was made as previously described. When the mice regained the righting reflex after ethanol administration, they were immediately injected ICV (5 μl) with (A) cysteine sulfinic acid (25 μmol/kg) by itself or with bicuculline methiodide (10 or 50 nmol/kg), (B) cysteic acid (25 μmol/kg) by itself or with bicuculline methiodide (10 nmol/kg) and (C) GABA (25 μmol/kg) by itself or with bicuculline methiodide (10 nmol/kg). The return of the LORR was recorded. Blood samples (20 μl) were obtained from the orbital sinus of mice when they regained the righting reflex after the ICV injection of drug or drugs.

Statistical Analysis

Significant differences were determined by analysis of variances (ANOVA). All multiple comparisons with a control and comparisons among the experimental groups were done by ANOVA followed by Scheffe's test. In the tables, data are expressed as the means ± standard error.

RESULTS

In Table 1, the data show that cysteine sulfinic acid, an excitatory amino acid, enhances the central depressant properties of ethanol. When cysteine sulfinic acid was administered ICV to animals immediately after regaining the righting reflex following ethanol injection (IP), cysteine sulfinic acid produced a return of

TABLE 1

EFFECTS OF CYSTEINE SULFINIC ACID (CSA) TO PRODUCE A RETURN TO THE LOSS OF THE RIGHTING REFLEX (LORR) IMMEDIATELY AFTER REGAINING THE RIGHTING REFLEX FOLLOWING ETHANOL (ETOH) ADMINISTRATION

Group	N	Onset to LORR (s)	ETOH-LORR (min)	CSA-Return to LORR (min)*	Blood ETOH (mg/ml)
ETOH† and Saline (Controls)	9	88 ± 3	55.6 ± 6.8	0.8 ± 0.04	3.38 ± 0.05
ETOH + CSA (1)	9	101 ± 3	55.0 ± 13.6	12.0 ± 2.9	3.25 ± 0.09
ETOH + CSA (15)	9	92 ± 5	63.9 ± 6.8	24.6 ± 2.6‡	3.15 ± 0.07
ETOH + CSA (25)	9	94 ± 2	57.4 ± 5.4	41.3 ± 6.8‡§	2.98 ± 0.05¶

*CSA injected (μmol/kg, ICV) immediately after regaining the righting reflex following ETOH administration.
†ETOH was given at 4.2 g/kg, IP.
‡Significantly different from controls ($p<0.01$).
§Significantly different from CSA (1) and CSA (15) groups ($p<0.05$).
¶Significantly different from controls ($p<0.05$).

TABLE 2

INTERACTION BETWEEN ETHANOL (ETOH) AND CYSTEIC ACID (CA) ON RETURN TO LOSS OF RIGHTING REFLEX (LORR)

Group	N	Onset to LORR (s)	ETOH-LORR (min)	CA-Return to LORR (min)†	Blood ETOH (mg/ml)
ETOH* and Saline (Controls)	8	87 ± 5	53.0 ± 3.1	1.6 ± 0.8	3.45 ± 0.03
ETOH + CA (1)	6	93 ± 3	50.8 ± 3.2	7.0 ± 2.4	3.40 ± 0.09
ETOH + CA (15)	7	94 ± 6	56.4 ± 7.7	42.8 ± 4.7†§	3.20 ± 0.17
ETOH + CA (25)	8	97 ± 5	58.8 ± 5.4	55.7 ± 8.5‡§	3.04 ± 0.12

*ETOH was given at 4.2 g/kg, IP.
†CA injected (μmol/kg, ICV) immediately after regaining the righting reflex following ETOH administration.
‡Significantly different from controls ($p<0.01$).
§Significantly different from CS (1) group ($p<0.01$).

the LORR in a dose-dependent manner. The doses of cysteine sulfinic acid at 15 and 25 μmol/kg ICV caused a 105 and 244% increase, respectively, in the duration of the return to the LORR when these doses were compared with the 1 μmol/kg dose. There was an inverse relationship between the duration of the cysteine sulfinic acid (CSA) return to the LORR and the blood ethanol concentrations which were obtained at the end of the return to the LORR period (Table 1). The onset to the LORR following ICV injection of the amino acid was approximately 30 s. In these experiments, one animal died after the ICV injection of the highest dose of cysteine sulfinic acid.

In the next experiments, cysteic acid was injected ICV in the presence of ethanol. Table 2 shows that cysteic acid caused a return to the LORR when it was administered immediately after the animal regained the righting reflex from the previous injection (IP) of ethanol. This enhancement of the central depressant effect of ethanol by cysteic acid occurred in a dose-response fashion. The onset to the return of the LORR was about 15 s after the completion of the ICV injection of cysteic acid in the presence of ethanol.

In the following experiments, cysteine sulfinic acid or cysteic acid was injected (ICV) into mice in the absence of ethanol to determine if either compound by itself could cause a loss of the righting reflex. Mice were administered saline (0.02 ml/g, IP) and then 60 min later injected (ICV) with saline, cysteine sulfinic acid (25 μmol/kg) or cysteic acid (25 μmol/kg). Each group contained 5 animals. The controls (saline), cysteine sulfinic acid group and cysteic acid group had lost the righting reflex for 0.3 ± 0.2, 1.0 ± 1.0, and 0.9 ± 0.4 min, respectively. Since these compounds did not produce any significant degree of the LORR when they were injected alone, the results in Tables 1 and 2 indicate that the combination of ethanol and cysteine sulfinic acid or cysteic acid was responsible for the observed effects (return to LORR). When cysteine sulfinic acid was injected by itself, this amino acid caused convulsions for 30 s followed by running activity for 15 s, and then the animals appeared to be calm. Two animals died from the ICV injection of cysteine sulfinic acid at 10 and 22 min postinjection. Cysteic acid injection (ICV) caused a rolling motion in the mice that lasted from 10 to 30 s. One animal exhibited convulsions and later died. No other behavioral effects were observed when cysteine sulfinic acid- or cysteic acid-treated mice were compared with control for 2 h postinjection.

In a previous work (11), GABA was administered ICV under the same experimental conditions as outlined in this study for cysteine sulfinic or cysteic acid. GABA (1, 15 or 25 μmol/kg) caused a return to the LORR in the presence of ethanol in a dose-dependent manner. Table 3 shows that bicuculline methiodide, a GABA antagonist, inhibited the effect of GABA to produce a return to the LORR. Since it is reported that cysteine sulfinic acid can cause the release of GABA in neuronal tissue (2,3), the next experiments were designed to determine if bicuculline methiodide could reduce the effect of cysteine sulfinic acid to cause a return to LORR in the presence of ethanol. In Table 4, the effect of cysteine sulfinic acid to induce a return to the LORR was antagonized by bicuculline methiodide. Blood ethanol concentrations were higher in cysteine sulfinic acid-bicuculline methiodide-treated groups than in the cysteine sulfinic acid-treated group.

The final experiments were performed to assess if the effect

TABLE 3

THE ANTAGONISM OF GABA-INDUCED RETURN TO THE LOSS OF THE RIGHTING REFLEX (LORR) BY BICUCULLINE METHIODIDE (BIC) IN THE PRESENCE OF ETHANOL (ETOH)

Group	N	Onset to LORR (s)	ETOH-LORR (min)	GABA-Return to LORR (min)†	Blood ETOH (mg/ml)
ETOH* + GABA	8	98 ± 4	53.9 ± 6.8	39.1 ± 2.8	3.00 ± 0.06
ETOH + GABA + BIC¶	8	93 ± 3	57.2 ± 6.9	2.1 ± 0.6‡	3.33 ± 0.07§
ETOH + BIC¶	7	95 ± 4	53.3 ± 6.3	0.4 ± 0.3‡	3.44 ± 0.10§

*ETOH was given at 4.2 g/kg IP.
†Drug was injected (25 μmol/kg, ICV) immediately upon regaining the righting reflex after ETOH administration (IP).
‡Significantly different from ETOH + GABA group ($p<0.01$).
§Significantly different from ETOH + GABA group ($p<0.05$).
¶BIC was given at 10 nmol/kg, ICV.

TABLE 4

ANTAGONISM BY BICUCULLINE METHIODIDE (BIC) ON THE RETURN TO THE LOSS OF THE RIGHTING REFLEX (LORR) INDUCED BY CYSTEINE SULFINIC ACID (CSA) IN THE PRESENCE OF ETHANOL (ETOH)

Group	N	Onset to LORR (s)	ETOH-LORR (min)	CSA-Return to LORR (min)†	Blood ETOH mg/ml
ETOH* + CSA	9	93 ± 4	62.2 ± 5.0	40.2 ± 5.0	2.92 ± 0.07
ETOH + CSA + BIC (10)	6	96 ± 3	55.8 ± 7.7	15.3 ± 1.7‡	3.36 ± 0.07‡
ETOH + CSA + BIC (50)	6	88 ± 4	57.3 ± 1.6	3.5 ± 0.08‡	3.38 ± 0.05‡
ETOH + BIC (10)	7	97 ± 3	63.1 ± 8.0	7.0 ± 3.1‡	3.43 ± 0.06‡
ETOH + BIC (50)	5	95 ± 2	55.4 ± 5.5	3.0 ± 1.4‡	3.43 ± 0.09‡

*ETOH was given at 4.2 g/kg, IP.

†CSA, (25 μmol/kg, ICV), BIC (nmol/kg, ICV) or CSA plus BIC was injected (ICV) immediately after regaining the righting reflex following ETOH administration.

‡Significantly different from ETOH + CSA group ($p<0.01$).

of cysteic acid to induce a return to the LORR in the presence of ethanol could be altered by ICV administration of bicuculline methiodide. The results in Table 5 showed that the GABA antagonist reduced the effect of cysteic acid to produce a return to the LORR.

In this study, when bicuculline methiodide was injected (ICV) in the absence of GABA, cysteine sulfinic acid or cysteic acid, but in the presence of ethanol, most mice exhibited an excitatory effect ranging from mild running activity to tonic-clonic convulsions. In those animals that received ICV injections of bicuculline with GABA, cysteine sulfinic acid or cysteic acid, approximately 30% of them manifested some excitatory effect when they regained the righting reflex, especially when bicuculline was administered at a dose of 50 nmol/kg.

DISCUSSION

In this investigation, cysteine sulfinic acid, an excitatory amino acid, enhances the central depressant action of ethanol. When cysteine sulfinic acid is administered ICV in the presence of ethanol, the animals return to a second loss of the righting reflex. This effect of cysteine sulfinic acid occurs in a dose-dependent manner (Table 1). Other studies show that taurine (9, 10, 18), cysteine (11), and GABA (11), which exhibit inhibitory effects in the central nervous system, also enhance the depressant properties of ethanol upon ICV administration in the same experimental design.

The effect of cysteine sulfinic acid to return animals to a second loss of the righting reflex after the initial administration of ethanol (IP) is a drug-induced effect and not related to an osmotic effect of the concentration that is injected. Other compounds that are administered ICV in similar or higher concentrations do not augment the depressant properties of ethanol (11). Although μmol/kg doses are required in these experiments, this concentration of drug in the ventricle appears to be necessary to reach the target cells, since the drug must undergo the processes of absorption and distribution in the brain. The ICV administration of GABA, an inhibitory neurotransmitter, also requires μmol/kg doses to cause a second loss of the righting reflex after ethanol (IP) injection when this ICV technique is used (Table 3) (11).

The mechanism by which cysteine sulfinic acid enhances the central depressant properties of ethanol is unknown. It might be expected that an excitatory amino acid would reduce the depressant action of ethanol, but there occurs in these experiments an enhancement of the depressant effect of ethanol. It may be that some excitatory actions of cysteine sulfinic acid are reduced by the presence of ethanol, and this effect of ethanol allows the manifestation of inhibitory properties of cysteine sulfinic acid. There is the possibility that the GABAergic system may be involved in the interaction between ethanol and cysteine sulfinic acid. Several reports indicate that cysteine sulfinic acid can release GABA from neuronal tissue (2, 3, 7, 21). One report (21) suggests that cysteine sulfinic acid causes an excitatory effect on

TABLE 5

BICUCULLINE METHIODIDE (BIC) ANTAGONIZES THE RETURN TO THE LOSS OF THE RIGHTING REFLEX (LORR) INDUCED BY CYSTEIC ACID (CA) IN THE PRESENCE OF ETHANOL (ETOH)

Group	N	Onset to LORR (s)	ETOH-LORR (min)	CA-Return to LORR (min)†	Blood ETOH (mg/ml)
ETOH* + CA	7	96 ± 5	55.8 ± 5.8	53.0 ± 6.4	3.05 ± 0.12
ETOH + CA + BIC	8	86 ± 4	53.2 ± 3.8	15.5 ± 3.1‡	3.50 ± 0.09†
ETOH + BIC	9	94 ± 4	53.3 ± 5.3	0.5 ± 0.2‡	3.47 ± 0.08

*ETOH was given 4.2 g/kg, IP.

†CA (25 μmol/kg, ICV), BIC (10 nmol/kg, ICV) or CA plus BIC was injected (ICV) immediately after regaining the righting reflex following ETOH administration.

‡Significantly different from ETOH + CA group ($p<0.01$).

§Significantly different from ETOH + CA group ($p<0.05$).

GABAergic neurons resulting in the opening of sodium channels which play a role in the release of GABA from the neurons. The ICV administration of GABA (Table 3) or cysteine sulfinic acid (Table 4) produces a return to the loss of the righting reflex in the presence of ethanol, and this effect of GABA or cysteine sulfinic acid is attenuated by the ICV administration of bicuculline, a GABA antagonist. These results suggest that a GABAergic component may be involved in the interaction between ethanol and cysteine sulfinic acid. It is also reported that the GABAergic system is involved in some of the effects of ethanol (24,25).

Another factor that should be considered in the mechanism of action for cysteine sulfinic acid to augment the depressant properties of ethanol is the metabolism of cysteine sulfinic acid (1). In the metabolic pathway of cysteine sulfinic acid, this amino acid is converted to taurine or cysteic acid. The latter is decarboxylate to taurine (12). Previous investigations show that taurine can enhance the depressant properties of ethanol (9, 10, 18). When cysteic acid is given IP to mice, it prolongs the ethanol-induced loss of the righting reflex (20). In this study, Table 2 indicates that cysteic acid produces a return to the LORR in the presence of ethanol quite similar to cysteine sulfinic acid (Table 1). In addition, this effect of cysteic acid is antagonized by bicuculline (Table 5). Although cysteine sulfinic acid can be metabolized to cysteic acid and taurine, it appears that only a small fraction is formed since most of cysteine sulfinic acid is converted to pyruvate and sulfite (8,12). When cysteine sulfinic acid is injected ICV, the onset of its effect is rapid and occurs within 30 s or less. It seems that some time would be required to convert cysteine sulfinic acid to taurine or cysteic acid since the reaction is not spontaneous in nature.

Both cysteine sulfinic acid and cysteic acid produce their effects to enhance the depressant properties of ethanol by themselves and not through biotransformation products. Although GABA may play a role in the interaction between cysteine sulfinic acid or cysteic acid, further experiments are needed to fully delineate the exact mechanism of action by which these excitatory amino acids augment the central depressant actions of ethanol.

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