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Methionine Enhances Alcohol-Induced Narcosis in Mice

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MIQUEL, M., M. CORREA AND C. M. G. ARAGON. *Methionine enhances alcohol-induced narcosis in mice.* PHARMACOL BIOCHEM BEHAV. **64**(1) 89–93, 1999—Methionine is an essential amino acid that has been used as a therapeutic drug in some disorders. In this study we questioned whether methionine affects ethanol-induced loss of righting reflex (narcosis). One hour after IP methionine administration (60, 120, 240, 480, 720, 960, and 1280 mg/kg), mice were injected with ethanol (4.0 g/kg), and the duration of loss of righting reflex was recorded. Methionine, at the higher doses (960 and 1280 mg/kg), significantly increased this effect on ethanol-treated animals. A time-course study revealed that methionine increased the duration of the loss of righting reflex induced by ethanol until 4 h after being injected. Because methionine did not affect blood ethanol levels, no change in peripheral alcohol can explain the observed effects. This potentiation was not specific for ethanol because methionine increased 3-methyl-1-butanol (0.6 g/kg) and 1-propanol (2.4 g/kg)-induced loss of righting reflex as well. Therefore, the results obtained in this study suggest the need for further investigation into methionine–ethanol interactions prior to the use of methionine as an agent that can be used as an antidepressant and to prevent damage to organic tissue in alcoholism. © 1999 Elsevier Science Inc.

Alcohol Narcosis Methionine 3-Methyl-1-butanol 1-Propanol Mice

METHIONINE is an essential amino acid that is converted into *S*-adenosyl-methionine (SAMe) in the organism (3). SAMe is synthesized by the transfer of an adenosyl group from ATP to the sulphur atom of methionine (27). In rodents, the modulation of monoamines by methionine has been reported (22). Thus, Messiha (22) demonstrated that methionine administration increases dopamine (DA) turnover in some mouse strains. In the same way, it has been shown that SAMe, in peripheral administration, also possesses central nervous system pharmacological properties, and their central actions depend on the ability of this compound to act as a methyl donor (6). Furthermore, other reports have also shown, in humans, changes in monoamine metabolism with an intraperitoneal (IP) SAMe treatment (5,18). Giving further support to the monoaminergic hypothesis of the depressive disorders, it has been proven that SAMe presents an antidepressant effect. Therefore, this compound has been successfully used as an antidepressant drug in depressive illness (1,6,8,9,26). Also, SAMe has been utilized as a therapeutic tool in fibromyalgia, because it reduces the symptoms and improves the mood of the patients (14).

On the other hand, Tabakoff, Eriksson, and von Wartburg (28) have demonstrated a physiological interaction between methionine and ethanol. Methionine reduces blood levels of acetaldehyde, the first ethanol oxidative metabolite. However, to observe these effects, methionine has to be administered 1 h prior to ethanol injection. Examination of the time course of action of this amino acid suggests that the administered methionine may need to be metabolically transformed to reduce blood acetaldehyde levels, because their effects were not observed with a simultaneous methionine administration (28). Consequent upon these results, these authors suggest that methionine could be used as an agent aimed to diminish the high circulating levels of acetaldehyde that may predispose alcoholics to tissue damage when consuming high doses of ethanol (28).

Because of the therapeutic use of methionine as an antidepressant, and because a physiological interaction with ethanol has been described, we consider that it is relevant to further investigate the putative behavioral interaction between methionine and ethanol. The aim of the present study was to analyze the effect of methionine on the ethanol-induced narcotic effect in mice. Ethanol-induced narcosis was evaluated by means of the loss of righting reflex following an injection of a high ethanol dose. Because early reports had demonstrated that methionine antagonized the lethal effect of ethanol (19),

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and the depressant effect induced by ethanol on avoidance behavior (23), we tried the narcosis test to evaluate a different ethanol-induced depressant effect.

METHOD

Animals

Swiss albino mice purchased from Interfauna Barcelona (Sprague–Dawley Co.) were used in this study. Mice were housed in groups of three or four per cage, with laboratory chow (Panlab, S. A. Spain) and tap water available ad lib. The animals were allowed 1 week of adaptation to the animal colony prior to experimentation. At the time of the experiment the animals weighed 30–35 g. Animals were maintained in rooms at 22°C with 12 L:12 D cycles. Testing was always carried out during the light cycle. All experimental procedures complied with the European Community Council Directive (86/609/ECC) for the use of laboratory animal subjects.

Drugs

L-Methionine (Sigma–Aldrich Quimica S.A. Spain) was dissolved in saline and the pH of the solution was adjusted to 3.5 with HCl. Solutions of 30, 60, 120, 240, 360, 480, and 960 mg/10 ml were prepared. For control groups, saline was adjusted at the same pH (3.5) as L-methionine solution.

Ethanol (20 and 25% v/v), 3-methyl-1-butanol (2.8% v/v) and 1-propanol (13% v/v) solutions were prepared from 95% ethanol, 98% 3-methyl-1-butanol, and 99.5% v/v 1-propanol in saline. Alcohols were purchased from Panreac Quimica, S. A. (Spain).

Procedure

Subjects received IP injections of saline or 60, 120, 240, 480, 720, 960, or 1280 mg/kg of methionine. One hour after administration, mice received an IP injection of ethanol.

To study the time course of methionine effects, mice received injections of saline or methionine (960 mg/kg) at 0, 60, 120, 240, 480, or 960 min before an IP ethanol injection (4.0 g/kg).

Specific effects of methionine on ethanol induced loss of righting reflex were analyzed challenging animals with 3-methyl-1-butanol (0.6 g/kg) or 1-propanol (2.4 g/kg), 1 h after treatment with saline or methionine (960 mg/kg). These alcohol doses produce a significant loss of righting reflex in mice (13).

In all cases, following the alcohol injections, mice were left in a Plexiglas cage until they lost the righting reflex and then, were placed on their backs in a V-shape bed. The duration of narcosis was defined as the time elapsed from loss of righting reflex to the time the righting reflex was regained (narcosis time). Recovery was determined when subjects could right themselves three times in 60 s after being placed on their backs (2). All the animals recovered the righting reflex.

Blood Ethanol Assays

To analyze blood ethanol levels, mice were treated simultaneously with methionine (960 mg/kg) or saline, and either ethanol (40 g/kg) or saline. Then, truncal blood was collected 30, 60, or 120 min after treatments. Plasma ethanol levels were enzymatically determined with an Alcohol Diagnostic Kit from Sigma–Aldrich Quimica, S.A. (Spain). Data are expressed in mg/dl.

Statistical Analysis

All data were analyzed by means of two-way ANOVAs. Tukey's tests were performed to evaluate the differences between means. The statistical computer programme Systat 5.2. by SYSTAT Inc. (IL) was used in all analysis.

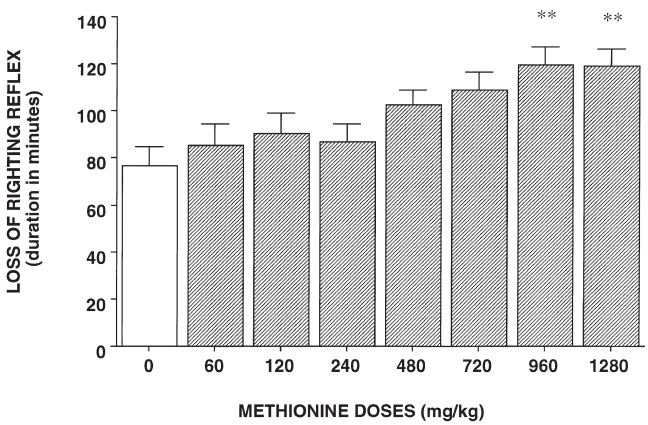

FIG. 1. Effect of methionine dose or saline on ethanol-induced loss of righting reflex. Mean ± SEM minutes for all treatment groups ($n = 14$ per group). Mice were treated with saline or methionine (60, 120, 240, 480, 720, 960, or 1280 mg/kg, IP) 1 h prior to receiving ethanol (4.0 g/kg, IP) (**$p < 0.01$). Open columns, saline; filled columns, methionine.

RESULTS

The effect of doses of methionine on ethanol-induced narcosis is presented in Fig. 1. When methionine was administered 1 h prior to saline in a preliminary study, this amino acid was unable to induce the loss of righting reflex (data not shown). A one-way analysis of variance (ANOVA) revealed a significant effect of dose of methionine, $F(7, 104 = 4.27, p < 0.001)$. Pairwise comparisons using the Tukey test revealed that doses of 960 and 1280 mg/kg boosted the loss of righting reflex on ethanol-treated (4.0 g/kg) animals ($p < 0.01$). The duration of the loss of righting reflex was 54.4% (960 mg/kg) and 52.1% (1280 mg/kg) more than control animals.

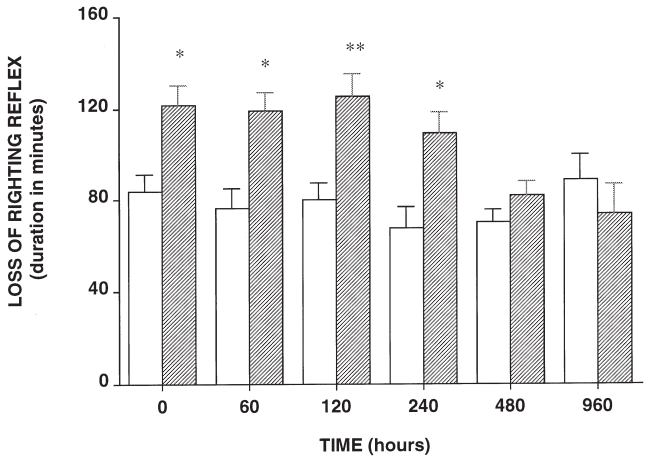

FIG. 2. Time course of methionine effect on ethanol-induced loss of righting reflex. Mean ± SEM minutes for all treatment groups ($n = 12$ per group). Mice were treated with saline or methionine (960 mg/kg, IP) at 0, 60, 120, 240, 480, or 960 min prior to an ethanol injection (4.0 g/kg, IP) (*$p < 0.05$) (**$p < 0.01$). Open columns, saline: filled columns, methionine.

TABLE 1

EFFECT OF METHIONINE OR SALINE ON 3-METHYL-l-BUTANOL AND l-PROPANOL-INDUCED LOSS OF RIGHTING REFLEX

	Saline	Methionine
3-Methyl-l-butanol	28.2 ± 1.8 (n = 12)	36.1 ± 2.2* (n = 12)
l-Propanol	121.9 ± 3.2 (n = 14)	147.8 ± 6.5† (n =14)

Mean ± SEM loss of righting reflex (duration in minutes) for 3-methyl-l-butanol and for l-propanol treatment groups. Mice were pretreated IP with saline or methionine (960 mg/kg) 1 h before 3-methyl-l-butanol (0.6 g/kg) or l-propanol (2.4 g/kg) injection.

*$p < 0.05$; †$p < 0.01$.

This effect extends to other ethanol doses. An analysis of the duration (in minutes) of the loss of righting reflex in animals treated with methionine (960 mg/kg) or saline and injected after 1 h with 4.0 (n = 14) or 4.5 g/kg (n = 14) ethanol doses demonstrated a significant effect of methionine, $F(1, 52) = 17.23$, $p < 0.01$, a significant effect of ethanol doses, $F(1, 52) = 20.13$, $p < 0.01$, and a nonsignificant interaction between the two factors $F(1, 52) = 3.66$, $p > 0.05$. The duration of the loss of righting reflex for control animals was 76.7 ± 8.3 min when administered the 4.0 g/kg ethanol dose, and 121.8 ± 5.8 min for the 4.5 g/kg ethanol dose. This study shows that methionine treatment potentiates this ethanol-induced behavior by 55.8% (4.0 g/kg) and 40.1% (4.5 g/kg).

To further evaluate the effect of methionine, ethanol was administered to mice at different times after methionine pretreatment. Figure 2 represents the time course of the effect of methionine on ethanol induced loss of righting reflex. A two-way ANOVA (methionine × time) showed a significant effect of methionine, $F(1, 152) = 29.74$, $p < 0.01$, a significant effect of time, $F(5, 152) = 3.43$, $p < 0.01$, and a significant interaction between the two factors $F(5, 152) = 3.52$, $p < 0.01$. The Tukey test between saline- and methionine-treated animals showed that methionine increased ethanol induced loss of righting reflex until 4 h after being injected ($p < 0.01$ and $p < 0.05$). Nevertheless, 4 h after methionine injection the effect declined ($p > 0.05$).

The results shown in Table 1 summarize the effects of methionine on other alcohols. A t-test for independent samples revealed that the effect of methionine is not specific for ethanol. Methionine increased 3-methyl-1-butanol ($p < 0.05$), and 1-propanol ($p < 0.01$) induced loss of righting reflex as well.

The effects of methionine on ethanol metabolism are presented in Table 2. A two-way ANOVA (methionine × time) demonstrated an effect of time, $F(2, 30) = 21.77$, $p < 0.001$, but there was neither a significant effect of methionine, $F(1, 30) = 0.034$, $p > 0.05$, nor a significant interaction of methionine and time, $F(2, 30) = 2.83$, $p > 0.05$. Therefore, methionine administration did not change blood ethanol levels compared to saline administration.

DISCUSSION

Data presented in this report demonstrated that methionine significantly boosted narcosis in ethanol-treated mice. This effect was elicited by the higher doses used in this study (960 and 1280 mg/kg). These methionine doses alone do not induce narcosis, as we were able to observe in a preliminary study. The effect of methionine was observed over a period of 4 h following the administration of this substance. Simultaneous administration of methionine and ethanol or methionine administration 1, 2 or 4 h prior to ethanol treatment, demonstrated an increase in the duration of narcosis compared to saline-pretreated mice. However, this effect was lost by prolonging the interval between pretreatment with methionine and the injection of ethanol. When methionine was administered to mice prior to the administration of other alcohols (3-methyl-1-butanol and 1-propanol), a significant lengthening of the duration of narcosis was also demonstrated.

It has been reported that methionine does not affect blood ethanol levels in mice, rats, and humans (28). Data from the present study support these results, because no change in peripheral alcohol levels were observed in methionine-pretreated mice compared to saline-pretreated mice. Therefore, changes in blood ethanol levels cannot explain the observed effects.

Even though the mechanism by which IP administered methionine boosts alcohol-induced narcosis remains unclear, some processes could be discussed in an attempt to provide a rational explanation of the effect of methionine on this ethanol- and alcohols-induced narcosis.

It is well known that methionine has a modulatory action on monamines and phospolipids (6,22). This action is probably exerted by means of the ability of SAMe to transfer methyl groups to them (6,22). In cell membranes, the methylation of phospholipids could increase membrane fluidity (12). Because membrane protein function, in part, depends on the physical condition of the membrane lipid environment, affecting lipid domains could result in changes in the normal functions of the neurone (20). It is interesting to note that ethanol, like other alcohols, increases the molecular motion within the bilayer of biological membranes, particularly, if these alcohols are in high concentration (higher than 50 mM for ethanol) (20,31). It has been suggested that this action on the cell membranes could explain some of the ethanol-induced intoxicating effects (7). In the present study, the administration of an ethanol dose of 40 g/kg produced ethanol levels higher than 50 mM during all time tested. Because we induced the loss of

TABLE 2

EFFECT OF METHIONINE OR SALINE ON BLOOD ETHANOL LEVELS

	Blood Ethanol (mg/dl)		
	30 min	60 min	120 min
Saline–ethanol	466.3 ± 22.3 (n = 6)	384.0 ± 27.4 (n = 6)	309.1 ± 10.8 (n = 6)
Methionine–ethanol	424.0 ± 6.1 (n = 6)	394.2 ± 3.8 (n = 6)	349.6 ± 7.9 (n = 6)

Mean ± SEM blood ethanol levels for all treatment groups. Mice were pretreated with methionine (960 mg/kg) or saline, and then were injected with saline or ethanol (40 g/kg). Truncal blood was collected 30, 60, or 120 min after ethanol injection. Data are expressed in mg/dl.

righting reflex with an ethanol dose of 40 g/kg, the effects of methionine on alcohol-induced narcosis could be explained through a synergistic action carried out by both compounds on membrane fluidity.

On the other hand, as Tabakoff et al. (28) reported, methionine has the ability to lower circulating blood acetaldehyde levels. However, the time course of action for behavioral and physiological effects of methionine upon ethanol is different. Thus, methionine potentiation of the ethanol-induced loss of righting reflex took place immediately following methionine administration, but methionine needed to be administered 1 h before ethanol to reduce acetaldehyde levels. Moreover, the present study demonstrated that methionine also increased the loss of righting reflex produced by other alcohols, which are not metabolized to acetaldehyde. In addition, so far no data are found to demonstrate any relationship between peripheral acetaldehyde and ethanol-induced narcosis. Hence, methionine enhancement of ethanol-induced narcosis could not take place through the decrease of blood acetaldehyde levels. On the other hand, methionine is a precursor in the synthesis of other amino acids like cysteine and taurine in the organism (29,30), and it has been reported that cysteine and taurine also reduce blood acetaldehyde levels in rodents (24,25,29,30). The hypothesis that methionine could exert its effect through its conversion to cysteine has been postulated (28). However, as some studies have shown, both cysteine and taurine in a peripheral administration, reduce, instead of boosting, ethanol-induced loss of righting reflex (4,15,21).

Finally, our results agree remarkably well with those of other authors, who reported enhancement of sleeping time in response to ethanol and barbiturates with prior administration of l-asparagine (11) and l-tryptophan (16). Also, they reported that pretreatment of rats with these amino acids significantly decreased the LD_{50} previously determined for ethanol (11,16). The parallel effects of the three amino acids, potentiation of the loss of righting reflex, and protection against ethanol-induced lethality, may suggest a common mechanism of action. In this context, it is interesting to note, for example, that administration of methionine or tryptophan lead to a decrease in the nicotinamide adenine dinucleotide (NAD) content in the brain (17), and simultaneous injections of either methionine or tryptophan and ethanol caused similar alterations in the serum enzyme activities of rats (17). Moreover, the finding that methionine is able to alter the duration of narcosis induced by other alcohols, besides ethanol, indicates that the effect of these three amino acids is probably nonspecific for ethanol, and it is produced by means of a general mechanism shared by the three amino acids.

In conclusion, methionine administration is capable of eliciting potentiation of ethanol-induced loss of righting reflex in a dose- and time-dependent manner. A central interaction between methionine and ethanol may well be operative, and cannot be disregarded. It has been suggested that methionine could be used as a substance to diminish the high circulating levels of acetaldehyde that may predispose ethanol-consuming alcoholics to tissue damage (19,28). Moreover, some studies have informed that SAMe treatment did not have adverse effects when used as antidepressant therapy (1,8,9,10). However, methionine's ability to boost the ethanol-induced narcotic effect should be borne in mind. Therefore, the results obtained in this study suggest the need for further investigations on methionine-ethanol interactions prior to the use of methionine as an antidepressant agent and for preventing organic tissue damage in alcoholism.

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