Pharmacology Biochemistry & Behavior, Vol. 33, pp. 269–271. © Maxwell Pergamon Macmillan plc, 1989. Printed in the U.S.A. 0091-3057/89 $3.00 + .00

BRIEF COMMUNICATION

Administration of a GABA Antagonist Selectively Attenuates an Ethanol-Induced Conditioned Taste Aversion

BRIAN R. SMITH,[1] RENEE B. SEGAL AND ZALMAN AMIT

Centre for Studies in Behavioral Neurobiology, Department of Psychology
Concordia University, Montreal, Quebec, Canada, H3G 1M8

Received 15 July 1988

SMITH, B. R., R. B. SEGAL AND Z. AMIT. *Administration of a GABA antagonist selectively attenuates an ethanol-induced conditioned taste aversion.* PHARMACOL BIOCHEM BEHAV **33**(1) 269–271, 1989.—Pretreatment with the GABA antagonist picrotoxin attenuated the development of an ethanol-induced conditioned taste aversion (CTA), while no effect of this compound was observed on the development of an amphetamine-induced CTA. These findings suggested some specificity of the effects of picrotoxin to the psychopharmacological properties of ethanol related to CTA. On the other hand, the benzodiazepine inverse agonist, Ro15-4513, purported to a specific ethanol antagonist, was shown to attenuate both an ethanol- and amphetamine-induced CTA. The results support the notion that ethanol intoxication may be mediated in part by GABAergic mechanisms. These GABA-mediated properties of ethanol may in fact underlie the development of an ethanol-induced CTA.

GABA Picrotoxin Ro15-4513 Ethanol Conditioned taste aversion Amphetamine

IT has long been known that the administration of ethanol (EtOH) can produce biphasic effects in a variety of observed behaviors and in the actions of some central neurochemical processes (9). These biphasic effects are often characterized by an initial period of behavioral excitation which is subsequently followed by an increased inhibition usually observed as physical intoxication or sedation (9). It has been suggested that the behavioral excitation produced by EtOH may be mediated through the activation of catecholaminergic systems (4), while EtOH's physical intoxicating effects have been proposed to be mediated by GABAergic mechanisms (4).

GABAergic involvement in EtOH intoxication has been demonstrated in a number of behavioral paradigms including locomotor activity and sleep time in mice (3,7) and the tilt plane test using rats (5). A facilitation of GABAergic mechanisms was found to enhance EtOH intoxication as evidenced by increased locomotor sedation and longer sleep time observed in these animals (7). Furthermore, GABA antagonists were reported to block intoxication by EtOH as shown by improvements in tilt plane performance (5), increases in EtOH-induced locomotor stimulation and reduced duration of EtOH-induced sleep time (7). These studies support the notion that EtOH's intoxicating effects may be, at least in part, mediated by GABA processes.

No study has yet examined the role of GABA mechanisms in EtOH-induced conditioned taste aversion (CTA). It has been proposed that CTAs which are consistently observed following the administration of all psychoactive drugs are mediated by the psychopharmacological properties of these drugs (6,12). It has been proposed that these psychopharmacological properties may paradoxically be the same ones which underlie drug self-administration (6). These authors argued that the "positive" and "aversive" properties of psychoactive drugs which are seemingly reflected in self-administration and CTA studies are in fact functionally related and are mediated by the same neural substrate (6). EtOH and amphetamine (AMPH), two readily self-administered agents which are known to have distinctive pharmacological action, both pro-

[1]Requests for reprints should be addressed to Brian R. Smith, Ph.D., Centre for Studies in Behavioral Neurobiology, Department of Psychology, Concordia University, 1455 de Maisonneuve Blvd., W., H-1013, Montreal, Quebec, Canada, H3G 1M8.

duce a reliable CTA (1,12). The purpose of the present study was to investigate the possible involvement of GABAergic mechanisms in the mediation of EtOH- and AMPH-induced CTAs.

EXPERIMENT 1

METHOD

Subjects

Thirty-seven male Long-Evans rats (Charles River Canada) weighing 225–250 g were individually housed in a room controlled for constant temperature and humidity and a 12-hr on/off light schedule. Food and water were available ad lib until the animals reached a minimum weight of 300 g.

Procedure

The animals were first deprived of water for 23 hr 40 min daily. Animals were given access to water in plastic tubes with stainless steel ball-bearing spouts for 20 min daily between 1030–1130 hr. Fluid intake was measured for each session and this procedure was maintained until stable drinking scores were obtained.

On test day one (P1) all animals received sodium saccharin solution (1% w/v) in place of water during their drinking session. Pretreatment consisted of injections of either saline (IP) or picrotoxin (1 mg/kg/ml; IP), injected 30 min prior to saccharin presentation. Saccharin drinking levels were recorded to the nearest ml for P1 which constituted the baseline scores. Immediately after removal of the saccharin, one of three conditioning treatments was administered; saline (IP), EtOH (1.2 g/kg; 20% v/v; IP) or d/l AMPH (2.0 mg/kg/ml; IP). Animals were randomly assigned to treatment conditions such that all groups contained at least 6 animals. The selection of conditioning doses was based on previous studies examining the effects of these agents in CTA (1,12). On day 7 (P2), the same procedure as for P1 was again carried out. On test days 13 and 19 (T1 and T2, respectively), no drug treatments were administered and animals received saccharin in place of water for these drinking periods. On all intervening days animals received water over the 20-min drinking sessions.

RESULTS

ANOVA, performed on the data obtained from P2, T1, and T2, revealed a significant effect of conditioning drug on saccharin intake, $F(2,31)=26.90$, $p<0.05$. Both EtOH and AMPH induced CTAs of comparable magnitude (see Fig. 1; post hoc Tukey, $p<0.05$). Conditioning with these drugs resulted in a decrease in saccharin intake as compared to baseline. There was a significant effect of pretreatment with picrotoxin, $F(1,31)=5.25$, $p<0.05$, and an interaction between picrotoxin pretreatment and conditioning drug, $F(2,31)=5.69$, $p<0.05$. Post hoc tests revealed that the effect of picrotoxin was specific only to the animals conditioned with EtOH ($p<0.05$) as picrotoxin attenuated the development of an EtOH-induced CTA but did not alter the AMPH CTA.

EXPERIMENT 2

The administration of Ro15-4513, a benzodiazepine receptor inverse agonist, was recently reported to antagonize EtOH's intoxication effects in laboratory rats (13). This manipulation has also been reported to suppress operant responding for access to oral EtOH in the same species (10). Given the previous experiment's finding of picrotoxin blockade of EtOH-induced CTA, Ro15-4513 effect on EtOH and AMPH CTA was examined.

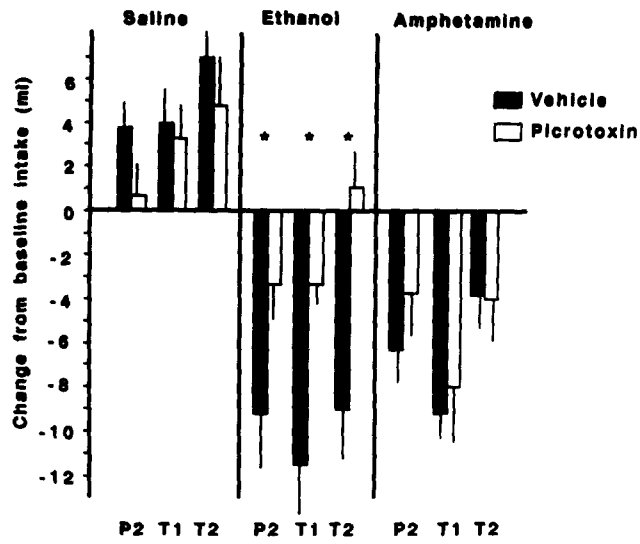

FIG. 1. Effect of picrotoxin pretreatment on ethanol- and amphetamine-induced CTA. Vertical lines represent SEM. *$p<0.05$.

METHOD

The same procedure as used in Experiment 1 was carried out in this experiment with the following changes. Ro15-4513 (3 mg/kg/ml; IP; graciously supplied by Drs. W. Haefely and R. Eigenmann, Hoffmann-La Roache, Basel, Switzerland) was used in the pretreatment condition in place of picrotoxin. Thirty-eight Long-Evans rats were randomly assigned to the various treatment conditions such that group size was between 6–8 animals.

RESULTS

Consistent with the results of Experiment 1, there was a significant effect of conditioning drug on saccharin intake, $F(2,36)=14.93$, $p<0.05$. Post hoc analysis revealed that both EtOH and AMPH administration resulted in significant CTAs. In addition, there was a significant effect of pretreatment of Ro15-4513 on the

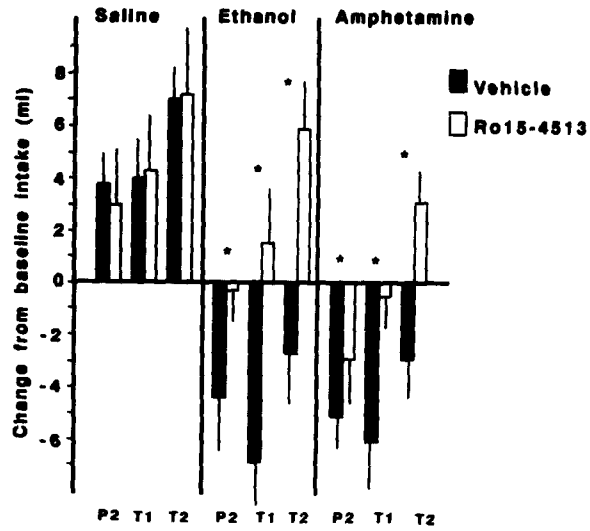

FIG. 2. Effect of Ro15-4513 pretreatment on ethanol- and amphetamine-induced CTA. Vertical lines represent SEM. *$p<0.05$.

development of these CTAs, $F(1,36) = 9.81$, $p < 0.05$. The interaction between pretreatment and conditioning drug was significant at an alpha level equal to 0.08, $F(2,36) = 2.71$, $p = 0.08$. Tests of simple main effects revealed that Ro15-4513 was equally effective in attenuating both an EtOH- and AMPH-induced CTA.

GENERAL DISCUSSION

The findings of the present study suggest that GABAergic mechanisms may play an improtant role in the mediation of an EtOH-induced CTA. It was observed that pretreatment with picrotoxin was sufficient to attenuate EtOH's induction of a CTA. This action of picrotoxin appeared to be specific to EtOH since no similar alteration in the development of an AMPH CTA was observed. These findings are in agreement and tend to support the notion that GABA may play a specific role in the actions of EtOH in general (4, 5, 7) and in EtOH CTA in particular. It has been proposed that EtOH may potentiate and stimulate GABA receptor coupled chloride ion channel function (14). Picrotoxin is believed to block chloride influx at this specific ionophore (11). The results of the present study are consistent with previous research which has demonstrated that picrotoxin administration attenuated EtOH-induced physical intoxication as measured on titled plane (5) and locomotor depression (7). Given GABA's putative role in the mediation of physical intoxication produced by EtOH, the present findings suggest that these intoxicating effects may serve as important stimulus cues in the development of an EtOH CTA.

Ro15-4513 was also seen to attenuate an EtOH CTA, however, in contrast to the effects seen with picrotoxin, it was equally effective in reducing the magnitude of an AMPH CTA. The effects seen with Ro15-4513 on AMPH CTA may be reflective of its nonspecificity with regards to EtOH as there is now increasing evidence indicating that Ro15-4513's action on EtOH-induced behaviors may be the result of non-EtOH specific mechanisms (2,8).

Several studies have indicated that there may be common mechanisms which underlie CTA and self-administration of drugs of abuse (6), therefore, it is possible that these same physical intoxication properties of EtOH may also serve as important cues in voluntary EtOH intake. In conclusion, the data obtained in the present study support the notion that GABAergic mechanisms may be involved in the mediation of several of the psychopharmacological effects of EtOH.

REFERENCES

1. Booth, D. A.; Pilcher, C. W. T.; D'Mello, G. D.; Stolerman, I. P. Comparative potencies of amphetamine, fenfluramine and related compounds in taste aversion experiments in rats. Brain Res. Bull. 61:669–677; 1977.
2. Britton, K. T.; Ehlers, C. L.; Koob, G. F. Is ethanol antagonist Ro15-4513 selective for ethanol? Science 239:648–650; 1988.
3. Dudek, B. C.; Fanelli, R. J. Effects of gamma-butyrolactone, amphetamine and haloperidol in mice differing in sensitivity to alcohol. Psychopharmacology (Berlin) 68:89–97; 1980.
4. Engel, J.; Liljequist, S. The involvement of different central neurotransmitters in mediating stimulatory and sedative effects of ethanol. In: Pohorecky, L.; Brick, J., eds. Stress and alcohol use. New York: Elsevier/North Holland; 1983:153–169.
5. Hakklinen, H-M.; Kulonen, E. Ethanol intoxication and γ-aminobutyric acid. J. Neurochem. 27:631–633; 1976.
6. Hunt, T.; Amith, Z. Conditioned taste aversion induced by self-administered drugs: Paradox revisited. Neurosci. Biobehav. Rev. 11:107–130; 1987.
7. Liljequist, S.; Engel, J. Effects of GABAergic agonists and antagonists on various ethanol-induced behavioral changes. Psychopharmacology (Berlin) 78:71–75; 1982.
8. Lister, R. G.; Nutt, D. J. Is Ro15-4513 a specific alcohol antagonist? Trends Neurosci. 10:223–225; 1987.
9. Pohorecky, L. A. Biphasic action of ethanol. Biobehav. Rev. 1: 231–240; 1976.
10. Samson, H. H.; Tolliver, G. A.; Pfeffer, A. O.; Sadeghi, K. G.; Mills, F. S. Oral ethanol reinforcement in the rat: Effect of partial inverse benzodiazepine agonist Ro15-4513. Pharmacol. Biochem. Behav. 27:517–519; 1987.
11. Simmonds, M. Classification of some GABA antaognists with regard to site of action and potency in slices of rat cuneate nucleus. Eur. J. Pharmacol. 80:347–358; 1982.
12. Sklar, L. S.; Amit, Z. Manipulations of catecholamine systems block the conditioned taste aversion induced by self-administered drugs. Neuropharmacology 16:649–655; 1977.
13. Suzdak, P. D.; Glowa, J. R.; Crawley, J. N.; Schwartz, R. D.; Skolnick, P. and Paul, S. M. A selective imidazobenzodiazepine antagonist of ethanol in the rat. Science 234:1243–1247; 1986.
14. Suzdak, P. D.; Schwartz, R. D.; Skolnick, P.; Paul, S. M. Ethanol stimulates γ-aminobutyric acid receptor-mediated chloride transport in rat brain synaptoneurosomes. Proc. Natl. Acad. Sci. USA 83: 4071–4075; 1986.