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Reduced Tolerance to Certain Pharmacological Effects of Ethanol After Chronic Administration in Perinatally Undernourished Rats

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CORDOBA, N. E., C. M. BORGHESE, M. P. AROLFO AND O. A. ORSINGHER. *Reduced tolerance to certain pharmacological effects of ethanol after chronic administration in perinatally undernourished rats.* PHARMACOL BIOCHEM BEHAV. **57**(4) 659–663, 1997.—We have previously reported that recovered adult rats undernourished at perinatal age failed to develop tolerance to the anticonflict effect of ethanol after chronic ethanol administration (1 g/kg/day during 30 days) (4). To further study the extent of this finding, we examined the effect of a similar chronic ethanol treatment on the hypothermic and anticonvulsant effects of ethanol in perinatally deprived rats. Hypoalgesic activity was assessed in ethanol treated rats during 15 days. After chronic ethanol treatment, a similar development of tolerance to the hypothermic effect of ethanol was observed in control and deprived rats. However, tolerance to the anticonvulsant and hypoalgesic effect of ethanol was significantly reduced in deprived as compared with control animals. Thus, early undernutrition differentially affects the development of tolerance elicited by chronic ethanol administration. © 1997 Elsevier Science Inc.

Perinatal undernutrition Chronic ethanol Tolerance Hypothermia Hypoalgesia Anticonvulsant Rat

SEVERAL lines of evidence have proved that perinatal undernutrition induces changes in different neurotransmitter systems, which persist even after a long period of nutritional recovery (24). These changes may account for altered reactivity to different agonists, acting both at central or peripheral levels (1,3,6,7). As regards drugs with anxiolytic effect, such as ethanol and diazepam, changes in reactivity in opposite directions were detected in adult rats undernourished at perinatal age. Thus, after acute treatment, they developed a higher hypothermic response than that observed in controls (2,5), while a reduced reactivity to the anxiolytic effect was detected on different tasks (3,5). Following a chronic ethanol treatment (1 g/kg/day during 30 days), controls developed tolerance to the anxiolytic effect assessed in the elevated plus-maze test. Conversely, perinatally deprived rats showed an increased reactivity to the anticonflict effect of ethanol together with a significant increase in the number of $GABA_A$ receptor sites from cerebral cortex (4).

Although ethanol affects different neurotransmitter, neuromodulator, and neuroendocrine systems (20,22), a good amount of evidence demonstrates that ethanol, like benzodiazepines and barbiturates, exerts its anxiolytic, sedative, hypnotic, and anticonvulsant effect through the supramolecular $GABA_A$ receptor, increasing the chloride ion conductance. Ethanol enhances the neuronal GABA inhibition (18), and facilitates chloride flux through $GABA_A$ receptor-linked channel (21,23).

Following chronic ethanol exposure, development of tolerance to different effects of ethanol, such as hypothermia, ataxia, startle response and analgesia have been described (20). Tolerance to the hypothermic effect of ethanol involves specific 5-HT pathways, since lesions of the median raphe nucleus impair the development of tolerance to this effect (11). As regards the molecular/cellular mechanisms involved in the development of tolerance, it has been reported that chronic ethanol exposure reduces $GABA_A$ receptor-mediated $^{36}Cl^-$

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uptake in cortical synaptoneurosomes, as well as the ethanol enhancement of muscimol stimulated $^{36}Cl^-$ uptake (16,17). Furthermore, chronic ethanol exposure induces a significant reduction in brain $GABA_A$ receptor α-subunit mRNA (13,17). Thus, it has been postulated that functional alterations of the $GABA_A$ receptor-complex may account for development of tolerance and symptoms of withdrawal following chronic ethanol exposure (16).

Tolerance is a complex phenomenon involving adaptive changes in different neurotransmitter and/or neuromodulator systems. Development of tolerance may depend on several factors, such as duration of treatment, inter-dose interval, and the behavioral effect under study. On the other hand, early undernutrition induces changes in reactivity to different pharmacological treatments, both after acute or chronic administration (12). Thus, the aim of the present study was to investigate whether the lack of tolerance to the anxiolytic effect of ethanol following chronic administration observed in perinatally undernourished rats, may extend to other pharmacological parameters. Accordingly, we assessed the hypothermic, anticonvulsant, and hypoalgesic effects of ethanol both in control and deprived rats submitted to a repeated ethanol schedule.

METHOD

Animals

A protein deprivation schedule, as previously described, was used (5). Briefly, female pregnant rats (Wistar strain, from our own colony) were divided into two groups at 14th day of pregnancy, housed in individual polyethylene cages and fed isocaloric diets containing 24 and 8% casein (controls and protein-deprived, respectively). Diet composition is described in Table 1. Litters from both groups were culled to eight pups. After weaning (30 days), pups continued consuming the same diet as their dams until the end of the deprivation period (50 days of age). Thereafter, both groups were given balanced standard chow for at least 40 days prior to trials. In all experiments, only one animal within each control and deprived group came from the same litter, thus sibling replication was consistently avoided. Since the reported lack of tolerance to the anxiolytic effect of ethanol was assessed in deprived female rats, 4–6 month old female rats were used in all experiments.

TABLE 1
DIET COMPOSITION

Ingredient	Control (g/kg diet)	Deprived (g/kg diet)
Casein	240.0	80.0
Sucrose	444.5	580.2
Cornstarch	103.0	137.3
Hydrogenated vegetable oil	150.0	150.0
Corn oil	9.2	9.2
Vitamin mix*	12.5	12.5
Minerals†	40.0	40.0
DL-Methionine	4.0	4.0

*Provided (mg/kg diet): *p*-aminobenzoic acid, 110; ascorbic acid, 1018; biotin, 0.44; vitamin B-12, 7.5; calcium D-pantothenate, 66; choline chloride, 1756.7; folic acid, 2; inositol, 2; menadione, 50; nicotinic acid, 99; pyridoxine, 22; riboflavine, 22; thianine chloride, 22; vitamin A (200,000 IU/g), 250; all *rac*-α-tocopherol (1000 IU/g), 200; vitamin D (150,000 IU), 3.8.

†Provided (g/kg diet): $CaCO_3$, 21.7; $MgCO_3$, 1; $MgSO_4$, 0.64; NaCl, 2.8; KCl, 2.5; KH_2PO_4, 8.5; $FeCl_3{\cdot}6H_2O$, 0.9; Kl, 0.0032; $MnCl_2$, 0.012; NaF, 0.004; $Al(SO_4)_2K$, 0.047; $CuSO_4{\cdot}5H_2O$, 0.036.

Animals were maintained at 22 ± 2°C in a 12L:12D cycle (lights on at 0700 h). Operators followed the guidelines to the Guide for the Care and Use of Laboratory Animals (NCR, 1985).

Chronic Ethanol Administration

In experiments carried out to assess the effect of chronic ethanol administration on the hypothermic and anticonvulsant effects, rats of both groups (control and deprived), were treated IP during 30 days with ethanol (1 g/kg/day, 20% V/V in saline) or equal volume of saline. Based on a pilot study, the effect of chronic treatment on the hypoalgesic activity of ethanol was determined in rats treated during 15 days with a similar administration schedule.

Hypothermic Response After Chronic Ethanol Administration

Control and deprived rats, from different litters, weighing 266 ± 9 and 195 ± 5 g, respectively, at the outset of the treatment, were allocated in two groups (saline or ethanol) for each nutritional state, and treated daily during 30 days according to the schedule previously described. The day after the last injection, basal values of rectal temperature were measured by inserting a lubricated ALKZ electronic thermometer 5 cm into the rectum for 30 sec or longer until a stable reading was obtained. After this, the hypothermic effect of 1.5 g/kg IP of ethanol was measured at 15, 30, 45, 60 and 90 min after ethanol injection at room temperature. The hypothermic effect was expressed as the maximum change in rectal temperature calculated as the difference between the basal value and its maximal drop over the lapse studied. Differences between groups were analyzed by two-way ANOVA and subsequent post-hoc comparisons were performed using Fisher's Protected Least Significant Difference test.

Antagonism of the Convulsant Effect Induced by Pentylenetetrazol Following Chronic Ethanol Administration

Control and deprived rats, from different litters, weighing 240 ± 4 and 198 ± 6 g, respectively, at the beginning of treatment, were chronically treated with saline or ethanol during 30 days according to the schedule previously described. On day 31, anticonvulsant activity was evaluated against tonic-clonic seizures induced by pentylenetetrazole (PTZ) in chronically ethanol or saline treated rats of both groups (control and deprived). Saline or ethanol (1.5 g/kg IP) was administered 30 min before IP injection of PTZ (55 mg/kg IP). Thereafter, three groups per each nutritional state were defined: chronic saline-saline, chronic saline-ethanol and chronic ethanol-ethanol. Animals were observed for occurrence of seizures within 1 h after PTZ administration and anesthetized with ether immediately after the onset of seizures. Differences between groups were analyzed by Fisher Exact test.

Hypoalgesic Effect of Ethanol After Chronic Ethanol Administration

The hypoalgesic effect of ethanol after chronic ethanol treatment was assessed in groups of control and deprived rats, weighing 251 ± 4 and 196 ± 9 g, respectively, at the beginning of treatment. Two groups for each nutritional state were allo-

cated (saline or ethanol) and treated during 15 days, as previously described. The day after the last chronic saline or ethanol administration, hypoalgesic effect was assessed by means of the Tail-flick latency procedure (Tail-flick Unit, Ugo Basile, Varese, Italy). After determination of baseline latency, control and deprived rats chronically treated with saline or ethanol, were injected with ethanol (1.5 g/kg IP) and Tail-flick latency was estimated every 20 min for 2 h. Results were analyzed by two-way Repeated Measures ANOVA; subsequent post-hoc comparisons were performed using Scheffé Post-hoc test and Fisher's Protected Least Significant Difference test.

RESULTS

Hypothermic Response to Ethanol Following Chronic Administration

The hypothermic response elicited by acute ethanol after chronic saline administration was significantly higher in deprived animals as compared with controls [$F(1,18) = 37.0, p < 0.001$]. Following chronic ethanol treatment, a lower response was detected in both control and deprived rats [$F(1,18) = 10.5, p < 0.001$] showing similar tolerance development (Fig. 1). No significant interaction (diet × treatment) effect was observed.

Anticonvulsant Effect of Ethanol Following Chronic Administration

Figure 2 shows the influence of chronic ethanol treatment on the anticonvulsant effect of this drug. In saline treated groups, seizures elicited by PTZ were observed in 86% (12/14) of controls and in 100% (13/13) of deprived rats (n.s.). Acute ethanol was able to reduce seizures up to 0% (0/16) in controls and up to 20% (3/15) in deprived animals (n.s.). Chronic ethanol administration induced development of partial tolerance to the anticonvulsant effect in controls (44%, 7/16) but not in deprived rats, since the percentage of animals undergoing seizures was not modified in deprived rats, as compared to the respective saline treated group (19%, 3/16).

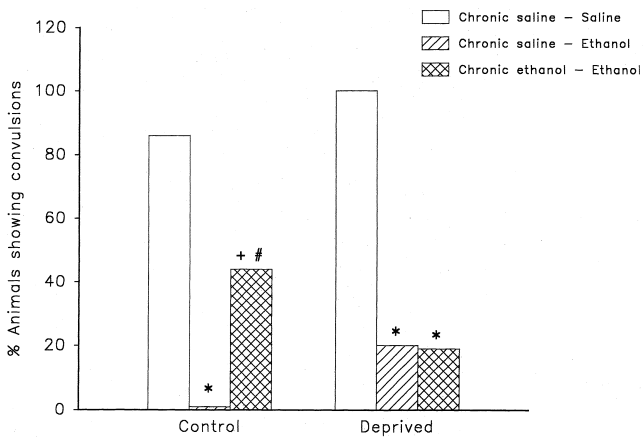

FIG. 2. Anticonvulsant effect of ethanol (1.5 g/kg IP) administered 30 min before PTZ (55 mg/kg IP) in control and deprived animals chronically treated with saline or ethanol (1 g/kg/day IP for 30 days). Bars represent % animals with convulsions after PTZ. n = 13-16 rats/group. *Significantly different from respective chronic saline-saline group, $p < 0.001$; $^{+}$Significantly different from control chronic saline-ethanol group, $p < 0.005$; $^{\#}$Significantly different from control chronic saline-saline group, $p < 0.05$.

Hypoalgesic Effect of Ethanol Following Chronic Administration

The hypoalgesic effect of ethanol, determined by the Tail-flick latency in both control and deprived rats after repeated saline or ethanol treatment is shown in Fig. 3. A three-way ANOVA revealed a significant interaction effect between treatment, diet and latency [$F(6, 264) = 2.519, p < 0.05$]. Post-hoc Scheffé test demonstrated that chronic ethanol administration induced a significant reduction in the hypoalgesic effect of ethanol in controls ($p < 0.0001$) but not in deprived animals (a significant difference was observed only at 20 min). Saline treated deprived animals showed a milder hypoalgesic

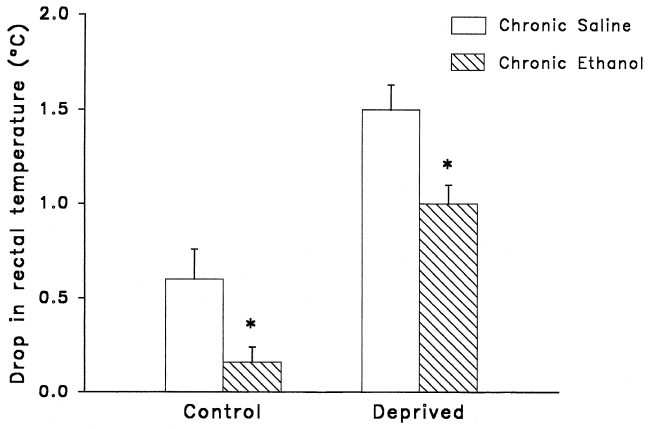

FIG. 1. Hypothermic effect of ethanol (1 g/kg IP) in control and deprived animals chronically treated with saline or ethanol (1 g/kg/day IP for 30 days). Bars represent means ± S.E.M. of 6 animals. *Significantly different from respective chronic saline treated group, $p < 0.05$.

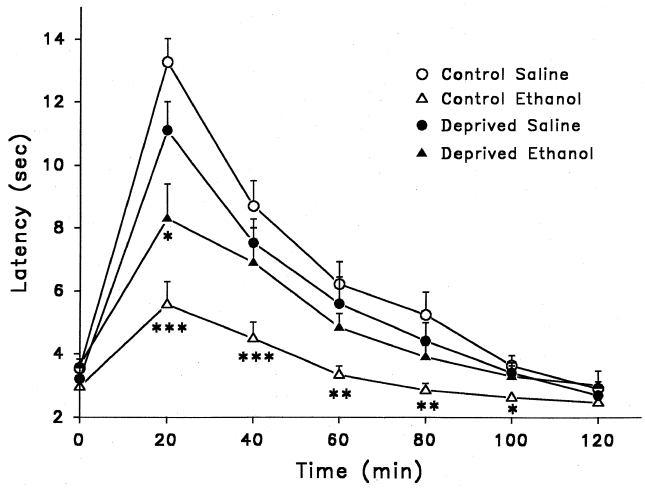

FIG. 3. Hypoalgesic effect of ethanol (1.5 g/kg IP) in control and deprived animals chronically treated with saline or ethanol (1 g/kg/day IP for 15 days). Each point is the mean ± S.E.M of 11–12 animals. Significantly different from respective chronic saline group, *$p < 0.05$, **$p < 0.005$, ***$p < 0.001$.

response to ethanol than controls after acute ethanol administration (non-significant difference).

DISCUSSION

We have previously reported that a mild chronic ethanol treatment to control rats induced tolerance to the anticonflict effect of ethanol as well as cross-tolerance to diazepam and pentobarbital when assayed in the elevated plus-maze test. Conversely, perinatally undernourished rats submitted to a deprivation schedule similar to that used in our experiments showed an increased reactivity to the anticonflict effect of ethanol and lack of cross-tolerance to diazepam and pentobarbital. In addition, chronic ethanol treatment did not modify the $GABA_A$ receptor binding in brain cortex in controls, but induced a significant increase in the density of $GABA_A$ receptors in deprived animals (4).

In the present study, we assessed whether the lack of tolerance development to the anticonflict effect of ethanol detected in deprived rats after chronic ethanol administration also applied to other parameters, such as hypothermic, hypoalgesic and anticonvulsant effects.

In agreement with a previous report (5), in chronically saline treated rats, acute ethanol provoked a higher hypothermic response in deprived as compared with control animals. Following chronic ethanol administration, a similar reduction in the hypothermic response elicited by ethanol was observed in both control and deprived rats, indicating the development of similar tolerance in both groups. Development of tolerance to the hypothermic effect of ethanol is delayed after lesions of the median raphe nuclei, indicating that the functional integrity of the 5-HT mesolimbic pathway is necessary for the development of tolerance after chronic ethanol exposure (11). It is interesting to point out that perinatally undernourished rats showed an altered response to the hypothermic effect of different agonists after acute administration (2). Thus, apomorphine, naphazoline and diazepam, like ethanol, elicited a higher than normal hypothermic response in deprived rats, whereas clonidine showed a lower effect. In particular, 5-methoxy-N,N-dimethyltryptamine (5-MeODMT), a $5\text{-}HT_1$ agonist, showed a similar hypothermic response in control and deprived animals, suggesting that 5-HT pathways involved in temperature regulation are not significantly affected by early undernutrition. Thus, it is possible that the 5-HT pathways involved in the development of tolerance to the hypothermic effect of ethanol are not affected in deprived animals, and consequently a similar degree of tolerance develops in both groups.

Pharmacological effects of ethanol have been attributed to different mechanisms, such as changes in neural membrane fluidity or alterations in different neurotransmitter/neuromodulator systems. Furthermore, noradrenergic, serotonergic and vasopressin neurons have been involved in the development of tolerance to ethanol (20,22). Notwithstanding, an increasing body of evidence suggests that some of the effects of ethanol, like those of benzodiazepines and barbiturates, are exerted specifically through the supramolecular $GABA_A$ receptor-linked channel, increasing the transmembrane chloride flux (18,21,23). After chronic ethanol exposure, down-regulation of different $GABA_A$ receptor α-subunit mRNAs has been reported and this fact may account for development of tolerance and symptoms of withdrawal (13,14). Thus, it is possible that deprived rats cannot develop adaptive changes, and consequently, development of tolerance to the convulsant effect of PTZ is impaired.

Different lines of evidence demonstrate that ethanol induced analgesia is ruled by opioid and non-opioid mechanisms. Thus, naloxone partially antagonizes the analgesic effect of ethanol (19) and chronic ethanol exposure decreases the affinity of opioid receptor binding (20). On the other hand, it was reported that MK-801, an NMDA receptor antagonist, blocks the non-opioid component of the ethanol induced analgesia, and the associated treatment of naloxone and MK-801 completely antagonizes the ethanol induced analgesia (15). Consequently, it is possible that changes in the opioid and/or NMDA receptor functions may be engaged in the development of tolerance to the analgesic effect of ethanol, and the induction of such changes may be impaired as a consequence of early undernutrition. Further studies are desirable in order to investigate the effects of perinatal undernutrition on the functional state of these neuronal systems under basal conditions and after chronic ethanol exposure.

The possibility that differences in reactivity to ethanol detected in deprived rats after chronic ethanol administration were a consequence of dispositional changes might be ruled out for the following reasons:

1. As previously reported, after acute (5) or chronic ethanol administration (4), ethanol clearence rate did not differ between control and deprived rats submitted to a deprivation schedule similar to that used in these experiments;
2. In deprived rats, ethanol, like diazepam, induced changes in reactivity in opposite directions: while a higher than control hypothermic response was detected after acute ethanol; anxiolytic effects, tested on different tasks, were lower in deprived rats (5). Pharmacokinetics changes should promote variations in reactivity in the same direction;
3. Results from our laboratory demonstrated that daily diazepam or pentobarbital administration during 15 days induced tolerance to the anticonflict effect of these drugs assessed in the elevated plus-maze test in controls, but not in deprived animals.

Since plasma and brain levels of diazepam and pentobarbital after acute or chronic treatment did not differ between control and deprived animals, dispositional changes may be discarded. Consequently, the involvement of the $GABA_A$ receptor-complex function in the lack of tolerance to drugs acting through the $GABA_A$ receptor-complex detected in deprived rats may be suggested (unpublished data).

As a whole, tolerance is considered as the result of adaptive changes in the organism likely to decrease the sensitivity to a drug following repeated exposure. In this regard, it is interesting to point out that perinatally deprived rats failed to produce adaptive changes in response to different experimental events. Thus, chronic desipramine treatment did not induce down-regulation of β-adrenergic receptors in brain cortex from deprived rats, as it did in controls (8). Moreover, development of supersensitivity of $5\text{-}HT_1$ receptors induced by repeated stress in control rats was not observed in deprived animals. Since morphine injections restored the increased reactivity to $5\text{-}HT_1$ agonist, a possible deficiency in the functional role of the opioid system involved in the process of adaptation to stress has been suggested (10). Furthermore, repeated stress or desipramine treatment failed to induce hypoactivity of presynaptic dopaminergic or α_2 adrenergic receptors in deprived rats, as observed in controls (9). These data, together with the results from the present study, suggest that the insult produced by early undernutrition induces functional disturbances, involving different neurotransmitter and neuro-

modulator pathways that may be involved in the development of adaptive changes related to the maintenance of homeostasis and normal behavior.

In summary, our results demonstrate that early undernutrition alters the mechanisms involved in the development of tolerance to ethanol after chronic administration. This disorder, previously described for anxiolytic activity, is now extended to anticonvulsant and hypoalgesic effects. The fact that the hypothermic response was seemingly affected both in control and deprived rats after chronic ethanol treatment, indicates that neuronal pathways underlying different physiological outputs are differentially affected by early undernutrition and stresses the complexity of alterations and the functional relevancy of early nutritional insult upon adulthood.

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