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Effects of Ethanol, Barbital, and Lorazepam on Brain Monoamines in Rat Lines Selectively Outbred for Differential Sensitivity to Ethanol

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HELLEVUO, K. AND K. KIIANMAA. *Effects of ethanol, barbital, and lorazepam on brain monoamines in rat lines selectively outbred for differential sensitivity to ethanol.* PHARMACOL BIOCHEM BEHAV **29**(1) 183–188, 1988.—The acute effects of ethanol, barbital, and lorazepam on the synthesis and metabolism of brain monoamines were studied in the AT (Alcohol Tolerant) and ANT (Alcohol Nontolerant) lines of rats, which have been selected for differential motor impairment after ethanol administration. The ethanol-sensitive ANT rats are also more sensitive than the ethanol-insensitive AT rats to the motor impairment caused by barbital and lorazepam. Ethanol increased, whereas barbital and lorazepam decreased, the synthesis of catecholamines in several regions of the brain. Ethanol did not affect the formation of DOPAC, whereas barbital and lorazepam reduced it. Similarly, the accumulation of 5-HTP was increased after administration of ethanol, but was decreased after administration of barbital or lorazepam. Ethanol, barbital and lorazepam decreased the formation of 5-HIAA. The rat lines did not differ in any of these responses. Some differences could, however, be demonstrated between the AT and ANT rats in the effects of the three drugs on the levels of the brain monoamines. Although the importance of these differences in the differential sensitivity to these drugs between the two lines is difficult to determine, the role of central monoaminergic mechanisms cannot be excluded. These findings also suggest that the motor impairment induced by ethanol, barbiturates, and benzodiazepines is probably not primarily based on the monoaminergic systems.

Ethanol Barbital Lorazepam Monoamines Selected lines Intoxication Motor impairment

RAT and mouse lines selected for differences in ethanol related behaviors provide a good tool to study the neuronal mechanisms of ethanol sensitivity. The AT (Alcohol Tolerant) and ANT (Alcohol Nontolerant) rats have been outbred for their differential ethanol intoxication at the Research Laboratories of the Finnish State Alcohol Company [14]. An acute dose of ethanol (2 g/kg) impairs the motor performance of the ANT rats substantially more than that of the AT rats at the same blood level, when measured by the tilting plane test.

A number of investigations have established that ethanol alters the functioning of central monoaminergic neurons (cf. [36,41]). Consequently, a role for central monoaminergic neuronal mechanisms has been suggested in the mediation of ethanol-induced locomotor activity [30], motor impairment, hypothermia, and loss of righting reflex [24–26]. These findings have justified studies to determine whether the difference in sensitivity to ethanol between the AT and ANT rats can be explained in terms of differences in central monoaminergic neuronal functions. The level of dopamine (DA) and the rate of DA synthesis has been found to be higher in the brain of ANT rats than in the brain of AT rats [1,27], while no difference in the activity of catecholamine synthesizing enzymes was found between the two lines [38]. Moreover, an acute dose of ethanol increases the synthesis and metabolism of DA similarly in the brain of both AT and ANT rats [27]. These findings do not, however, seem to explain the difference in sensitivity to ethanol between the two rat lines.

The selection of the AT and ANT rat lines has not been specific for ethanol, since both barbital and lorazepam, a barbiturate and a benzodiazepine, also impair the motor performance of the ANT rats significantly more than that of the AT rats [21,40]. The primary target of the latter two drugs is probably the GABA-benzodiazepine receptor complex [10,37]. They also exert effects on central monoaminergic neurons [7, 9, 43], which are at least partially under GABAergic control [2, 12, 18]. Thus, the effect of barbiturates and benzodiazepines on motor performance might be mediated via monoaminergic neurons, which have been implicated in the motor effects of ethanol [25,30]. Furthermore, GABA antagonists have been reported to diminish ethanol-induced motor impairment in rats [20], and GABA mimetics have been reported to suppress ethanol-induced locomotor stimulation [11].

The purpose of this study was primarily to clarify the

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importance of monoamines in the differential sensitivity to the motor impairment from 2 g/kg ethanol between the two rat lines. The ANT rats are also more sensitive to motor impairment produced by both barbital and lorazepam. Consequently, the effects of 2 g/kg ethanol, and of doses of barbital and lorazepam that produced degree of motor impairment similar to 2 g/kg ethanol, on brain monoaminergic functions were compared in the two rat lines to see whether there was also a difference in sensitivity to the neurochemical effects of the drugs. If the monoaminergic neuronal systems were important in the difference between the two lines, a difference in sensitivity to the neurochemical effects of the drugs would be expected: the ANT line would be more sensitive than the AT rats.

Secondly, the aim was to get further information about the role of monoamines in the ethanol-induced motor impairment. If the monoamines played a part in the impairment of motor performances, some similarity could be expected in the neurochemical effects of the three drugs.

METHOD

Male AT and ANT rats of generation F_{24} were used in all experiments at the age of 12 weeks; their body weights were 320±9 g (N=25) (mean±SE) and 331±8 g (N=29), respectively. The ambient temperature was 22±2°C, relative humidity 50–55%, and light-dark cycle 12/12 hr. All animals were housed in group cages of 6–8 rats with free access to standard rat chow R3 (Ewos Ab, Södertälje, Sweden) and tap water.

Neurochemical Studies

The acute effects of ethanol, barbital (sodium salt of 5,5-diethylbarbituric acid; Merck, Darmstadt, F.R.G.), and lorazepam (Wyeth/Huhtamäki Oy Pharmaceuticals, Turku, Finland) on the synthesis and metabolism of brain catecholamines and 5-hydroxytryptamine (5-HT) were measured after inhibition of brain aromatic acid decarboxylase with 3-hydroxybenzyloxamine dihydrogen phosphate (NSD-1024; Sandev, Harlow, Essex, U.K.) [4,42]. The rates of catecholamine and 5-HT synthesis were estimated from the accumulations of 3,4-dihydroxyphenylalanine (DOPA) and 5-hydroxytryptophan (5-HTP), respectively. Formation of 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) was used as the measure of DA metabolism, and that of 5-hydroxyindoleacetic acid (5-HIAA) was used as the measure of 5-HT metabolism.

Barbital (120 mg/kg, IP) and lorazepam (3 mg/kg, IP) were injected 90 min before decapitation, while ethanol (2 g/kg, IP) was given 30 min before killing the animals. The dosage of ethanol and the time of administration were the same as those used in the selection of the AT and ANT rats [14]. The doses of barbital and lorazepam were chosen to produce behavioral effects comparable to that from the ethanol dose, and the times administration so as to avoid the absorption phase, as determined in an earlier study [21]. Lorazepam (dissolved in ethylenglycol), barbital, and ethanol were all diluted with saline. The rats received NSD-1024 (200 mg/kg, IP) in saline 30 min before decapitation. The control groups were treated with vehicle at the respective times. The brain was dissected into the cerebral cortex, frontal cortex, striatum, limbic forebrain (containing tuberculum olfactorium, nucleus accumbens and septum), hypothalamus, lower brain stem (containing pons and medulla), and cerebellum. The rest was discarded. The tissue samples were stored at −80°C until the monoamine concentrations were assayed with high performance liquid chromatography, using electrochemical detection.

The tissue samples were homogenized with a Polytron homogenizer in 2.2 ml of 0.1 M perchloric acid containing 0.2% EDTA and 0.5% sodium disulphite as antioxidant, and 2-methyl-3-(3,4-dihydroxyphenyl)-2-alanine (α-methyl-DOPA) and 5-hydroxy-Nw-methyltryptamine oxalate (N-m-5-HT) as internal standards for catecholamines and indoleamines, respectively. The samples were centrifuged at 16,000×g for 15 min at +4°C. Three hundred μl of the supernatant was collected for the chromatographic injections of indoleamines, and 1.8 ml of the supernatant was collected for the catecholamine analysis. The catecholamines were extracted with alumina [42], with slight modification. The samples were stored at −80°C for chromatograph injections.

The liquid chromatograph system consisted of a Waters Model 510 pump, a Waters Intelligent Sample Processor WISP 710 B with a thermostated sample unit, and an amperometric detector LC-4B (Bioanalytical Systems Inc., West Lafayette, IN) with a glassy carbon working electrode.

The sample components were separated in an isocratic reversed-phase system under two different conditions. The working electrode was set at 0.7 V vs. an Ag/AgCl reference electrode for the analysis of DOPA, DA, DOPAC, and noradrenaline (NA). The compounds were separated with a column, Nucleosil 5 C_{18} 200 mm × 4 mm i.d. (Macherey-Nagel, Düren, F.R.G.). The mobile phase contained 42 mM citric acid, 11 mM Na_2HPO_4, 0.6 mM sodium octyl sulphate, 0.05 mM EDTA, and 7% methanol in water. The pH was adjusted to 2.9 with 5 M NaOH. The mobile phase was filtered through a 0.22 μm filter (GVWP 04700, Millipore, Bedford, MA) and then degassed under vacuum before use. The rate of flow was 1.2 ml/min.

For the analysis of 5-HTP, 5-HT, 5-HIAA, and HVA the procedure was the same, with the following exceptions. The working electrode was set at 0.8 V vs. an Ag/AgCl reference electrode. The compounds were separated with a column, Nucleosil 5 C_{18} 250 mm×4 mm i.d. (Macherey-Nagel, Düren, F.R.G.). The mobile phase contained 34 mM citric acid, 41 mM Na_2HPO_4, 0.2 mM sodium octyl sulphate, 0.05 mM EDTA, and 7% methanol. The pH was adjusted to 4.0 with 5 M NaOH. The rate of flow was 1.0 ml/min.

Standard solutions were prepared from authentic salts. DOPA, DOPAC, 5-HIAA, HVA, α-m-DOPA and HCl salts of both DA and 5-HT were purchased from Sigma Chemical Co. (St. Louis, MO); N-m-5-HT from Aldrich (Beerse, Belgium); 5-HTP and NA-HCl from Fluka AG (Buchs, Switzerland).

Statistical Analysis

Differences between the groups were studied using Student's *t*-test, or by analysis of variance followed by Student-Newman-Keuls test or *t*-test.

RESULTS

Synthesis of Catecholamines

Ethanol significantly increased the accumulation of DOPA in the striatum, limbic forebrain, and hypothalamus of both AT and ANT lines, and in the lower brain stem of the AT rats (Fig. 1). The rat lines did not differ significantly in these responses. In contrast to ethanol, both barbital and lorazepam reduced catecholamine synthesis in every analyzed region of the brain. Both rat lines were similar in this effect as well.

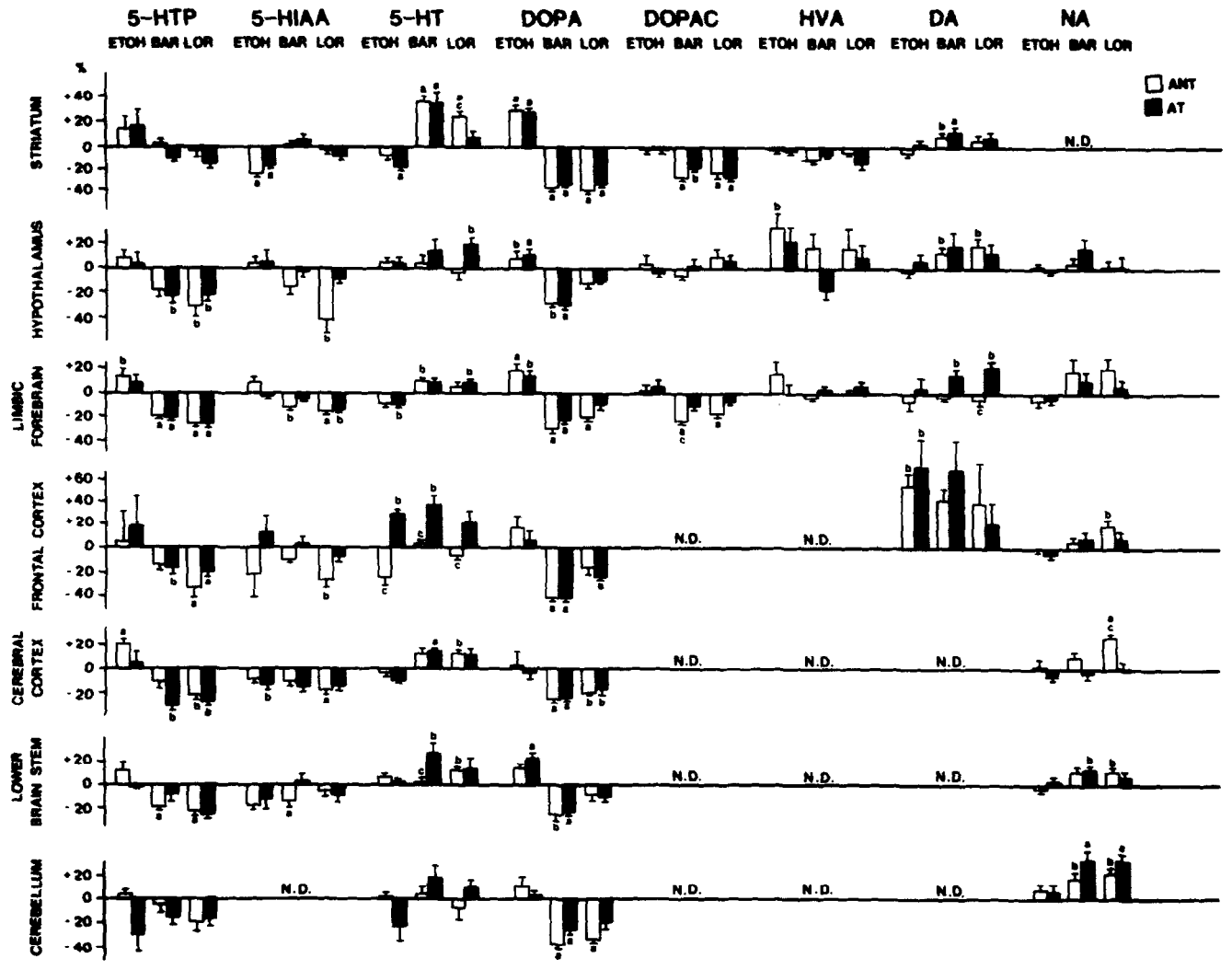

FIG. 1. The effect of ethanol (ETOH; 2 g/kg IP), barbital (BAR; 120 mg/kg IP) and lorazepam (LOR; 3 mg/kg IP) on the synthesis and metabolism of catecholamines and 5-HT in different parts of the brain of AT and ANT rats. Results are expressed as a percent of saline control (mean±SE, N=6–18). N.D.=not determined; a=$p<0.01$; b=$p<0.05$ compared to the saline control, Student-Newman-Keuls test; c=significant rat line × drug interaction.

Metabolism of Catecholamines

Ethanol did not affect the formation of DOPAC in any region of the brain of either the AT or the ANT rats, although it significantly increased the levels of HVA in the hypothalamus of the ANT rats. Barbital and lorazepam did not influence the levels of HVA, but they significantly reduced the levels of DOPAC in the striatum of both rat lines and in the limbic forebrain of the ANT rats. A significant rat line × drug interaction ($p=0.038$) was found in the effect of barbital on the level of DOPAC in the limbic forebrain. This indicated that the ANT rats were more sensitive than the AT rats to this effect of barbital.

Catecholamine Levels

Ethanol significantly increased the levels of DA in the frontal cortex of both lines but had no effect on them in other regions. An increase in the levels of DA was also found in the striatum of both rat lines after administration of barbital. Both barbital and lorazepam significantly increased the concentration of DA in the hypothalamus of the ANT rats and in the limbic forebrain of the AT rats. The AT line differed from the ANT line in the effect of lorazepam in the limbic forebrain, as revealed by a significant rat line × drug interaction ($p=0.039$).

Ethanol did not affect the levels of NA in any region of the brain. Only lorazepam significantly increased the concentration of NA in the frontal cortex and the cerebral cortex of the ANT rats. There was a significant interaction between the rat lines and the effect of the drug ($p=0.032$) in the cerebral cortex, which indicated that this effect of lorazepam depends on the line. The cerebellar concentration of NA in the AT and ANT lines was significantly increased after administration of barbital and lorazepam. The responses of the rat lines, however, were alike.

Synthesis of 5-HT

Ethanol significantly increased the synthesis of 5-HT in the limbic forebrain and the cerebral cortex of the ANT rats

(Fig. 1). A significant difference, however, could not be shown between the rat lines in this effect. In contrast to ethanol, barbital and lorazepam decreased the accumulation of 5-HTP in the limbic forebrain, cerebral cortex, frontal cortex, hypothalamus, and lower brain stem of both rat lines.

Metabolism of 5-HT

Ethanol decreased the metabolism of 5-HT in the striatum and cerebral cortex of both rat lines. Both barbital and lorazepam reduced the formation of 5-HIAA in the limbic forebrain of both AT and ANT rats, whereas lorazepam decreased the levels of 5-HIAA in the cerebral cortex, frontal cortex, and hypothalamus of the ANT rats. Barbital decreased the accumulation of 5-HIAA in the lower brain stem of the ANT rats. A difference in these responses between the two rat lines could not be demonstrated.

Levels of 5-HT

Ethanol significantly decreased the level of 5-HT in the striatum and the limbic forebrain of the AT rats, whereas it increased the level in the frontal cortex of the AT rats. There was a significant rat line × drug interaction ($p=0.002$) in the latter response. Barbital and lorazepam increased the concentration of 5-HT in the striatum, limbic forebrain, cerebral cortex, and lower brain stem of both rat lines, but only lorazepam increased the concentration in the hypothalamus of the AT rats. The lines seemed to be differentially sensitive to the effects of barbital and lorazepam on 5-HT concentrations, since a significant interaction between the rat lines and the effect of the drug was found in the striatum after administration of lorazepam ($p=0.024$), in the lower brain stem after administration of barbital ($p=0.015$), and in the frontal cortex after administration of lorazepam ($p=0.039$) or barbital ($p=0.022$).

DISCUSSION

In this study the effects of ethanol, barbital, and lorazepam on the functional state of central monoaminergic neurons were estimated by monitoring the synthesis and metabolism of monoamines. Since the effects of the three drugs on central catecholamine functions were studied in different parts of the brain innervated by the principal DA and NA neuronal systems (cf. [33,34]), some of which are rich only in either DA or NA, the results may be expected to reflect the responses of both DA and NA to the three drugs. It has also been established that metabolite levels, under conditions in which aromatic amino acid decarboxylase is inhibited with NSD-1024, can be considered as indicators of monoamine metabolism or release [42].

Ethanol, barbital, and lorazepam could significantly affect the synthesis and metabolism of the brain monoamines. This study also demonstrated line-specific differences between the ethanol-sensitive ANT and the ethanol-insensitive AT rats in the effects of these drugs on brain monoamines.

Thus, an acute dose of 2 g/kg of ethanol increased the synthesis of catecholamines and formation of HVA in the brain similarly in both the AT and ANT rats. Ethanol did not affect the levels of DA and NA, excluding the frontal cortex, where an increase in the level of DA was found. These findings agree with numerous earlier studies showing increased catecholamine synthesis and release after acute ethanol administration [5, 6, 23]. Also, no significant differences in catecholamines between the AT and ANT rats after administration of ethanol have been found in our earlier studies [27].

Barbital and lorazepam, in contrast to ethanol, decreased the synthesis and metabolism of catecholamines in both rat lines. The elevated levels of DA and NA may also suggest reduced catecholamine release. These results agree with earlier papers reporting decreased catecholamine synthesis [3] and utilization of DA [9,17] after administration of diazepam or chlordiazepoxide. However, chlordiazepoxide has also been reported to have no effect on the synthesis of catecholamines [32]. In accordance with this study, pentobarbital and phenobarbital have been found to decrease utilization of catecholamines but not to affect the levels of DA and NA in the brain [7,28].

Ethanol increased the synthesis of 5-HT and decreased the formation of 5-HIAA. The level of 5-HT was increased in the frontal cortex but was decreased in the striatum and limbic forebrain. There seems to be some controversy about the effects of acute ethanol administration on central 5-HT neurons: increased [39], decreased [22], and unchanged 5-HT turnover have all been reported [16,19]. However, in agreement with this study, decreased or unchanged metabolism of 5-HT after administration of ethanol has been reported earlier [8,15].

Barbital and lorazepam decreased the synthesis and metabolism of 5-HT, whereas the levels of 5-HT were increased. The results accord with earlier studies. Diazepam and chlordiazepoxide are known to decrease synthesis and utilization of 5-HT [3, 13, 29, 32]; an increase in the 5-HT content after chlordiazepoxide has been reported [31]. Two barbiturates, phenobarbital and pentobarbital, have also been found to reduce utilization of 5-HT but not to affect the levels of 5-HT [8,29], although an increase in the level of 5-HT after administration of pentobarbital has also been found [35].

Strain-specific differences could be demonstrated in the effects of ethanol, barbital and lorazepam on brain monoamines. The levels of NA seemed to be higher in the cerebral cortex in the ANT than in the AT rats after administration of barbital or lorazepam. On the other hand, the level of DA tended to increase in the limbic forebrain of the AT rats but not in that of the ANT rats after treatment with barbital or lorazepam. This may be related to the finding that there was at least a tendency to a smaller suppression in the accumulation of DOPA in the AT rats than in the ANT rats. Furthermore, the formation of DOPAC was reduced less in the AT rats than in the ANT rats. These findings taken together may suggest that the AT rats were less sensitive than the ANT rats to these effects of barbital and lorazepam in the limbic forebrain. A similar pattern appeared in the effects of ethanol, barbital and lorazepam on the levels of 5-HT in the frontal cortex: an increase was seen in the AT rats while no change was found in the ANT rats. These findings should, however, be examined with caution, since the monoamine levels were measured under conditions in which aromatic amino acid decarboxylase was inhibited.

Thus, the AT and ANT rat lines seem to differ in some responses of the monoaminergic neurons to ethanol, barbital, or lorazepam. Interestingly, in an earlier study all three drugs impaired the motor performance of the ANT rats more than that of the AT rats [21]. It is, however, difficult to estimate the importance of the neurochemical differences found here to the differential sensitivity to the three drugs between the AT and ANT rats. Consequently, the role of brain monoaminergic systems needs further clarification and cannot be excluded.

Furthermore, our findings also indicate that the changes induced by ethanol in the central monoaminergic functions are opposite to those induced by barbital and lorazepam. This may mean that central monoaminergic neuronal systems, studied by using neurochemical analyses of relatively gross sections of the brain, do not have a primary role in the motor impairment induced by ethanol, barbiturates, and benzodiazepines.

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