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Ethanol and Δ-Sleep-Inducing Peptide: Effects on Brain Monoamines

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Ethanol DSIP Limbic system Monoamines

THE mechanisms underlying alcoholism are not homogenous. By examining lines of animals that consume ethanol and respond to it differently, it is possible to study neurochemical mechanisms that may be involved in the actions of alcohol and the development of alcohol dependence (16,24).

One of the factors related to ethanol consumption is stress (21). The type of reaction during exposure to stress depends upon the general status of the organism, environment, and heredity. We suggest that different mechanisms of alcohol dependence may be distinguished by analyzing behavior in stressful situations. Depending upon the reaction of animals to stress induced by nonavoidance swimming, two groups of rats were selected. These groups possessed some neurophysiological differences, for example, the duration of slow-wave and paradoxical sleep time (25), sensitivity to the effect of psychotropic drugs, and differences in their dynamics in alcohol consumption (4,13).

There are data indicating that one of the endogenous factors regulating reaction to stress in Δ-sleep-inducing peptide (DSIP) (12). In addition, DSIP seems to participate during the development of experimental alcoholism because the brain level of DSIP is lower in animals with a predisposition toward ethanol consumption (5) and injection of DSIP alleviates alcohol abstinence syndrome (8). Despite the peptide's structure, DSIP crosses the blood-brain barrier, probably by simple transmembrane diffusion (23) and by a saturable high-affinity mechanism (27). It has been proposed that the action of DSIP is mediated through monoaminergic transmitters (12). Reward-induced ethanol consumption is partly mediated through dopaminergic neurons in the limbic system (9). However, other monoamines are also involved in alcohol consumption control (1,6,15), for example, specific inhibitors of serotonin (5-HT) uptake decrease ethanol consumption in free-choice situations in animals and in alcoholic patients to some extent (19).

In the present work, we studied the influence of ethanol and DSIP on dopamine (DA) and 5-HT metabolism in rats with different mobilities and sensitivities to stress. The groups

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were selected according to the time of immobilization in a nonavoidance swimming test. The levels of DA and 5-HT and their metabolites were determined in the medial prefrontal cortex (MFC), nucleus accumbens, and striatum.

METHOD

The experiment was conducted using random-bred male albino rats (raised in our animal colony) with initial weights of 200–250 g. Rats were selected according to their total time of immobilization (TTI) during a forced swimming test (3). Rats were placed in a plastic bath 320 mm in diameter and 500 mm high, filled with water at 25°C to a level of 250 mm. A rat was judged immobile if it remained floating in the water, in an upright position, while making only small movements to keep its head above water. Rats were further selected as high active (HA) if their TTI was less than 120 s during the 600-s testing period or low active (LA) if their TTI was more than 300 s. After the test, rats were placed in a warm cage and returned to the animal facility. Further experiments were made within 10 days.

Selected rats were divided into six groups. The first group (water) received water (8 ml/kg body weight) PO, while the second group (water + saline) was injected with saline (5 ml/kg) 1 h before water administration. The third group (ethanol) received ethanol PO (2 g/kg), the fourth group was injected with saline 1 h before ethanol (ethanol + saline), the fifth group (ethanol + DSIP) was injected with DSIP (0.1 mg/kg, IP) 1 h before ethanol, and the sixth group was injected with DSIP 1 h before water. One hour after ethanol administration, rats were decapitated and brains were rapidly dissected on ice. The MFC was removed as described by Fadda et al. (10), but the slice was taken between A = 12,500 and A = 10,300 according to the atlas by König and Klippel (17). The nucleus accumbens was dissected from a 2.3-mm thick slice taken between A = 10,300 and 7,900. A part of striatum was taken from the same slice, and the remainder was recovered from the next slice between 7,900 and 6,600. The dissected brain regions were immediately frozen in liquid nitrogen and weighed, then stored in liquid nitrogen until high-performance liquid chromatography (HPLC) analysis.

The concentrations of monoamines and their acidic metabolites were determined by HPLC using electrochemical detection (18). The brain samples were thawed and homogenized in 0.1 N $HClO_4$, and dihydroxybenzylamide (DBA, 100 ng/ml) was added as internal standard. The samples were centrifuged at 10,000 × g for 10 min. The supernatant was filtered through a Millipore filter (0.22 μm) and 20-μl samples were injected on to the column (RP-18 octadecylsilane, 4.6 × 250 mm) connected to a double amperometric detector (LC-4B) with a TL-5 cell. The working electrode had a potential of +850 mV. The mobile phase was 0.02 M citric acid buffer (pH = 3.6) containing 0.3 mM acetonitrile. The retention times (min) were: DBA, 2.35; DA, 2.64; dihydroxyphenylacetic acid (DOPAC), 3.04; homovanillic acid (HVA), 5.86; 5-HT, 4.06; and 5-hydroxyindoleacetic acid (5-HIAA), 4.29.

Blood samples from each rat were frozen for future determination of ethanol concentrations by head-space gas chromatography on the column (800 × 4 mm, porapak Q, 100–120 mesh) of a Shimadzu (Kyoto, Japan) GC 9A gas chromatograph equipped with flame ionization detector. The blood samples, 200 μl in 4-ml vials with gas-tight caps, were exposed to 37°C for 20 min and a vapor phase volume of 1 ml was injected. The oven temperature was 110°C and injector 130°C. The flow rate for the carrier gas (N_2) was 40 ml/min. Under these conditions, the retention time of ethanol was about 3 min. Quantitation was made using a C-R2AX Integrator (Shimadzu). The results of these experiments were analyzed by analysis of variance (ANOVA) followed by Scheffe's test.

DSIP was synthetized in the Institute of Biorganic Chemistry, USSR Academy of Sciences.

RESULTS

From the population of random-bred rats, we selected two groups: one of LA, that is, animals with TTI of 338.7 ± 32.5 s (mean ± SEM), and the other of HA, TTI 89.8 ± 28.4 s. Pretreatment determination of blood ethanol in LA and HA rats showed the endogenous values to be higher in HA rats. No differences in ethanol levels in HA and LA rats were observed 1 h after ethanol administration; injection of DSIP failed to affect the blood ethanol concentration (Table 1).

The concentrations of monoamines and their metabolites did not differ significantly between the rats within groups 1 and 2 (water) or groups 3 and 4 (ethanol); therefore, we combined the data from these groups. Also, there were no significant differences in the basic levels of DA and HVA between the HA and LA rats of groups 1 and 2 (Table 2). However, the concentration of DOPAC tended to be higher (Table 2) and the concentration of 5-HT (Table 3) lower in the MFC of LA rats. Also, the level of 5-HIAA in the striatum tended to be lower in LA compared to HA rats (Table 3).

Acute oral administration of ethanol (2 g/kg) tended to decrease the concentrations of DA and DOPAC in the MFC while increasing it in the striatum and nucleus accumbens of LA rats (Table 2), whereas the concentrations of DA, DOPAC, and HVA remained unchanged in HA rats following ethanol administration. DA concentration in the nucleus accumbens of LA rats was significantly higher than that of HA rats after ethanol administration (Table 2).

Administration of ethanol caused 5-HT concentration to decrease in the MFC and nucleus accumbens of HA rats. In the nucleus accumbens of HA rats (Table 3), the concentration of 5-HIAA also decreased. In addition, the concentration of 5-HIAA increased in the nucleus accumbens of LA rats compared to HA rats after ethanol administration.

DSIP injection (0.1 mg/kg) decreased 5-HT concentration in the MFC of LA and HA rats (Table 3) but did not affect the concentrations of 5-HT in the nucleus accumbens or striatum or 5-HIAA concentration in any region. DSIP did not have any effect on DA or DOPAC concentrations in investi-

TABLE 1

CONCENTRATION OF ETHANOL (μg/ml) IN BLOOD 1 h AFTER ETHANOL (2 g/kg) ADMINISTRATION

	HA	LA
Water	27.5 ± 2.9 (6)	11.3 ± 4.4 (6)*
Ethanol	987.9 ± 50.9 (7)	1,059.0 ± 74.9 (9)
Ethanol + DSIP†	1,061.0 ± 31.6 (5)	1,046.0 ± 37.2 (5)

Results are expressed as means with associated SEMs. The number of animals is indicated in parentheses.

*$p < 0.05$ compared to HA rats.

†0.1 mg/kg IP.

TABLE 2

EFFECTS OF ETHANOL AND DSIP ON THE LEVELS OF DA AND ITS METABOLITES IN THE MFC, NUCLEUS ACCUMBENS, AND STRIATUM IN HA AND LA RATS (MEANS ± SEM)

	MFC		Nucleus Accumbens		Striatum	
	HA	LA	HA	LA	HA	LA
DA						
Control	0.28 ± 0.06 (4)	0.33 ± 0.05 (4)	5.52 ± 0.74 (5)	4.92 ± 0.33 (5)	4.77 ± 0.37 (6)	4.15 ± 0.37 (6)
Ethanol	0.27 ± 0.05 (6)	0.25 ± 0.03 (7)	4.46 ± 0.41 (7)	5.65 ± 0.34 (9)†	4.57 ± 0.35 (6)	5.42 ± 0.37 (9)
DSIP	0.20 ± 0.02 (4)	0.37 ± 0.10 (4)†	5.52 ± 0.79 (4)	5.70 ± 0.40 (4)	5.01 ± 0.50 (4)	5.34 ± 0.38 (4)
DSIP + ethanol	0.23 ± 0.04 (8)	0.26 ± 0.03 (7)	5.70 ± 0.36 (7)	5.49 ± 0.43 (7)	4.60 ± 0.29 (8)	4.32 ± 0.41 (7)
DOPAC						
Control	0.11 ± 0.08 (3)	0.23 ± 0.10 (3)	0.84 ± 0.10 (5)	0.99 ± 0.05 (5)	0.53 ± 0.06 (6)	0.47 ± 0.02 (6)
Ethanol	0.07 ± 0.02 (6)	0.11 ± 0.04 (5)	0.93 ± 0.10 (7)	1.00 ± 0.06 (9)	0.53 ± 0.05 (6)	0.56 ± 0.04 (9)
DSIP	0.05 ± 0.01 (4)	0.08 ± 0.04 (4)	0.82 ± 0.18 (4)	0.68 ± 0.13 (4)	0.54 ± 0.11 (4)	0.55 ± 0.07 (3)
DSIP + ethanol	0.05 ± 0.01 (7)	0.04 ± 0.01 (6)*	0.88 ± 0.11 (10)	1.00 ± 0.01 (8)	0.59 ± 0.06 (7)	0.57 ± 0.05 (9)
HVA						
Control			0.52 ± 0.06 (5)	0.48 ± 0.11 (4)	0.41 ± 0.06 (6)	0.41 ± 0.05 (6)
Ethanol			0.46 ± 0.10 (4)	0.58 ± 0.09 (7)	0.45 ± 0.03 (7)	0.44 ± 0.03 (9)
DSIP			0.47 ± 0.04 (4)	0.41 ± 0.08 (3)	0.58 ± 0.08 (4)*	0.46 ± 0.06 (5)
DSIP + ethanol			0.60 ± 0.06 (10)	0.61 ± 0.04 (7)	0.46 ± 0.04 (9)	0.47 ± 0.07 (8)

The number of animals is in parentheses.
*$p < 0.05$ compared to the control group.
†$p < 0.05$ compared to HA rats.

gated brain regions, although it was associated with increased HVA concentrations in the striata of HA rats (Table 2).

In the MFC, DSIP + ethanol caused a greater decrease in 5-HT than ethanol alone in both groups (Table 3), while in the nucleus accumbens DSIP reversed the action of ethanol and returned the concentration of 5-HT and 5-HIAA in HA rats to the control level. The differences in the concentration of DA, induced by ethanol, between LA and HA rats in the striatum and nucleus accumbens were eliminated after DSIP injection, but the effects of ethanol on the concentration of DOPAC in the MFC were potentiated (Table 2).

DISCUSSION

The results indicate a clear difference in the endogenous concentration of blood ethanol in HA and LA rats. Similar results have been reported elsewhere (14).

HA and LA rats were selected according to their TTI under

TABLE 3

EFFECTS OF ETHANOL AND DSIP ON THE LEVELS OF 5-HT AND 5-HIAA IN THE MFC, NUCLEUS ACCUMBENS, AND STRIATUM IN HA AND LA RATS (MEANS ± SEM)

	MFC		Nucleus Accumbens		Striatum	
	HA	LA	HA	LA	HA	LA
5-HT						
Control	0.70 ± 0.08 (5)	0.54 ± 0.03 (5)	0.85 ± 0.13 (5)	0.73 ± 0.07 (6)	0.44 ± 0.04 (6)	0.39 ± 0.04 (6)
Ethanol	0.50 ± 0.04 (6)*	0.51 ± 0.03 (7)	0.50 ± 0.04 (6)*	0.65 ± 0.09 (11)	0.47 ± 0.04 (7)	0.42 ± 0.04 (10)
DSIP	0.39 ± 0.03 (4)*	0.33 ± 0.03 (4)*	0.63 ± 0.06 (4)	0.56 ± 0.08 (4)	0.57 ± 0.11 (4)	0.46 ± 0.01 (3)
DSIP + ethanol	0.43 ± 0.03 (10)†	0.41 ± 0.03 (7)†	0.70 ± 0.06 (10)	0.58 ± 0.05 (7)	0.45 ± 0.05 (10)	0.50 ± 0.06 (8)
5-HIAA						
Control	0.33 ± 0.04 (5)	0.29 ± 0.02 (5)	0.72 ± 0.07 (5)	0.68 ± 0.11 (6)	0.56 ± 0.05 (6)	0.42 ± 0.04 (5)
Ethanol	0.33 ± 0.05 (7)	0.28 ± 0.03 (10)	0.43 ± 0.05 (6)*	0.70 ± 0.11 (10)‡	0.53 ± 0.08 (6)	0.56 ± 0.05 (9)
DSIP	0.48 ± 0.16 (4)	0.38 ± 0.14 (4)	0.68 ± 0.12 (4)	0.54 ± 0.14 (4)	0.63 ± 0.07 (4)	0.48 ± 0.13 (3)
DSIP + ethanol	0.35 ± 0.07 (9)	0.43 ± 0.08 (8)	0.57 ± 0.06 (9)	0.60 ± 0.11 (8)	0.54 ± 0.03 (10)	0.54 ± 0.08 (8)

The number of animals is in parentheses.
*$p < 0.05$ compared to the control group.
†$p < 0.01$ compared to the control group.
‡$p < 0.05$ compared to HA rats.

conditions of nonavoidance swimming. Porsolt et al. (22) proposed this test for determining the depressive state in animals, and passive avoidance was considered a depressive reaction to the stress induced by nonavoidance swimming. It is not clear whether LA or HA rats are more sensitive to stress. There are data indicating that HA rats are more sensitive to stress. HA rats have a greater mortality under chronic stress, and the weight of adrenal glands increases in this group under stressful conditions. HA rats did not drink ethanol during the first 2 weeks in their individual cages, but under stressful conditions the percentage of animals drinking among HA rats increased to the same level as LA rats (our nonpublished data). These differences may be related to membrane peculiarities of HA rats, which show a greater viscosity and a higher level of protein clusterization (our nonpublished data). Also, the higher sensitivity of HA rats to stress appears to be related to their differences in monoamine metabolism compared to LA rats. The differences in serotonergic activity are likely to be particularly significant in their reaction to stress.

Some data indicate that the synthesis of 5-HT increases under stress (20). The activation of serotonergic neurones induces secretion of corticotropin-releasing factor (CRF) and corticotropin (ACTH) (11); also, the action of ethanol on the expression of these stress markers requires that the 5-HT system is intact (3). Our results suggest that HA rats have higher levels of 5-HT in the MFC. Perhaps ethanol acts as a stress protector for HA rats by decreasing the concentration of 5-HT in the MFC and nucleus accumbens.

The difference in ethanol consumption between LA and HA rats has been reported (4,13). After their first contact with ethanol, LA rats drink more than HA rats. There is experimental data showing that the euphoric action of ethanol is partly mediated via excitation of dopaminergic neurones in the limbic system (7). We studied the concentration of DA and its metabolites in the MFC and nucleus accumbens because these regions of the brain have been suggested to mediate the effect of ethanol and other narcotics on the reward system (2,7). Acute oral administration of ethanol in a moderate dose (2 g/kg) tended to decrease the concentration of DA in the MFC in both groups, while DA concentration in the nucleus accumbens of LA rats tended to be higher than that in HA rats after ethanol administration. We did not find any differences in DA metabolism between LA and HA rats. Ethanol administration did not affect the level of DA or its metabolites in HA rats, but slightly increased the DA level in LA rats. Perhaps the difference in ethanol consumption between these two groups is partly related to the dopaminergic system, but it seems, however, more likely that the difference in sensitivity to stress and different kinds of reactions to ethanol are connected with the serotonergic system. Apparently, a difference in the level of 5-HT between HA and LA rats exists (5-HT tended to be lower in LA rats in MFC) and ethanol selectively affected 5-HT metabolism only in HA rats.

DSIP affected mainly the 5-HT level in the MFC and nucleus accumbens, although an increase in the level of HVA in the striatum of HA rats was also found. It has been shown earlier that DSIP normalize the TTI by reducing the value for HA and increasing it in LA rats. We propose that this and other stress-protective actions of DSIP (26) are mediated through serotonergic system in the MFC.

DSIP counteracted ethanol effects on the metabolism of 5-HT in the nucleus accumbens, but enhanced the effect of ethanol in the MFC. DSIP decreased the rate of ethanol consumption in rats and mice (our unpublished data). Probably, this effect of DSIP is associated with its ability to attenuate the effect of ethanol on 5-HT metabolism in the nucleus accumbens.

In conclusion, we propose that the different behaviors in rats during nonavoidance swimming may be related to differences in the serotonergic system between animals and that the stress-protective action of DSIP is mediated through its effect on 5-HT metabolism in the nucleus accumbens and MFC. In addition, DSIP is able to counteract some of the effects of ethanol on monoamine metabolism; these results may partly explain the effect of DSIP on ethanol consumption. Therefore, these two groups of rats may be used as behavioral models for testing stress-protective drugs.

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