REACTIVITY OF THE HYPOTHALAMICO-HYPOPHYSEAL NEUROSECRETORY SYSTEM IN RATS WITH PREFERENCE AND AVERSION FOR ALCOHOL

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It was shown previously that in rats of the same population there are considerable differences in the level of initial alcohol consumption and, under the influence of stressors, both the number of individuals preferring alcohol and the doses of alcohol consumed by animals with a marked initial preference for it are increased [2, 3, 6]. However, the mechanism of this phenomenon has not been explained. At the same time, alcohol is known to modify the reactivity of the neurochromonal trigger component of the stress reaction, namely the hypothalamico-hypophyseal neurosecretory system (HHNS) [7].

Accordingly, to study the role of central stress-reactive mechanisms in the development of an inclination for alcohol, it was decided to compare, in the same experiment, individual attitudes of an animal toward alcohol with the reactivity of its HHNS under extremal conditions, and the results of this investigation are described below.

EXPERIMENTAL METHOD

Experiments were carried out on 60 noninbred male albino rats weighing 200 ± 10 g, kept eight in a cage, under ordinary animal house conditions. To determine the initial attitude of the animals toward alcohol, they were kept for 10 days in spacious individual cages in which they had free access to food and to two graduated feeding bowls containing 5% ethanol solution and water. The quantitative criterion of choice was the so-called coefficient of alcohol preference, or the ratio between the volume of alcohol solution consumed daily by the animal and the total volume of alcohol solution and water consumed during the same period. Animals statistically significantly preferring alcohol or water were selected for the remainder of the experiment. As an extremal factor for assessment of individual reactivity of the HHNS of the selected animals hypothermia was used; more than all other extremal situations, hypothermia can induce pathological changes connected with an inadequate response of the hypothalamico-hypophyseal system [1]. For this purpose, on the 2nd day of the experiment, after measurement of their rectal temperature, the selected animals were placed in restraint cages, restricting their movements considerably, and these were placed in a dark temperature-controlled chamber with a temperature of −4°C during the period of daylight (from 10 a.m. to 4 p.m.). The animals were removed after 1 and 6 h, their temperature was again determined, after which they were decapitated. Equal numbers of rats chosen in the first part of the experiment not exposed to cooling and of the group of intact animals (control) were decapitated at the same time. The brain and pituitary gland were fixed in Bouin's fluid and 96% ethanol solution and embedded in paraffin wax. Sections (5-7 μ) were stained with paraldehyde-fuchsine by the Gomori–Gabe method and with toluidine blue by Nissl's method. The state of the HHNS was assessed quantitatively on the basis of the usual histophysiological criteria: the number of neurons containing different amounts of neurosecretory material in the supraoptic and paraventricular hypothalamic nuclei (SON and PVN respectively) [4] and the quantity of neurosecretion in the median eminence (ME) and in the principal posterior lobe (PPL) of the neurohypophysis, in conventional units on a five-point system [5].

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TABLE 1. Effect of Hypothermia (−4°C) on Percentage of Different Types of Neurons in Hypothalamic Neurosecretory Nuclei of Rats Preferring, under Conditions of Free Choice, 5% Ethanol Solution (A) or Water (W) (M ± m; n = 5)

Type of neuron	Intact animals (control)	Experimental animals					
		before cooling		after cooling for 1 h		after cooling for 6 h	
		A	W	A	W	A	W
		Supraoptic nucleus					
1a	49,0±5,1	46,0±4,0	50,0±5,7	75,0±5,2*	65,0±4,2*	42,0±6,0	70,0±4,2‡
1b	19,0±2,3	18,0±2,5	21,0±3,2	5,0±1,6*	27,0±2,4‡	3,0±1,5*	13,0±2,1*
1c	18,0±1,9	15,0±1,5	13,0±2,5	1,0±0,8*	3,0±1,3*	0	5,0±0,8‡
2	8,0±1,5	9,0±1,3	9,0±1,1	0	0	0	0
3	6,0±1,3	12,0±2,1*	7,0±1,7	19,0±2,1*	5±1,7 †	55,0±5,1*	12,0±0,8‡
		Paraventricular nucleus					
1a	25,0±2,8	29,0±2,5	26,0±2,5	68,0±5,5*	47,0±4,2‡	45,0±4,9*	62,0±3,2†
1b	45,0±3,6	42,0±2,7	46,0±2,1	23,0±2,1*	32,0±2,9‡	7,0±3,0*	15,0±1,3‡
1в	20,0±2,8	18,0±3,0	16,0±2,5	2,0±1,5*	11,0±2,1‡	0	9,0±1,1‡
2	5,0±1,7	2,0±0,4	5,0±1,1	0	2,0±0,4†	0	0
3	5,0±0,8	9,0±1,7	7,0±0,8	7,0±2,1	8,0±1,7	48,0±4,2*	14,0±2,1‡

*Differences compared with control significant ($P \leq 0.05$).

†Differences for comparison of A and W under these experimental conditions significant ($P \leq 0.05$).

‡Differences for comparison with control and between A and W significant ($P \leq 0.05$).

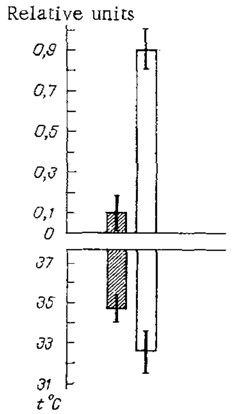

Fig. 1

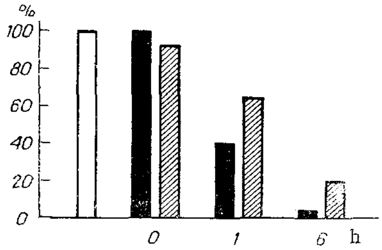

Fig. 2

Fig. 1. Body temperature of rats preferring (unshaded columns) and rejecting (shaded columns) alcohol, studied after exposure to hypothermia (−4°C) for 6 h. Ordinate: above) coefficient of preference for alcohol, below) body temperature.

Fig. 2. Content of neurosecretory material in PPL of neurohypophysis of rats with preference (black column) and aversion (obliquely shaded columns) for alcohol, investigated after exposure for 1 and 6 h to hypothermia (−4°C). Index for intact animals (unshaded column) taken as 100%. Abscissa, time; ordinate, quantity of neurosecretory material.

EXPERIMENTAL RESULTS

The results showed that animals which, if allowed free choice, preferred either alcohol or water, differed in their resistance to hypothermia. There is a distinct reciprocal relationship between the degree of preference of the animals for alcohol and their ability to maintain temperature homeostasis under conditions of hypothermia (Fig. 1).

When the state of the HHNS of the experimental rats was studied under these experimental conditions the following results were obtained. No significant differences were found in the morphological picture of the HHNS in animals with preference and aversion for alcohol, when tested immediately after 10 days' freedom of choice between 5% ethanol solution and water (Table 1; Fig. 2). The state of the HHNS of these animals likewise did not differ significantly from that of the intact animals of the control group. The only exception was a significantly larger number of dystrophic type 3 neurons in SON of rats preferring alcohol.

In rats investigated after exposure to hypothermia for different times, considerable changes were observed in the morphological picture of the HHNS, evidence that this extremal factor has a significant effect on its functional activity. For instance, by comparison with animals not exposed to hypothermia, a considerable decrease in the quantity of neurohormones deposited in ME and PPL was found in rats studied 1 h after introduction into a constant temperature chamber at −4°C, as reflected in a reduction in the quantity of neurosecretory material stained with paraldehyde-fuchsine; the difference was quantitatively more marked in the animals preferring alcohol (Fig. 2). In SON of the animals exposed to hypothermia, a considerable increase was observed in the number of type 1a neurons actively secreting neurohormones, and a sharp decrease or even the virtual disappearance of neurons of types 1c and 2, characterized by a high content of neurosecretory material as an index of predominance of neurohormone synthesis over secretion. However, whereas in animals preferring alcohol, in addition to the changes described above, there was also a decrease in the number of type 1b neurons, characterized by a high level of both synthesis and secretion of neurohormones, in the rats with aversion for alcohol the number of these cells not only was not reduced, but, on the contrary, it was actually higher than in the intact animals. Meanwhile, in SON of the rats with preference for alcohol, a considerable number of type 3 neurons with dystrophic features characteristic of functional exhaustion of the neurosecretory process, appeared. The response of PVN under these conditions was marked only by activation of secretion of neurohormones, which was expressed as a marked increase in the number of type 1a neurons among them and a corresponding decrease in the number of other types of cells. However, indices characterizing the intensity of this process were significantly higher under these conditions in animals preferring alcohol than in rats preferring water.

Even more marked differences in the reactivity of HHNS were found in animals preferring alcohol and water after exposure to hypothermia for 6 h. Under these conditions, in the PPL of rats with preference for alcohol, against the background of marked congestion of the blood vessels, only single endings of fibers of the hypothalamico-hypophyseal tract containing palely stained granules of neurosecretory material could be found. In the endings of fibers terminating in ME, no granules of neurosecretory material visible by light-optical methods could be seen. In PPL of rats preferring water, most endings of fibers of the hypothalamico-hypophyseal tract at this time of observation also contained no neurosecretory materia. However, a definite amount of stored neurosecretory material was still preserved, mainly in the form of granules homogeneously stained with paraldehyde-fuchsine, densely filling the large and giant endings (Herring's bodies). Neurons whose cytoplasm contained visible granules of neurosecretory material were virtually absent from PVN and, more especially, SON of rats with preference for alcohol. Most neurons showed dystrophic features characteristic of functional exhaustion of the neurosecretory process. The nuclei of these cells were reduced in size, often deformed, and the outlines of their cytoplasm were indistinct because of its well-marked vacuolation. Type 3 neurons with similar cytological characteristics, but far fewer in number, were found in SON and PVN of rats with preference for water. However, many neurons of types 1b and 1c, continuing to synthesize neurohormones actively, could be observed side by side with them in these nuclei.

It can thus be concluded from these observations that under conditions of hypothermia the reactivity of the HHNS of rats with preference and aversion for alcohol differs significantly. The presence of morphological features of rapid exhaustion of the hormone-synthesizing function of neurons in SON and PVN in rats with preference for alcohol, together with disappearance of their reserves in the neurohypophysis, are evidence of the relatively low protective-compensatory powers of the HHNS of these animals. The discovery of morphological features of continuation of the active synthesis of hypothalamic neurohormones, together with preservation of some of their reserves stored in the neurohypophysis, in rats with preference for water kept under similar experimental conditions, indicates that their HHNS possesses a higher protective compensatory potential.

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ROLE OF THE PYRAMIDAL TRACT IN THE MECHANISM OF DYSPNEA AND HYPERVENTILATION

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Hypoxemia by itself causes neither respiratory discomfort nor excessive hyperventilation in healthy subjects. However, both respiratory discomfort and excessive ventilation soon arise during hypoxemia if the subject attempts to carry out physical work [1]. Attempts to explain these phenomena by a change in afferentation from vascular chemoreceptors have not proved successful. Hypoxic work does not affect impulsation from vascular chemoreceptors [4]. Removal of the carotid sinuses (for bronchial asthma) does not prevent the onset of dyspnea and excessive hyperventilation during hypoxic work [5].

Physical exertion is induced by impulses from the sensomotor cortex which spread to the somatic muscles via the pyramidal tract. It is shown in this investigation that hypoxemia, induced by mechanical asphyxia, disturbs initially the generation of discharges in pyramidal tract neurons. This fact is of definite interest for the analysis of how both respiratory discomfort and excessive ventilation during hypoxemia are provoked by physical exertion.

EXPERIMENTAL METHOD

Experiments were carried out on 11 cats anesthetized with pentobarbital (40 mg/kg, intraperitoneally). N. saphenus and n. tibialis were divided in the region of the groin and knee, respectively, and their peripheral ends were placed on bipolar platinum electrodes with an interelectrode distance of 5 mm. These electrodes served for stimulation. Peripheral branches of n. saphenus were placed on similar electrodes for recording antidromic action potentials. Responses of the gastrocnemius muscle to stimulation of n. tibialis were recorded by bipolar wire electrodes, inserted into the thickness of the muscle by means of a surgical needle. The distance between the electrodes was 7-10 mm. Primary responses in the first somatosensory region of the cortex were recorded by monopolar silver ball electrodes. The indifferent electrode (steel needle) was fixed in the nasal bones. Discharges of the bulbar pyramidal tract and bulbar medial lemniscus were recorded by monopolar needle electrodes, inserted from the dorsal surface of the medulla at the level of the obex. Primary cortical responses, and discharges of the pyramidal tract and medial lemniscus were induced by stimulation of the contralateral forelimb. For this purpose, needle electrodes with an interelectrode distance of 10 mm were inserted beneath the skin of the dorsal surface of the foot. The exposed surfaces of the brain, nerves, and muscles were covered with warm mineral oil. Potentials were recorded before the tracheotomy tube, introduced beforehand into the animal, was covered and after covering for 1, 2, and 3-4 min.

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