Successful prevention of LPO activation and also, possibly, of the disturbance of prostaglandin synthesis with the aid of unithiol and magnesium sulfate suggested that these preparations might prove to be effective agents for the treatment of infectious diseases caused by Gram-negative microorganisms. Accordingly the protective action of unithiol and magnesium sulfate were studied in animals poisoned with endotoxins of *S. typhimurium* and *Sh. sonnei.* As the results in Table 3 show, unithiol had a marked protective action. Magnesium sulfate potentiated it.

Thus unithiol, alone and in combination with magnesium sulfate, neutralizes the damaging action of free oxygen and hydroxyl radicals formed during poisoning by breakdown products of gram-negative microoganisms, and protect the affected animals from death.

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MODIFYING EFFECTS OF NEUROTROPIN ON POSTRADIATION DISTURBANCES OF NEUROTRANSMITTER PROCESSES IN CENTERS REGULATING AUTONOMIC FUNCTIONS

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Previous investigations showed that in the early and relatively late stages after exposure to ionizing radiation in doses insufficient to cause acute radiation sickness, increased activity of the hypothalamo–hypophyseo–adrenocortical system characteristic of stress is observed; this phenomenon is due mainly to changes in the central component of that system [4, 6, 9]. In structures responsible for the regulation of autonomic and somatic functions, activation of both inhibitory and excitatory neurotransmitter processes is observed [1, 8]; disturbance of coordination of the latter, moreover, may lead to changes that constitute the picture of the diencephalic syndrome. Because of the facts described above it was decided to study postradiation changes in neurotransmitter relations in various structures of the brain stem, the parietal zone of the cerebral cortex, and the underlying bioenergetics of these processes.

The aim of this investigation was to study the possibility of correcting disturbances of neurotransmitter relations and the bioenergetics of the brain with the aid of neurotropin (Institute of Bioactive Science, Nippon Zoki, Osaka, Japan), which possesses a broad spectrum of action [11].

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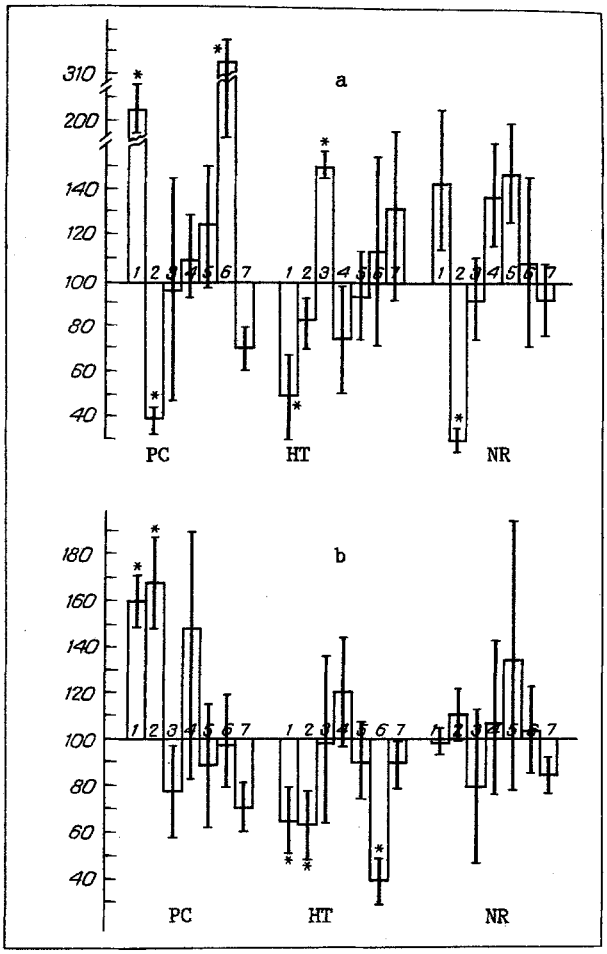

Fig. 1. Intensity of neuronal uptake of choline (1), serotonin (2), noradrenalin (3), dopamine (4), GABA (5), glycine (6), and reception of corticosterone (7) in PC, the mediobasal HT, and NR (in per cent of control). a) Six months after combined external x-ray irradiation in a dose of 0.5 Gy and injection of ^{131}I in a dose of 6.5 mCi/kg; b) 6 months after combined external x-ray irradiation in a dose of 0.5 Gy, injection of ^{131}I in a dose of 6.5 mCi/kg, followed 3 months later by intramuscular injection of neurotropin in a dose of 50 μl/kg. (Significant changes at the $p \leq 0.05$ level indicated by an asterisk).

EXPERIMENTAL METHOD

The investigation was conducted on mature male Wistar rats weighing 180-220 g, divided into three groups. The animals of Group 1 were subjected to whole-body x-ray irradiation in a single session on the RUM-11 apparatus under the following operating conditions: voltage 165 kV, current 10 mA, no filter, skin-focus distance 100 cm, exposure 7.5 min, dose 0.5 Gy. The rats of this group were then given an intraperitoneal injection of ^{131}I in a dose of 6.5 mCi/kg. Group 2 consisted of animals receiving three intramuscular injections of neurotropin in a dose of 50 μl/kg 3 months after the irradiation as described above. The animals of Group 3 served as the control (they were given injections of physiological saline). Altogether 60 animals were used and were kept on the standard animal house diet. The rats were killed by decapitation 6 months after irradiation and 3 months after receiving an injection of neurotropin. The criterion of the bioenergetics of the brain was activity of enzymes of the Krebs cycle, and of pyruvate dehydrogenase, contiguous with the cycle, in the mitochondria of the brain. Activity of the dehydrogenases was determined as in [3, 10] in the modification in [5]. Considering that asymmetry of the brain is biochemical in its basis, all the investigations were conducted on the left half of the brain only [2]. The intensity of neuronal uptake (uptake 1) of the neurotransmitters noradrenalin, serotonin, dopamine, GABA, and glycine, labeled with ^{3}H or ^{14}C, and the stable precursor acetylcholine, reflecting the functional state of the corresponding neurotransmitter systems, was determined as in [7], which we

adapted for work with microquantities of tissue (5-10 mg) from the parietal cortex (PC), the mediobasal hypothalamus (HT), the lateral vestibular nuclei (LVN), the locus coeruleus (LC), and the nuclei raphe (NR). Dependence of neurotransmitter relations on the level of receptor binding of ^{3}H-corticosterone and the cAMP concentration in the same structures also was studied. All the radioactive labels were obtained from Amersham International (England) and possessed high specific activity. A 0.1% homogenate of the corresponding tissue was prepared in calcium-free isolation medium. The intensity of neuronal uptake of neurotransmitters was judged by the difference between disintegrations of the label in the coarse synaptosomal fraction after incubation at 37°C, and in homogenates kept in the cold. Receptor binding of corticosterone was assessed as the difference between total and nonspecific binding. The cAMP level was determined with the aid of commercial RIA ^{125}I kits (Czechoslovakia).

EXPERIMENTAL RESULTS

Six months after combined irradiation under conditions of relative insufficiency of thyroid function a decrease in activity of serotonin-noradrenalin-dopamine-and GABA-ergic neurotransmitter processes was observed in PC, HT, LVN, and LC, accompanied by increased activity of glycinergic processes. The most marked changes in the parameters studied, and which are shown in Fig. 1a, took place against a background of an increase in corticosterone reception in HT, evidence of the relative insufficiency of the glucocorticoid function of the adrenal cortex developing in the late stages after irradiation. During the same period reduced activity of dehydrogenases of the Krebs cycle was observed in the brain mitochondria: isocitrate — by 25%, 2-oxoglutarate — by 20%, succinate — by 30%, pyruvate — by 35%, and malate dehydrogenase by 46%, further confirmation of the facts established previously that dehydrogenase activity of the brain mitochondria is dependent on glucocorticoids. All these changes were accompanied by activation of neuronal uptake of choline into PC and NR. After injection of neurotropin into the irradiated animals a tendency was noted for normalization of the activity of the neurotransmitter processes studied. The strongest normalizing action of neurotropin was found on activity of glycinergic processes. Normalization of activity of noradrenergic and dopaminergic processes also was observed in PC. These changes were accompanied by a significant fall in activity of the cholinergic system in PC and NR (Fig. 1b). Evidence of the normalizing effect of neurotropin also was given by restoration of the reciprocity of serotoninergic/dopaminergic relations and activity of the hypothalamo—hypophyseo—adrenocortical system characteristic of the adequate response of the animals to extremal influences. The cAMP level in PC and the pituitary gland was restored under these circumstances from 212 and 297% to 118 and 149% respectively. A tendency also was noted for activity of dehydrogenases of the Krebs cycle to be normalized.

The normalization of neurotransmitter relations in the various brain structures discovered in these experiments and of activity of the hypothalamo—hypophyseo—adrenocortical system suggests that neurotropin can perhaps be used as a preparation moderating the picture of chronic radiation stress and diencephalic changes, lying at the basis of disturbances of functions of several systems of the body, in the late period after irradiation.

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