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ROLE OF THE PERIPHERAL ADRENERGIC COMPONENT IN EFFECT OF ANTIDEPRESSANT ON EXPERIMENTAL BEHAVIORAL DEPRESSION IN CATS

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Pharmacological, biochemical, and neurochemical factors of psychotropic activity of the new antidepressant befol (synthesized at the Research Institute of Pharmacology Academy of Medical Sciences of the USSR, and Institute of Organic Chemistry, Academy of Sciences of the Ukrainian SSR) have been studied on models of experimental depressive states. It has been shown that its normalizing therapeutic effect is based on activation of functionally weakened adrenergic and serotoninergic structures of the central and peripheral nervous system [1-3]. Various other antidepressants and, in particular, nialamide, which possess similar mechanisms of action on neurotransmitter systems, have been used on the same model for the purpose of comparative study [5, 7, 9, 10]. The object for special study in the investigation described below was the morphological and functional state of peripheral adrenergic nerves in a reserpine model of behavioral depression in cats, and also dependence of restoration of their neurotransmitter activity on the action of befol and nialamide.

EXPERIMENTAL METIIOD

Experiments were carried out on 30 noninbred male cats weighing 3.5-4.5 kg. A state of behavioral depression was induced by subcutaneous injection of reserpine in a single dose of 0.1 mg/kg [4]. Befol in a dose of 0.5 mg/kg and nialamide in a dose of 15 mg/kg were injected by the enteral route. In the case of treatment of depression, the drugs were admini stered twice a day (24-48 h after reserpine), whereas for prevention, they were given 3 h before the experiment began. The duration of the experiments varied from 24 to 144 h. At each stage of development of depression various parameters of somatic and autonomic disorders and also changes in the emotional and motivational spheres characteristic of the state of depression in the experimental animals were recorded. Material for histochemical study consisted of different parts of the serous membranes (mesentery, pericardium, and pleura). Their adrenergic innervation was demonstrated by the Falck–Hillarp fluorescence-microscopic method. For quantitative evaluation of the intensity of noradrenalin-induced luminescence, the FÉU-19 photosensitive attachment was used with the ML-2 microscope as described previously [6]. Material was taken 24, 48, 96, and 144 h after the beginning of the experiment. The animals were killed by air embolism.

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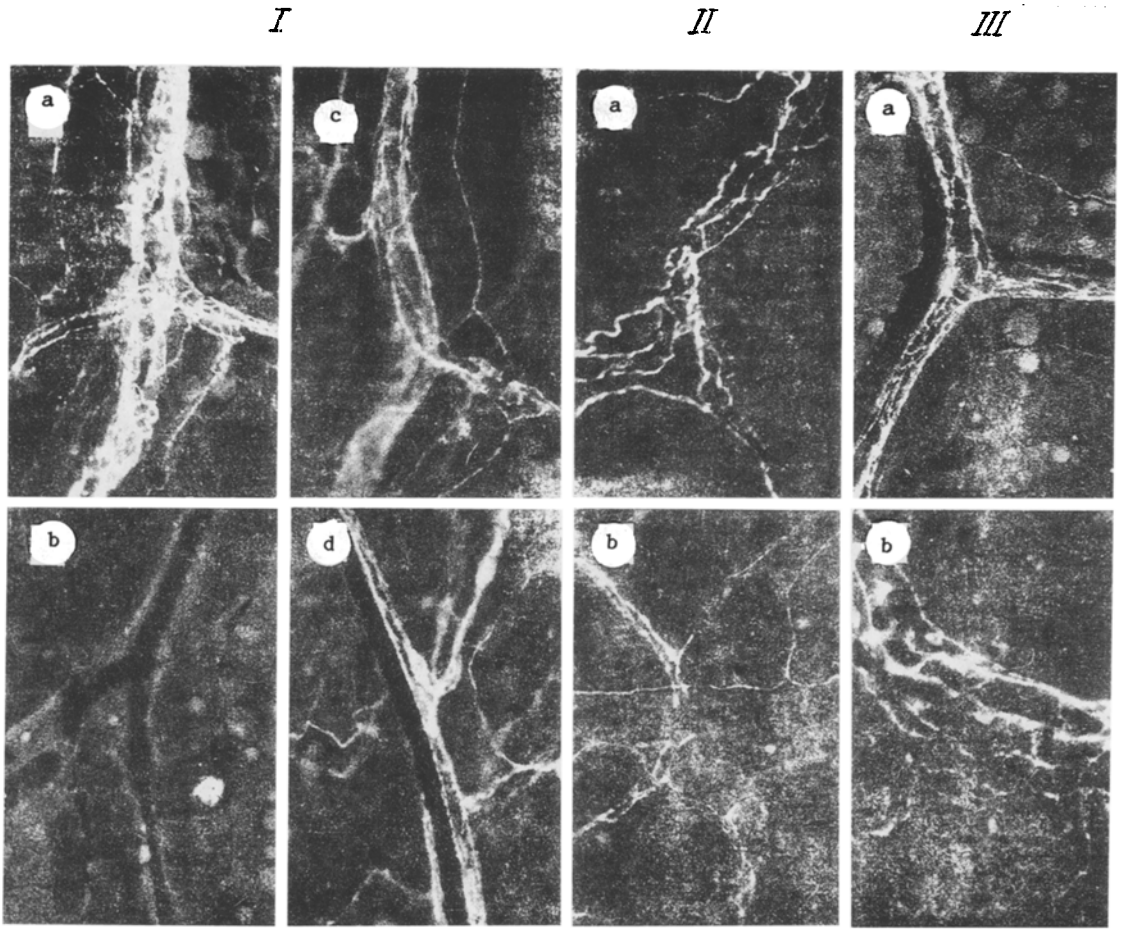

Fig. 1. Adrenergic innervation of microvessels of cat mesentery. Method of Falck and Hillarp. Ia) Control (normal); Ib, c, d) 24, 48, and 144 h after injection of reserpine. IIa, b) 48 h after administration of befol (a) and nialamide (b) (prevention). IIIa, b) 96 h after administration of befol (a) and nialamide (b) (treatment).

TABLE 1. Intensity of Luminescence (conventional units) of Adrenergic Nerves of Cat Mesentery at Different Stages of Depressive State ($M \pm m$)

Drug	Time of observation, h	
	48	144
Reserpine	9,2±2,2	51,7±4,4
Befol (treatment)	11,3±2,5	52,6±4,8
Nialamide (treatment)	10,5±2,5	50,8±5,1
Befol (prevention)	24,6±2,7*	53,1±4,5
Nialamide (prevention)	18,4±1,8*	52,4±5,3

Legend. Intensity of luminescence of adrenergic nerves in normal (intact) cats was 100 ± 4.5 conventional units. $^{*}p \leq 0.05$. Significant differences between effects of befol and nialamide.

EXPERIMENTAL RESULTS

To assess the morphological and functional state of adrenergic nerves of the serous membranes under the influence of befol and nialamide, we used as our starting point data characterizing the level of neurotransmitter activity of the corresponding innervation apparatus in normal (intact) cats, and also in reserpinized control animals. According to our observations, the fiber, preterminal, and terminal divisions of the adrenergic nerves normally possess a sufficiently high level of noradrenalin luminescence (Fig. 1a). Quantitative expression of their neurotransmitter activity, in conventional luminescence units, we adopted as the

starting point, and by comparison with this parameter a comparative evaluation was made of the state of the adrenergic nerves in all series of experiments (Table 1). Such a sharp decrease in noradrenalin luminescence took place 24 h after injection of reserpine that the adrenergic nerves virtually were invisible (Fig. 1b). After 48 h the intensity of luminescence of the adrenergic nerves was not more than 10% of the original (normal) level. Later neurotransmitter activity gradually recovered. Toward the end of the 4th day the intensity of luminescence of the adrenergic nerves reached 40%, and after 6 days it reached 50% of the initial level (Table 1; Fig. 1c, d).

Comparative analysis of the histochemical preparations showed that in the experiments with befol and nialantide the time course of neurotransmitter activity of the adrenergic nerves largely depended on the times of injection of the antidepressants. As was stated above, the drugs for prevention of the state of depression were injected 3 h before reserpine, those intended for treatment 24 h after reserpine. In the first case, at the 48 h stage the intensity of luminescence of the adrenergic nerves was 20% of the initial level, twice as high as the quantitative parameters characterizing the degree of transmitter activity at the same stage in the control experiments. It must be pointed out that the intensity of luminescence of adrenergic, nerves after administration of befol was higher on the whole than the corresponding values in the experiments with nialamide (Table 1). After 4 days had elapsed the effect of the drugs was no longer significant. The reason for this was evidently that at this stage of the experiments marked recovery of neurotransmitter activity had taken place, and against the background of this regular process, the action of antidepressants was virtually impossible to detect. These remarks apply equally to later stages of the experiments, which were characterized by further recovery of neurotransmitter activity of the adrenergic nerves, independently of the action of the drugs. In the experiments in which befol and nialamide were given 24 h after reserpine, i.e., on the model of treatment of a depressive state, no effect of pharmacological correction of neurotransmitter activity could be found. At all stages of development of depression the intensity of luminescence of the adrenergic nerves revealed no significant dependence on the therapeutic action of thee antidepressants, and it virtually corresponded to the time course of neurotransmitter activity of these innervational structures as recorded in the control experiments (Table 1, Fig. 1).

On the basis of the results of this investigation definite agreement was found between the morphological and functional state of the peripheral adrenergic component (with particular reference to adrenergic nerves of serous membranes) and the character of development of a reserpine model of behavioral depression in cats. The many manifestations of somatic and autonomic disorders developing 24 h after injection of reserpine (hypodynamia, catalepsy, diarrhea, ptosis, etc.), and also signs of deep behavioral depression coincided in time with the depressant action of reserpinization on neurotransmitter activity of adrenergic terminals. The duration of this period (2nd-4th days after injection of reserpine) corresponds to the period of enhancement of the whole symptom-complex of pathological changes characterizing the stage of marked depression of behavior. The after effect of reserpine began to return to normal toward the era of the 4th day, but even after 6 days neurotransmitter activity of the adrenergic nerves was not fully restored, but had reached only 50% of the initial level. This period corresponded to the beginning of emergence of the animals from the state of depression.

As has been pointed out, administration of befol and nialamide for therapeutic purposes (24 h after reserpine) did not have the expected effect. The reason evidently is that antidepressants were used at the stage of the least destructive action of reserpine, leading essentially to a state of functional desympathization of all organs and tissues (including brain structures). Not only total exhaustion of the neurotransmitter reserves, but also temporary blockade of its resynthesis in adrenergic structures [8, 11] ruled out any possibility of activation of monoaminergici processes, whether with befol or with nialamide. At the same time, it has to be pointed out that the ability of befol to raise the tone of the serotoninergic system (as shown by the results of our biochemical investigations) could lead to an effect of pharmacological correction of the depressive state and, in particular, in the sphere of the emotional and motivational behavior.

The distinct protective action of the two antidepressants was observed in experiments with prevention of depression, when the drugs were given 30 min before reserpine. Under these conditions, it was still possible for intensification of adrenergic processes to take place, and against this background subsequent administration of reserpine did not exert such an inhibitory action on neurotransmitter activity of the adrenergic nerves. This state of affairs to some extent determines the higher level of noradrenergic luminescence of neural structures than in the control experiments, observed in the early stages of development of the depressive state. As was pointed out above, after administration of befol the intensity of luminescence of the adrenergic nerves and, consequently, the level of their neurotransmitter activity, was characterized by higher values than in the experiments with nialamide.

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EFFECT OF ANTIOXIDANTS ON MEMBRANE-TOXIC EFFECTS OF ANTICHOLINESTERASES

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Some biologically active compounds are known to damage cell membranes [1]. One of the principal mechanisms of the membrane-toxic action of xenobiotics is acceleration of lipid peroxidation (LPO) under their influence. For instance, some anticholinesterases such as malathion, possess a natural pro-oxidant action, whereas other (0,0-dimethyl-2,2-dichlorovinyl phosphate; DDVP) do not possess pro-oxidant activity [3]. For this reason, specific methods of treatment of the corresponding forms of poisoning are frequently insufficiently effective.

The aim of this investigation was to study the possibility of correcting membrane-toxic effects of poisons by means of antioxidants. The organophosphorous insecticides, possessing membrane-stabilizing properties [5], and combining antioxidative activity (AOA) with ability to block Ca^{2+}-channels [2, 6, 8], were used in the experiments.

EXPERIMENTAL METHOD

Experiments were carried out on male albino rats (150-180 g) and albino mice. The velocity of LPO was determined by a chemiluminescence method based on slowing of the rise of the "slow flash" of chemiluminescence in supernatant obtained after

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