inhibited serotonin uptake by 60-70%, only in a concentration of 500 μM. All the antidepressants studied in this concentration inhibited GABA uptake by 50-70%. In a concentration of 50 μM only chlorimipramine and azaphen significantly inhibited GABA uptake by 30-45%; all other substances studied did not affect GABA uptake in this concentration.

These data on the inhibitory effect of antidepressants on serotonin and GABA uptake by rat brain synaptosomes are in agreement with analogous results obtained for imipramine in experiments with a pure synaptosomal fraction [2-4].

It can thus be postulated that the inhibitory effect on the neuronal uptake of serotonin plays a definite role in the mechanism of action of the atypical antidepressants inkazan and trazodone, and in this respect they are similar to imiprazine and its analogs. Inhibition of ^{3}H-GABA uptake observed for most substances only in high concentrations, evidently plays a minor role in the effect of the atypical antidepressants.

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EFFECT OF BENACTYZINE AND GALANTHAMINE ON BEHAVIORAL EFFECTS OF APOMORPHINE IN RATS

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KEY WORDS: apomorphine; benactyzine; galanthamine.

Apomorphine stereotypy is one of the most frequently used behavioral tests of the dopaminergic neurotransmitter system. However, analysis of the behavioral effects of apomorphine is often rough and descriptive in character; often other forms of an animal's motor activity are not taken into account although these are important, for example, for analysis of the action of a drug on particular brain structures that participate in the regulation of motor activity and for the interpretation of relations between neurotransmitter systems in these structures.

The object of this investigation was to study the effects of apomorphine depending on the dose used, either separately or in conjunction with the reversible acetylcholinesterase inhibitor galanthamine and the central cholinolytic benactyzine.

EXPERIMENTAL METHOD

Experiments were carried out on 75 noninbred male albino rats weighing 180-250 g. The animals' motor activity was studied by means of an Animex type DSE apparatus, the sensitivity of which was set at the levels of 40 and 10 μA, so that it was possible to record the total number of all movements in a chosen time unit and, at the same time, to analyze motor acts characteristic of locomotor activity. From the total number of all the animal's movements the number of changes of place was subtracted, to give the number of characteristic motor acts of the stereotypy. The experiments were conducted in daylight hours between 9 a.m. and 4 p.m., and the behavior of only one animal was studied each time. The investigation began with a 30-min period of adaptation, and the number of small movements and changes of place during 5 min in

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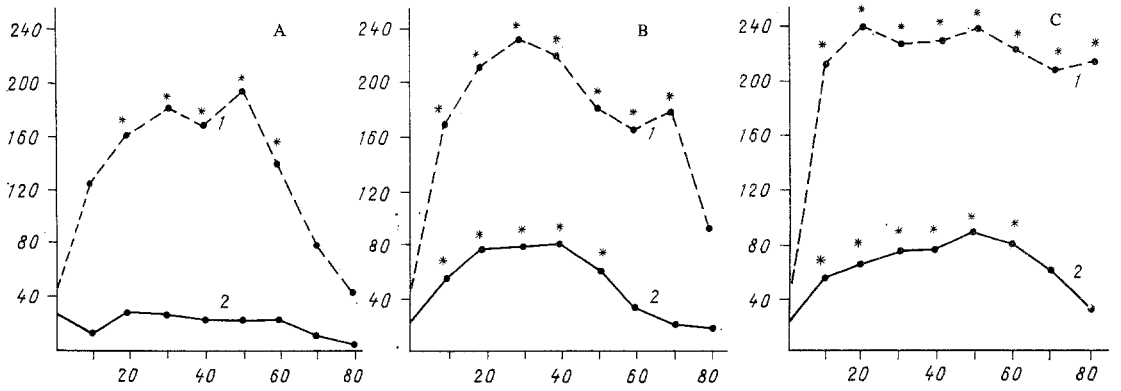

Fig. 1. Number of small movements (1) and changes of place (2) of rats under the influence of subcutaneous injection of apomorphine in doses of 1.0 (A), 2.5 (B), and 5.0 mg/kg (C). Abscissa, duration of experiment (in min); ordinate, number of movements. Asterisk indicates significance of differences from background level. Movements recorded after injection of apomorphine.

the second half of this period, averaged for all series of experiments, was taken as the background level. In all experiments both types of movements were recorded for 5 min during each 10-min interval after administration of the drugs; the total duration of observation was not less than 80 min.

Animals of the first three groups (1, 2, and 3) were given a subcutaneous injection of a freshly made up solution of apomorphine in doses of 1.0, 2.5, and 5.0 mg/kg, respectively. The number of small movements and changes of place of the animal every 10 min after injection of apomorphine (the average for each group) was compared with the background value, and the significance of differences was determined by Student's t-test. The effect of apomorphine was later studied after preliminary administration of galanthamine in a dose of 2.5 mg/kg, benactyzine in a dose of 1.0 mg/kg (both injected intraperitoneally), and a combination of the two, in the following groups of experiments: 4) galanthamine only, 5) benactyzine only, 6) galanthamine + 1.0 mg/kg apomorphine 10 min later, 7) benactyzine + 1.0 mg/kg apomorphine 15 min later, 8) benactyzine + galanthamine 5 min later, followed by 1.0 mg/kg apomorphine 15 min later, 9) galanthamine + 2.5 mg/kg apomorphine 10 min later, 10) galanthamine + 2.5 mg/kg apomorphine 40 min later. In all experiments movements began to be recorded from the time of injection of apomorphine. Data on the same movements of the animals at corresponding moments of the experiment but after injection of apomorphine alone in the same doses served as the control. The volume of all solutions injected was 1.0 ml/kg.

EXPERIMENTAL RESULTS

In a dose of 1.0 mg/kg apomorphine evoked a distinct stereotypy in the animals of group 1, which appeared in the form of intensive and monotonous sniffing, small nodding movements of the head, and licking, and a significant increase in the number of small movements recorded from the 20th minute after injection of the drug, and which was observed thereafter for 40 min. The number of changes of place during the experiment did not differ from the background level (Fig. 1A). Apomorphine in a dose of 2.5 mg/kg (group 2) evoked not only the stereotypy, but also motor hyperactivity with a significant increase in the number of changes of place as early as by the 10th minute, and which lasted 40 min. In the animals of this group compared with the previous one the number of small movements began to increase 10 min earlier, and this increase was noted for 60 min (Fig. 1B). An increase in the dose of apomorphine to 5.0 mg/kg (group 3) led to an increase in the number of small movements in the course of the experiment, and the number of changes of place was significantly greater than the background level during the first 50 min (Fig. 1C).

Injections of benactyzine alone or of galanthamine alone caused no changes in the animals' spontaneous behavior. In the rats of group 6, after injection of apomorphine in a dose of 1.0 mg/kg after preliminary injection of galanthamine, the number of small movements characteristic of stereotypy in the course of 40 min remained significantly less than in the control (group 1), and the number of changes of place was unchanged (Fig. 2A). Preliminary injection of benactyzine did not modify the behavioral effect of subsequent injection of apomorphine (group 7, Fig. 2B). However, in the animals of group 8, which were given benactyzine first, followed by galanthamine, and finally apomorphine in a dose of 1.0 mg/kg, by contrast with the rats of group 6, the number of small movements and changes of place did not differ significantly from the corresponding control, in which the animals received apomorphine only, in the same dose. If galanthamine was injected 10 min before apomorphine in a dose of 2.5 mg/kg (group 9) the effect of the latter was considerably modified: The number of changes of place characteristic of locomotor activity in the course of 50 min after injection was significantly less than in the control animals of group 2, which received apomorphine in the same dose; the number of small movements also remained less than in the control in the course of 40 min (Fig. 3A). With an increase in the interval between injections of galanthamine and the subsequent injection of apomorphine to 40 min the action of the latter on the rats of group 10 was the same as when apomorphine only was given in the control (Fig. 3B).

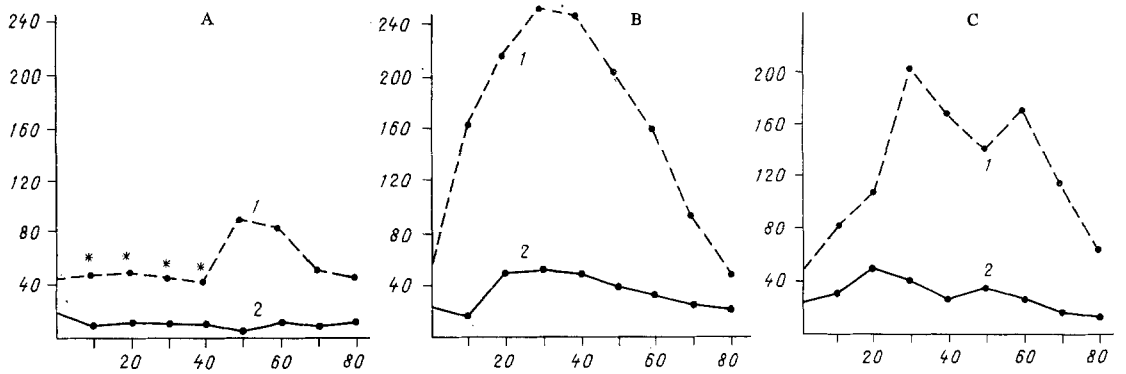

Fig. 2. Number of small movements and changes of place by rats receiving different combinations of drugs. A) Galanthamine 2.5 mg/kg + apomorphine 1.0 mg/kg 10 min later, B) benactyzine 1.0 mg/kg + apomorphine 1.0 mg/kg 15 min later, C) benactyzine 1.0 mg/kg + galanthamine 2.5 mg/kg 10 min later, + apomorphine 1.0 mg/kg 15 min later. Asterisk denotes significance of difference with control (apomorphine 1.0 mg/kg). Remainder of legend as in Fig. 1.

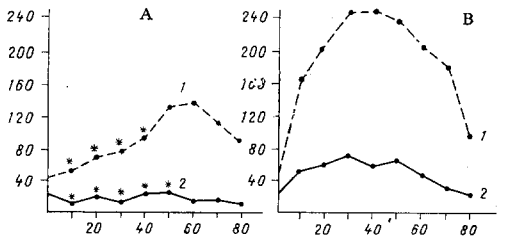

Fig. 3. Number of small movements and changes of place by rats receiving different combinations of drugs. A) Galanthamine 2.5 mg/kg + apomorphine 2.5 mg/kg 10 min later, B) galanthamine 2.5 mg/kg + apomorphine 2.5 mg/kg 40 min later. Asterisk indicates significance of differences from control (apomorphine 2.5 mg/kg). Remainder of legend as in Fig. 1.

As shown above, the action of apomorphine may induce qualitatively different effects in rats depending on its dose: stereotypy if given in a dose of 1.0 mg/kg and an increase in locomotor activity if doses 2.5 and 5 times larger are given. Accepting some modern views on the characteristics of function of dopamine (DA) receptors [1-4, 7, 15], the experimental results suggest that DA systems not only of the neostriatum, but also of mesolimbic structures participate in the organization of the behavioral effects of apomorphine. The differences found in the behavior of the animals under these circumstances were due to changes in these systems and disturbance of the balance between them [4]. In a dose of 1.0 mg/kg apomorphine evidently stimulates the DA receptors of the neostriatum, thus inducing stereotypy. Meanwhile, although only a very weak antagonist of mesolimbic DA receptors, in large doses (2.5-5.0 mg/kg) apomorphine evidently depresses them, so that besides stimulation it also leads to the apppearance of locomotor excitation in the neostriatum. Participation of striopallidal and mesolimbic structures in the formation of the behavioral effects of apomorphine, which other investigations have shown [11-13], suggests that the stereotypy and locomotor activity are mediated by different mechanisms [14].

The results of the present experiments also suggest that the influence of the cholinergic system on DA mediation in the brain structures mentioned above is not necessarily characterized by strict antagonism. Changes in the functional state of the cholinergic system produced by galanthamine, although not evoking behavioral reactions, were sufficient to reverse the effects of the direct DA agonist, apomorphine. This observation is evidence of the antagonism which was observed also when the effect of physostigmine on apomorphine-induced stereotypy was studied in mice [10]. When the activity of the cholinergic system was depressed by benactyzine, likewise causing no changes in behavior when given alone, the effect of subsequent administration of apomorphine (1.0 mg/kg) was unchanged. Had antagonism been presented between the cholinergic and DA systems, under the present experimental conditions changes in the behavioral response of the rats to apomorphine might have been expected – the appearance of locomotor hyperactivity. The dose of benactyzine was so chosen in these experiments that even a very small increase could evoke motor hyperactivity in the rats when given alone. The results of this series of experiments show that the effect of the cholinergic system on DA mediation in individual brain structures may be not only antagonistic, but also modulating in character, as was suggested in [6, 9].

The characteristic behavioral effects of apomorphine (2.5 mg/kg) developed in the rats 40 min after injection of galanthamine, i.e., after an interval during which the anticholinesterase action of the reversible inhibitor, significant under the experimental conditions used, was evidently exhausted. This fact, and also observations in which preliminary administration of benactyzine completely prevented antagonism between galanthamine and apomorphine, in agreement with existing views [6], are evidence that the effects of the drugs used, which modified activity of the cholinergic system, were effected through muscarine acetylcholine receptors. These receptors are known to be localized in the mesolimbic structures presynaptically, on DA terminals [8], whereas in the neostriatum, the influence of the cholinergic system on DA mediation is effected through interneurons [5]. The present investigations suggest that the method of separate quantitative analysis of changes in behavioral reactions to apomorphine after preliminary injection of cholinolytics or cholinomimetics can be used to judge the contribution of cholinergic neurotransmitter systems of the various brain structures to the central regulation of movement.

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EFFECT OF GLUCOCORTICOIDS ON FRACTIONAL COMPOSITION AND DERIVATIVES OF HEMOGLOBIN IN RATS

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KEY WORDS: glucocorticoids; fractions; derivatives; hemoglobin; rats.

Natural and synthetic glucocorticoid preparations are widely used for the treatment of patients with many diseases, including iron deficiency, hypoplastic, aplastic, and other forms of anemias, and including diseases due to the presence of abnormal forms of hemoglobin [1, 5]. Information on the effect of hormone preparations on the qualitative composition of hemoglobin cannot be found in the literature.

The object of this investigation was to determine the fractional composition and derivatives of hemoglobin in experimental animals after prolonged administration of natural and synthetic glucocorticoids most frequently used in clinical practice.

EXPERIMENTAL METHOD

Experiments were carried out on 48 noninbred male albino rats weighing 180-220 g. Preparations of hydrocortisone and its synthetic analogs were used in doses giving equivalent effects: hydrocortisone acetate 10.0 mg/kg, prednisolone

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