EFFECT OF AMINOESTERS OF SUBSTITUTED GLYCOLLIC AND ACETIC ACIDS ON NORADRENALIN CONTENT IN THE RAT BRAIN

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Aminoesters of diphenylglycollic acid (benactyzine and glypin – 40 mg/kg, n-methyl-4-hydroxypiperidylbenzilate (MPB) – 10 mg/kg), like amphetamine (5 mg/kg) produced motor excitation in rats and lowered the noradrenalin (NA) concentration in the brain tissues. The dynamics of the changes in NA concentration in the brain correlated with changes in the animals' behavior. Aminoesters of diphenylacetic acid (adiphenine and tropazine, 40 mg/kg each) had the opposite action: inhibition of motor activity of the animals and an increase in NA concentration in the brain tissue. Derivatives of glycollic acid, in the writers' opinion, like amphetamine can liberate unstably bound NA in a physiologically active state from the depots.

As reported previously [3], some central cholinolytics belonging to the group of aminoesters of diphenylglycollic acid, such as benactyzine, glypin, and n-methyl-4-hydroxpiperidylbenzilate (MPB), unlike their acetic analogs (adiphenine and tropazine), produce motor excitation in rats which, if the cholinolytics are given in large doses, changes into a state of stereotyped behavior resembling the phenomenon of the "amphetamine stereotype" [11]. Pharmacological analysis of the mechanism of development of this excitation [4, 7-9] led to the suggestion that aminoesters of diphenylglycollic acid, besides blocking cholinergic systems, can participate in some way in the function of adrenergic brain mechanisms.

It is thus necessary to investigate the effect of cholinolytics on the catecholamine level in the rat brain at various times after their administration and, by studying the dynamics of this process, to determine whether a correlation exists between changes in the level of these amines and the degree of motor activity of the animals.

EXPERIMENTAL METHOD

Experiments were carried out on male rats weighing 180-200 g. The concentration of catecholamines in the brain was determined 1, 2, 4, and 24 h after intraperitoneal injection of the compounds. In each experiment a parallel study was made of the concentration of catecholamines in the brain of control animals that received physiological saline. The rats were sacrificed by decapitation, the brain (without the cerebellum) was removed and treated by the method of Euler and Lishajko [18], catecholamines were oxidized by the method of Euler and Floding [17], and they were subsequently estimated by the use of the spectrofluorometer developed by Krylov and co-workers [5].

EXPERIMENTAL RESULTS AND DISCUSSION

The NA concentration in the brain tissues of control rats differed slightly in different batches (from 0.38 ± 0.02 to 0.458 ± 0.008 μg/g), but within each batch the variations were negligible. Values obtained in

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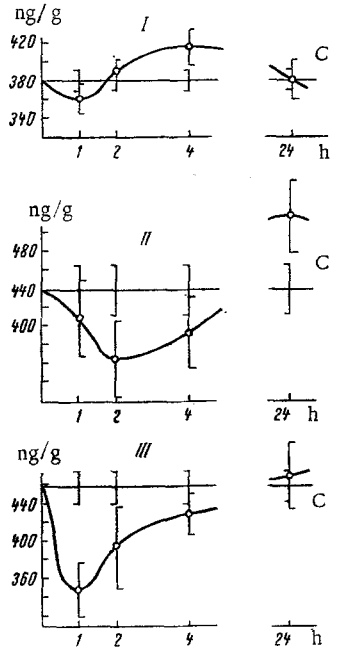

Fig. 1. NA concentration in rats' brain after injection of glypin in a dose of 40 mg/kg (I), benactyzine, 40 mg/kg (II), and MPB, 10 mg/kg (III). C – control. Abscissa, time of determination (in h); ordinate, NA concentration (in ng/g tissue).

the present experiments for the NA concentration in the brain of intact rats agreed with those given in the literature [1, 10, 15, 26, 27]. Virtually no adrenalin could be detected (traces only) in the brain tissue, in agreement with results obtained by other workers [13, 15, 17].

Following injection of benactyzine and glypin, in doses of 40 mg/kg in each case, and of MPB in a dose of 10 mg/kg, the rats developed marked motor excitation, interspersed with periods of disturbance of normal locomotion with features of stereotyped reactions. Under the influence of MPB and benactyzine, the NA concentration in the brain tissues fell considerably (Fig. 1), the effect reaching its maximum after 1-2 h, after which the level of NA began to recover and after 24 h it was actually higher than in the control experiments (especially in experiments with benactyzine). Under the influence of glypin, the NA concentration in the rats' brain also was decreased, only for a short time, but by a significant degree. Smaller doses of benactyzine, glypin, and MPB did not cause motor excitation among the rats and had no significant effect on the NA concentration in the brain tissues.

Two facts from this series of experiments appear to be particularly noteworthy. First, a definite resemblance was observed between the character of the curve showing the decrease in NA concentration during the action of glycollic acid derivatives (especially MPB and benactyzine) and of amphetamine in a dose of 5 mg/kg (Fig. 2), which was taken for comparison. Second, a parallel was revealed between the intensity of excitation of the rats and the degree of lowering of the NA level in the brain. Whereas a characteristic feature of the action of benactyzine and MPB was a rapid increase in motor excitation during the 1-2 h after injection of the drugs, followed by gradual relaxation and recovery of normal behavior at about the 4th hour of observation, after injection of glypin the period of excitation lasted only about 1 h, following which the motor activity of the animals was considerably inhibited. The results of this series of experiments agree with those obtained by Sharov [10], who demonstrated a definite connection between the severity of motor excitation in rats and the decrease in NA concentration in the animals' brain following administration of pipradrol and amphetamine. Following injection of adiphenine and tropazine in a dose of 40 mg/kg, the opposite effect was observed: definite inhibition of the rats' motor reactions and a marked increase in the NA concentration in the brain tissues (Fig. 3). With restoration of the animals' normal behavior, the NA concentration in the brain was restored.

The motor excitation of the rats developing under the influence of aminoesters of diphenylglycollic acid could be explained on the basis of the basic property of these compounds: their high central cholinolytic activity. Several workers [12, 14], for example, regard this effect of excitation as the result of blocking of central cholinergic systems, in consequence of which the activity of the brain's adrenergic mechanisms predominates over its cholinergic.

Disturbance of the balance between the cholinergic and adrenergic systems evidently plays some role in the enhanced manifestation of function of the central sympathetic structures. However, it is impossible on this basis to understand the fundamentally different effects of cholinolytics which are derivatives of acetic and glycollic acids on the motor activity of rats. It was concluded from the earlier pharmacological analysis of motor excitation arising during the action of glycollic analogs that the effects of this group of central cholinolytics are exerted on adrenergic mechanisms of the brain [3, 7-9]. The results of the present investigation are direct evidence in support of this hypothesis. In the first place, the decrease in NA concentration in the brain and motor excitation were observed only following administration of glycollic acid derivatives. In addition, this effect was observed only when the tested preparations were given in large doses, much higher than doses required for manifestation of their cholinolytic action. It must be emphasized that no strict causal connection could be discovered between the cholinolytic activity of the tested compounds and their effect on the concentration of noradrenalin in the brain.

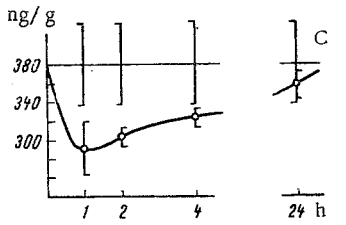

Fig. 2.

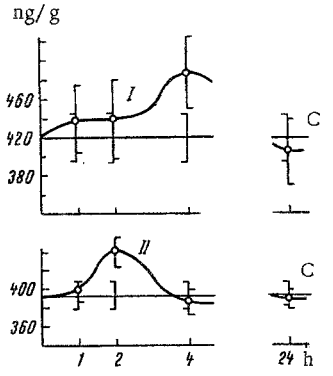

Fig. 3.

Fig. 2. NA concentration in rats' brain after injection of amphetamine in dose of 5 mg/kg. Legend as in Fig. 1.

Fig. 3. NA concentration in rats' brain after injection of adiphenine in dose of 40 mg/kg (I) and tropazine in dose of 40 mg/kg (II). Legend as in Fig. 1.

Although the fact that the NA level in the brain tissues was reduced is without doubt weighty evidence in support of direct interference with the function of the adrenergic systems of the brain in the presynaptic component, it does not answer the question through what mechanisms this decrease in NA concentration in the brain is brought about. Many drugs which exhaust the catecholamine reserves in the brain differ in their action on animal behavior: from deep "depression" in the case of reserpine to acute excitation after administration of the sympathomimetic amines [1, 2, 6, 10, 22, 23, 26, 28]. The reason for this difference in the effects of these drugs, as subsequent investigations [16, 19-21, 24, 25] have shown, is that the compounds have different points of application to the complex processes of biosynthesis, assimilation, storage, mobilization, and inactivation of catecholamines. The similarity between the character of action of the aminoesters of the substituted glycollic acids with the action of amphetamine, pipradrol, and meridil as shown by the "stereotype" and "group toxicity of amphetamine" tests in experiments on reserpinized animals [3, 4, 7, 9], and also the results of the present investigation, all suggest that aminoesters of glycollic acid derivatives have the ability, like amphetamine [20], to liberate unstably bound NA from its depots in a physiologically active state, thus causing the animals to develop motor excitation.

The mechanism of elevation of the NA level in the rat brain during the action of aminoesters of acetic acid derivatives (adiphenine and tropazine) still remains obscure and requires special investigation.

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