# ROLE OF ADRENERGIC MECHANISMS IN THE DEVELOPMENT OF MOTOR EXCITATION IN RATS CAUSED BY BENACTYZINE

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Previous investigations [1] showed that central cholinolytics of the group of amino esters of diphenylglycolic acid, for example benactyzine, in certain conditions cause behavior disturbances in rats, manifested by intensive motor excitation. This excitation, as a preliminary pharmacological analysis showed, cannot be attributed wholly to blocking of the cholinergic receptors of the central nervous system. Moreover, of the large group of substances having a predominant action on the central nervous system, only the phenylalkylamines (amphetamine, ephedrine, meridil, and pipradrol) caused the same motor excitation as the amino esters of diphenylglycolic acid.

The results of our investigations suggested that glycolic acid derivatives may act on certain links of the adrenergic mechanisms of the brain. To test this hypothesis a comparative study was made of the action of a series of adrenergic blocking agents on the motor excitation of rats caused by the cholinolytic benactyzine and the sympatheticomimetic agent amphetamine.

## EXPERIMENTAL METHOD

The behavior reactions of rats were studied by our modification of the technique* of Naess and Rasmussen [6]. By this technique the following indices could be examined: the latent period of the reflex (the time from the moment of placing the rat in the chamber until it began to drink water from the dish), the number of shocks with the current during the attempt to drink water, the number of approaches to the dish (goal-directed motor reaction) and the general motor activity. In profound disturbances of the behavior reactions in the animals "subcortical automatisms" were observed – uniform movements of the animal against the background of general motor inhibition, called stereotypy for short.

As representative of the amino esters of diphenylglycolic acid, benactyzine (the Soviet preparation amizil) was selected, and of the adrenergic blocking agents we investigated cinchocaine, dihydroergotamine (DHET), sympatholytin (the bromide analogue of dibenamine) and chlorpromazine.

## EXPERIMENTAL RESULTS

It is clear from the table that benactyzine excitation was characterized by a disturbance of the conditioned-reflex component of the motor reaction (lengthening of the latent period of the reflex), a considerable increase in the number of approaches to the drinking bowl, intensification of the general motor activity, and the appearance of stereotyped movements. In response to the combined action of the cholinolytic and adrenergic blocking agents, only chlorpromazine completely abolished the benactyzine excitation. The other adrenergic blocking agents (DHET, cinchocaine, sympatholytin) diminished the disturbance of the behavior reactions but did not abolish them completely. It should also be noted that after administration of benactyzine in conjunction with adrenergic blocking agents, a clear increase was observed in the number of electric shocks received by the animal during its attempt to drink water. The mechanism of this phenomenon remains uninvestigated.

* An article describing the technique is in the press.

Effect of Adrenergic Blocking Agents on Motor Excitation Caused by Benactyzine and Amphetamine

| Compounds investigated (doses in mg/kg in parentheses) | Latent period of reflex (in sec) | Number of electric shocks | Number of approaches to drinking bowl | General motor activity | Stereotyped reactions |
|---|---|---|---|---|---|
| Physiological saline (control) | 2 | 2.7 | 8.7 | 21.6 | Absent |
| Benactyzine (30) | 56.4 (P = 0.02) | 3.9 | 45.7 (P < 0.001) | 110.5 (P < 0.001) | Present |
| Cinchocaine (10) | 2 | 3.5 | 6 | 12 | Absent |
| Benactyzine (30) + cinchocaine (10) | 53.5 (P < 0.02) | 10.2 (P < 0.001) | 4.3 | 20.5 | Present |
| DHET (1) | 1.8 | 3.5 | 2.8 | 12.5 | Absent |
| Benactyzine (30) + DHET (1) | 6.3 (P < 0.01) | 5 (P < 0.001) | 37.3 (P < 0.01) | 93 (P < 0.001) | Present |
| Sympatholytin (40) | 2.5 | 3.2 | 7 | 13.3 | Absent |
| Sympatholytin (40) + benactyzine (30) | 63.6 (P = 0.01) | 9.3 (P = 0.02) | 40.7 (P < 0.05) | 99.6 (P < 0.01) | Present |
| Chlorpromazine (2) | 2 | 2.2 | 3.2 | 11.4 | Absent |
| Chlorpromazine (2) + cinchocaine (10) | 87.7 (P < 0.001) | 14.2 (P < 0.01) | 17.6 | 43.2 | " |
| Benactyzine (30) + chlorpromazine (2) | 41 (P < 0.01) | 18 (P < 0.05) | 28.5 | 61.8 | " |
| Amphetamine (10) | 9 – ∞* | 1 | 6 | 28 | Present |
| Amphetamine (10) + cinchocaine (10) | 3 | 0 | 0.5 | 1.5 | " |
| DHET (1) + amphetamine (10) | 5 | 0 | 9 | 41 | " |
| Sympatholytin (40) + amphetamine (10) | 6 | 0.2 | 6.2 | 19.8 | " |
| Amphetamine (10) + chlorpromazine (2) | 1 | 2 | 4 | 12 | Absent |

* During the experiment the rat did not approach the drinking bowl.

The motor excitation caused by amphetamine was characterized by a considerable increase in the length of the latent period of the reflex and by continuous stereotyped movements, which as a rule masked the other indices of the animals' motor activity. It is clear from the table that all the adrenergic blocking agents restored the latent period of the reflex. Meanwhile the stereotyped reactions, characteristic of the profound disturbances of the animals' behavior, as in the case of excitation with benactyzine were abolished only by chlorpromazine. Sympatholytin merely diminished the severity of these disturbances, while cinchocaine and dihydroergotamine were ineffective.

Of the adrenergic blocking agents investigated only chlorpromazine completely abolished the disturbances of the behavior reactions evoked both by the cholinolytic and by the sympatheticomimetic drug. The results of our experiments are in good agreement with the results of investigations in which motor excitation in the animals was produced by liberation of endogenous catecholamines from the bound state by means of reserpine and monoamine oxidase inhibitors [2, 3]. This type of motor excitation, as in our experiments, was abolished only by chlorpromazine, whereas the other adrenergic blocking agents (dibenamine, ergotamine, and yohimbine) were ineffective [3].

It is interesting to compare the results obtained by studying the behavior reactions of animals with the results of electrophysiological investigations [4, 5] showing that only chlorpromazine and phenoxybenzamine abolish the characteristic changes in the electrical activity of the brain arising after administration of amphetamine. Dibenamine was much less active, and DHET, phentolamine (closely related in structure to cinchocaine), and azapetine were inactive. As the results of these investigations show, the adrenergic blocking agents were arranged in the same order of activity as in our experiments when the behavior reactions of the animals were studied. Meanwhile the results of our experiments do not support the conclusions of these authors [4, 5] that the difference in the activity of the adrenergic blocking agents may be attributed to the difference in the permability of the blood-brain barrier to these compounds, for the disturbance of the conditioned-reflex component of the rats' behavior by amphetamine was abolished by all the adrenergic blocking agents used in our experiments. At the same time, the lengthening of the latent period of the reflex caused by the cholinolytic was not corrected by the adrenergic blocking agents, indicating that different mechanisms are concerned in the disturbances of this component by the action of amphetamine and benactyzine.

The similarity in the character of the motor excitation of the animals caused both by amino esters of diphenylglycolic acid (for example benactyzine) and by sympatheticomimetic amines (for example, amphetamine), and also the order of placing of the adrenergic blocking agents as regards their ability to abolish motor excitation and electrophysiological changes, from our point of view provide weighty evidence in support of the theory that the motor excitation evoked by glycolic acid derivatives is brought about by activation of the adrenergic mechanisms of the brain.

## SUMMARY

An investigation was made of behavior reactions of rats under the effects of benactyzine and phenamine, along with the influence exerted by adrenergic blocking agents upon the motor excitation, produced by these preparations. Chlorpromazine was effective in fully eliminating disturbed behavior reactions produced by benactyzine, dihydroergotamine, benzolin (prescolin) while sympatholytin – did this only partially. Under the effect of amphetamine all of the adrenergic blocking agents were capable of restoring the latent reflex period; but stereotype reactions, produced by the action of amphetamine, could be abolished only by chlorpromazine.

The above data prove that these disturbances appearing under the effect of the glycolic acid derivatives are caused by the activation of adrenergic mechanisms of the brain.

## LITERATURE CITED

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