Journal of Neural Transmission 36, 327—333 (1975)

Antagonism by Baclophen of the *d*-Amphetamine-Induced Disruption of a Successive Discrimination in the Rat

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With 3 Figures

Received February 5, 1975

Summary

Male rats were trained to perform a conditioned avoidance response combined with a successive discrimination in a shuttle-box. The administration of *d*-amphetamine, 4 mg/kg i.p., caused a disruption of the discriminative but not the avoidance behaviour. Baclophen (*β*-[-4-chlorophenyl]-*γ*-aminobutyric acid), a GABA-derivative, given in a dose (4 mg/kg i.p.) that had no effect *per se* on the behaviour in this test situation antagonized the *d*-amphetamine-induced abnormal behaviour without affecting the *d*-amphetamine-induced hypermotility.

The present findings that baclophen antagonized a biochemically induced abnormal behaviour point to an "antipsychotic" action of baclophen in a successive discrimination avoidance test.

Introduction

In a recent experiment (*Ahlenius* and *Engel*, 1975) we have found that l-Dopa, given to rats trained to perform a conditioned avoidance response combined with a successive discrimination, disrupts the discrimination but not the avoidance behaviour. This biochemically induced behavioural abnormality could be normalized by the antipsychotic agent haloperidol, indicating the potential value of a successive discrimination test in the evaluation of antipsychotic drugs.

A recent clinical observation indicates that the GABA-derivative baclophen (β-[-4-chlorophenyl]-γ-aminobutyric acid) may possess antipsychotic properties (*Frederiksen,* 1975). In the present experiments we have therefore investigated whether baclophen has behavioural actions similar to those of haloperidol on the biochemically induced abnormal behaviour in a successive discrimination test. In these experiments the abnormal behaviour was induced by *d*-amphetamine. Unpublished data of this laboratory indicate that haloperidol is capable of restoring normal behaviour also when *d*-amphetamine is used.

Methods

Animals

Nine male Sprague-Dawley rats (Anticimex, Stockholm), weighing about 350 g were used. They were kept under constant temperature and regulated light/dark conditions (light period 6.00 a.m. to 6.00 p.m.). All experiments were performed in the beginning of the dark cycle.

Discrimination Test

The animals were trained to perform a successive discrimination (*Woodworth* and *Schlosberg,* 1954) in a two-way shuttle-box described in detail earlier (*e.g. Ahlenius* and *Engel,* 1975). A buzzer tone served as a conditioned stimulus (CS) signalling the onset of an electric shock, the unconditioned stimulus (UCS), delivered through the grid floor of the box. The partition between the two halves of the box had two openings and the rat could prevent the onset of the electric shock by passing through the right or left door depending on a visual cue light that was placed on the partition. If the visual cue light was on, the rat had to pass through the right opening, and if not the rat had to pass through the left, opening, in order to avoid the shock.

A response within 10 sec after the presentation of the CS was recorded as either a correct conditioned avoidance response (a response through the correct door) or as an incorrect avoidance response (a response through the wrong door). Immediately after any incorrect avoidance response the rat was punished with the UCS until a correct response was made. After 10 sec the CS was followed by the UCS plus CS for maximally another 10 sec, and correct escape or incorrect escape responses were recorded during this time interval. All crossings through the partition between the trials were recorded as intertrial crosses.

Training sessions, 40 trials/session, with an intertrial interval of 15—30 sec, lasted 20—30 min. The rats were trained until at least 3 consecutive sessions with 90 % correct avoidance responses had been achieved (15—20 sessions). Experimental sessions, consisting of 10 trials, lasted 7.5 min.

Drugs

The following drugs were used: *d*-amphetamine sulphate (Smith, Kline and French Lab., Ltd.) and baclophen (β-[-4-chlorophenyl]-γ-aminobutyric acid, Lioresal®, Ciba-Geigy). The doses refer to the forms given.

Results

Effects of d-Amphetamine on Successive Discrimination (Figs. 1 and 2)

The administration of *d*-amphetamine (2 mg/kg i.p.) caused a slight and statistically not significant decrease in the correct avoidance responding 20 and 40 min after the injection. A slight and statistically significant increase in the incorrect avoidance responding was observed 40 min after the injection of *d*-amphetamine (2 mg/kg). There was a very marked increase in the number of intertrial crosses at all time intervals studied.

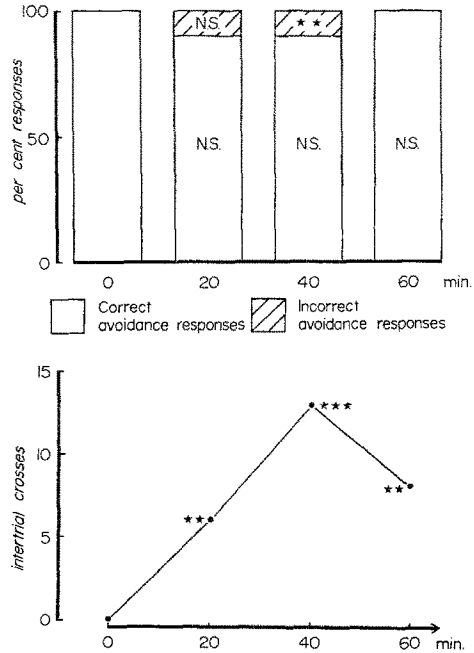

Fig. 1. Effects of *d*-amphetamine (2 mg/kg i.p.) on successive discriminative avoidance behaviour of the rat at different times after the injection. Shown are the medians of 9 rats. Statistical comparisons with "0 min" were performed according to Wilcoxon T-test.
*** $p < 0.01$, ** $p < 0.02$, N.S. $p > 0.05$

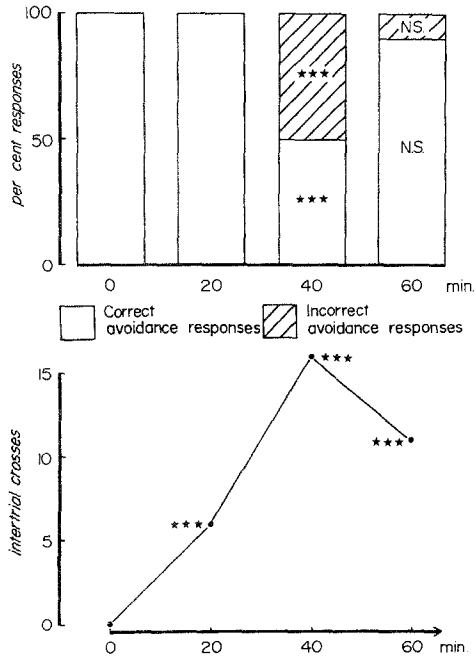

Fig. 2. Effects of *d*-amphetamine (4 mg/kg i.p.) on successive discriminative avoidance behaviour of the rat at different times after the injection. Shown are the medians of 9 rats (the same as in Fig. 1). Statistical comparisons with "0" were performed according to Wilcoxon T-test.
*** $p < 0.01$, ** $p < 0.02$, N.S. $p > 0.05$

Forty min after the injection of *d*-amphetamine in a two times higher dose, 4 mg/kg i.p. (Fig. 2) there was a marked suppression of the correct avoidance responses (50 %) and a corresponding increase in the incorrect avoidance responses (50 %), thus leaving the total number of avoidance responses unchanged and indicating a total and selective loss of the discriminative behaviour. At all time intervals there was a marked increase in intertrial crosses, which did not differ from that seen after 2 mg/kg of *d*-amphetamine. As assessed by gross observation the rats displayed signs of hyperactivity, slightly increased excitability and stereotyped sniffing.

Effects of Baclophen on Successive Discrimination (Fig. 3)

The administration of baclophen in a dose of 4 mg/kg had no effect on the correct avoidance responding when tested 10, 20 and 45 min after the injection (Fig. 3, and unpublished data). In pilot experiments higher doses (10 and 20 mg/kg) caused a marked

muscular hypotonia and the animals were unable to perform in this test situation.

Effects of Baclophen in Combination with d-Amphetamine on Successive Discrimination (Fig. 3)

Treatment with baclophen, 4 mg/kg, resulted in a statistically significant ($p < 0.01$) improvement of the *d*-amphetamine-induced disruption of discriminative behaviour. However, a complete restoration of performance to predrug levels was not achieved ($p < 0.05$).

It is interesting to note that baclophen did not affect the amphetamine-induced increase in intertrial crosses ($p > 0.05$), and, as assessed by gross observation these animals were indistinguishable from those treated with *d*-amphetamine alone.

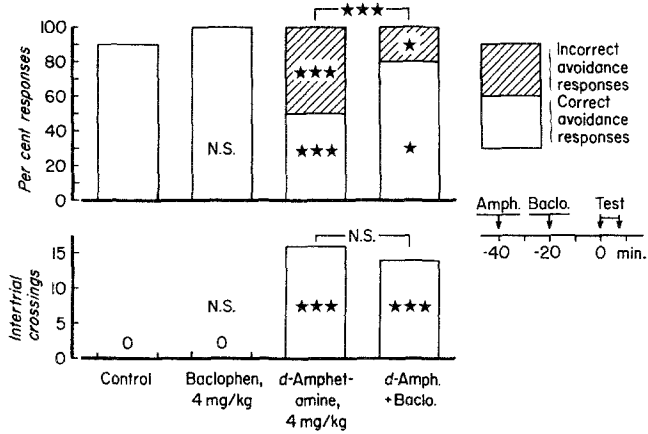

Fig. 3. Effect of *d*-amphetamine, baclophen, and both drugs in combination, on successive discriminative avoidance behaviour of rats. Schedules of drug injections (all i.p.), including doses are given in the figures. Shown are the medians of 9 rats (the same as in Figs. 1 and 2). Statistical comparisons with control and between *d*-amphetamine — *d*-amphetamine + baclophen were performed according to Wilcoxon T-test.

*** $p < 0.01$, ** $p < 0.02$, N.S. $p > 0.05$

Discussion

In the present experiments *d*-amphetamine like l-Dopa (*Ahlenius* and *Engel*, 1975) was found to produce an abnormal behaviour as indicated by the total loss of discriminative behaviour in an avoidance test. The finding that there was no interference with the total number of responses to the CS indicates a highly specific action and

points to a deficient interpretation of environmental stimuli. It is interesting to note that in humans "nontoxic" amphetamine psychosis with an intact sensorium is the model psychosis most closely resembling clinical schizophrenia (*Snyder,* 1974). Needless to say, whether the abnormal behaviour observed in the present experiments is a valid animal psychosis model must be further investigated.

The GABA-derivative, baclophen, was in the present experiments, like haloperidol (*Ahlenius* and *Engel,* 1975), found to improve a biochemically induced abnormal behaviour. However, unlike haloperidol, baclophen could restore discriminative behaviour without affecting the *d*-amphetamine-induced hypermotility. Furthermore, in contrast to haloperidol, baclophen *per se* had no effect on the avoidance behaviour, this indicating a more specific action of baclophen. It should be noted that the dose of haloperidol that normalized the l-Dopa-induced abnormal behaviour, by itself caused a complete suppression of the conditioned behaviour. Taken together, these data indicate that the GABA-derivative, baclophen, from the behavioural point of view has a mode of action different from that of the classical antipsychotic drug haloperidol. The possible role of GABA or other neurotransmitters in the behavioural actions of baclophen remains to be elucidated (cf. *Birkmayer,* 1972; *Davidoff* and *Sears,* 1974).

Acknowledgements

This work was supported by grants from the Swedish Board for Technical Development, "Magn. Bergvalls Stiftelse" and the Swedish Medical Research Council (04X-155 and 04X-502). For generous supply of baclophen we thank Ciba-Geigy, Mölndal, Sweden. The skilful technical assistance of Mrs. Ingela Olsson and Mr. Kenn Johannessen is gratefully acknowledged.

References

Ahlenius, S., and *J. Engel:* Antagonism of haloperidol of the l-DOPA-induced disruption of a successive discrimination in the rat. J. of Neural Transmission *36,* 43—49 (1975).

Birkmayer, W.: Spasticity — a topical survey. Bern-Stuttgart-Vienna: H. Huber. 1972.

Davidoff, R. A., and *E. S. Sears:* The effects of Lioresal on synaptic activity in the isolated spinal cord. Neurology *24,* 957—963 (1974).

Frederiksen, P. K.: Preliminärt meddelande angående Lioresal (baclofen) vid behandling av schizofreni. Läkartidningen 6, 456—458 (1975).

Snyder, S. H.: Catecholamines as mediators of drug effects in schizophrenia. In: The Neurosciences, third study program (*Schmitt, F. O.*, and *F. G. Worden*, eds.), pp. 721—732. Cambridge-London: The MIT Press. 1974.

Woodworth, R. S., and *H. Schlosberg:* Experimental Psychology, 3rd ed., pp. 582—589. London: Methuen & Co. 1954.

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