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Blockade of Audiogenic Seizures by Bromocryptine

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GONZÁLEZ PÉREZ, J. N. AND A. GONZÁLEZ-QUEVEDO. *Blockade of audiogenic seizures by bromocryptine.* PHARMAC. BIOCHEM. BEHAV. 12(5) 823–285, 1980.—In 21-day-old DBA/2H mice, bromocryptine (5 $mgKg^{-1}$) induces great reduction of total and lethal audiogenic seizures. This effect increases with time during the first hour after injection. In mice pretreated with spiroperidol (0.5 $mgKg^{-1}$), bromocryptine fails to produce this protective effect. These results suggest that dopaminergic pathways may be involved in inhibition of audiogenic seizures.

Audiogenic seizures Bromocryptine Spiroperidol Dopaminergic pathways

BROMOCRYPTINE (2 Br-α-ergocryptine) is an ergoline derivative which shares many of the dopamine (DA) receptor stimulating properties of the DA agonist apomorphine; it induces stereotyped behavior in rats [14], the same turning behavior as evoked by apomorphine in rats with unilateral 6-OHDA induced degeneration of the ascending DA neurons [9] and hypothermia in mice [7]; it decreases DA turnover in the forebrain of rats and prolactin release in different animal species [9,18]. The improvement of Parkinson's disease after bromocryptine treatment is also well known [8]. Since these effects are blocked by DA-receptor antagonists, it has been suggested that they are due to direct stimulation of central DA receptors. In a recent review article on pharmacological and biochemical properties of bromocryptine it has been proposed that it is a partial agonist, capable also of blocking postsynaptic DA receptors [11].

The protective effects against audiogenic seizures of some DA receptor agonists, have already been described [3, 4, 5]. The purpose of the present series of experiments was twofold: to test the anticonvulsive action of bromocryptine in our audiogenic sensitive strain of mice and to explore the consequences of DA receptor blockade on bromocryptine's effect.

METHOD

DBA/2H mice from the Animal House of the Institute of Oncology and Radiobiology, Cuba, were used as breeding stocks from which offsprings were obtained to serve as experimental subjects.

The mice were maintained with ad lib access to food (commercial rodent food) and tap water.

The seizures were induced with the conventional procedure [1]. The mouse was placed in a metal cylinder (50 cm dia.), open at the top, with a doorbell placed against its inside wall (90 ± 2 dB). Each animal was exposed to one trial, which consisted of two periods: one minute of habituation followed by another minute during which the bell rang continuously. In the experiments only 21-day-old mice were used, age at which the susceptibility is significantly higher [12].

The following responses were recorded: no-response; wild running (WR); total seizures (TS), which included clonic and more severe convulsions; lethal seizures (LS); latency (L) and duration (D) of seizures. Values for latency and duration are given as M ± SE.

Bromocryptine (Sandoz) and spiroperidol (Janssen) were dissolved in tartaric acid, and diluted with saline. Controls received the drug solvent. The standard volume injected (IP) was 0.02 ml g^{-1} body weight.

The statistical methods used were the test of significance between proportions [6] for comparing percentages of WR, TS and LS and the Mann-Whitney U test [20] for comparing latencies and duration of seizures.

RESULTS AND DISCUSSION

Bromocryptine produces an intense reduction in susceptibility to acoustic stimulation in 21-day-old DBA/2H mice. As shown in Table 1 this effect on WR, TS and LS increases with time during the first hour after injection.

When three different doses of bromocryptine (1; 2,5 and 5 $mgKg^{-1}$) were injected 60 min before the test, a dose dependent effect was observed (Table 1). Employing a similar experimental design, Anlezark *et al.* [5] have reported a significant decrease in audiogenic seizure response only after 25 $mgKg^{-1}$ (30 min before the test). However, in our DBA strain, bromocryptine exhibits an anticonvulsive action already at doses as low as 1 $mgKg^{-1}$, decreasing the percentage of TS ($p \leq 0.05$). The reduction of WR and LS was not significant. At higher doses bromocryptine produces a dose dependent reduction in all the recorded responses.

Latency and duration of seizures were not appreciably affected by bromocryptine. At the highest dose tested (5 $mgKg^{-1}$, n=5), the recorded values were: L=7.8 ± 0.9 sec;

TABLE 1

TIME AND DOSE EFFECTS OF BROMOCRYPTINE ON AUDIOGENIC SEIZURE SUSCEPTIBILITY

Bromocryptine			Response to auditory stimulation		
Dose (mg Kg^{-1})	t (min)	n	WR	TS	LS
0	10–60*	26	96	88	69
1	60	18	89	55†	55
2.5	60	19	63†	47‡	21‡
5.0	10	15	73†	37§	37‡
5.0	30	15	20§	7§	7§
5.0	60	15	0§	0§	0§

Mice were exposed to auditory stimulation 10, 30 and 60 min (t) after injection. WR=wild running; TS=total seizures; LS=lethal seizures. *Pooled data. Difference between the control and experimental groups are statistically significant as indicated: †$p \leq 0.05$, ‡$p \leq 0.01$ and §$p \leq 0.001$.

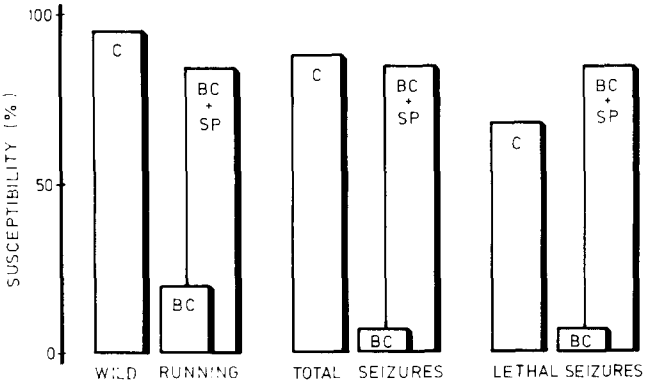

FIG. 1. Interference of the anticonvulsant effect of bromocryptine by spiroperidol. Spiroperidol (0.5 $mgKg^{-1}$) and bromocryptine (5 $mgKg^{-1}$) were administered, IP, 60 min and 30 min, respectively, before the assay. Control (pooled data) n=26; BC: bromocryptine n=15; BC+Sp=bromocryptine+spiroperidol n=13. Statistically significant differences for BC+Sp group: $p \leq 0.001$ compared with BC group.

D=16.4 ± 1.3 sec and for its control (n=12): L=6.9 ± 0.7 sec; D=16.6 ± 1.5 sec (figures refer to pooled data for 10, 30 and 60 min). On the other hand, Anlezark [4] observed an increase in seizure latency after 5 and 20 $mgKg^{-1}$ of bromocryptine.

In spite of some minor differences, our results and those of Anlezark *et al.* point to the same direction: bromocryptine protects DBA/2 mice against audiogenic seizures. This anticonvulsive action is quite similar to that reported for d- and l-amphetamine [12,13] and for apomorphine [3], the latter being confirmed by us in our DBA strain: injecting apomorphine (5 $mgKg^{-1}$) 15 min before the assay we obtained the following results: WR=25%, TS=25%, LS=0%, L=14.0 ± 2.0 sec and D=17.5 ± 0.1 sec; n=9.

Thus, one may assume that bromocryptine's anticonvulsive action is due to enhanced DA receptor activity [4,11]. This suggestion was tested with spiroperidol, a very well known specific DA antagonist [2]. As shown in Fig. 1, spiroperidol antagonizes bromocryptine's effect: in spiroperidol pretreated mice, the response to audiogenic stimulus is similar to that of control animals.

We think that these results confirm the general suggestion advanced from several lines of research, i.e., catecholaminergic pathways are involved in the mechanisms modulating audiogenic seizure susceptibility [15, 16, 17].

The precise contribution of DA and NA pathways in the protection against seizures is still discussed. Our results, very similar to those of Anlezark's [4,5], lead us to think that DA pathways are involved.

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