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Lack of Behavioral Evidence for Dopamine Autoreceptor Subsensitivity After Acute Electroconvulsive Shock

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CREESE, I., R. KUCZENSKI AND D. SEGAL. *Lack of behavioral evidence for dopamine autoreceptor subsensitivity after acute electroconvulsive shock.* PHARMAC. BIOCHEM. BEHAV. 17(2) 375–376, 1982.—A single electroconvulsive shock (ECS) delivered 7 days previously produced a significant decrease in spontaneous locomotion and rearing in non-habituated rats but did not alter the inhibition of these behaviors produced by low dose apomorphine administration. As such apomorphine effects are thought to be mediated by dopamine (DA) autoreceptors, these data are not consistent with previous reports that the ECS treatment produces a persistent subsensitivity of DA autoreceptors.

Electroconvulsive shock Dopamine autoreceptor Apomorphine Amphetamine

BIOCHEMICAL and behavioral experiments suggest that DA neurons possess DA receptors which inhibit DA neuron function [2,3]. Such "autoreceptors" have been studied by direct electrophysiological recording from DA neurons in the substantia nigra where peripheral or directly administered DA agonists lead to a reduction in spontaneous firing of these cells [1]. Biochemical studies of DA turnover also indicate the presence of DA autoreceptors on DA terminals within the striatum where DA agonists can reduce the release and synthesis of DA [5,6]. In a recent electrophysiological study [4] Chiodo and Antelman found that, in rats, single or multiple electroconvulsive shock (ECS) induces a subsensitivity of DA autoreceptors located in the substantia nigra as indicated by a reduced sensitivity to apomorphine-induced inhibition of DA neuron spontaneous activity. Either a single ECS treatment or 6 daily treatments produced comparable subsensitivity when measured 1 week following the first treatment.

Although high doses of apomorphine (in the order of 1 mg/kg, SC) stimulate motor activity in the rat, low doses of apomorphine (10–100 μg/kg, SC) reduce spontaneous motor activity [2]. It has been suggested that this inhibition of spontaneous activity is the result of apomorphine's stimulation of autoreceptors, resulting in a decrease in DA transmission in the striatum and/or limbic DA systems. Recently, Serra *et al.* [8] reported that repeated, but not single, ECS eliminated the sedative response to small doses of apomorphine. The failure to observe an effect after acute ECS may be due to the difference in treatment-test intervals used by this group (up to 4 days) and by Chiodo and Antelman (7 days) [4]. Because of the potentially important clinical and mechanistic implications of this time-related ECS effect, in the present study we sought to determine if the ability of apomorphine to inhibit spontaneous or amphetamine stimulated motor activity is reduced one week after a single ECS treatment as would be expected if such autoreceptors become subsensitive.

Twenty-five male Wistar rats (300–350 g) obtained from Hilltop Laboratories, received ECS consisting of a 1 second pulse of a 110 volt alternating current (60–100 mA) administered through earclip electrodes. All rats exhibited convulsions and a short period of unconsciousness. Twenty-five handled but unshocked animals with earclips were controls. One week later the rats were placed individually in sound-attenuated activity chambers immediately after injection with either saline, 10, 25 or 50 μg/kg apomorphine subcutaneously in the neck and locomotor cross-overs and rearings were recorded electronically for 30 minutes (see [7] for further details of activity chambers). Visual observation of the rats was also made by a "blind" observer to record sniffing behavior. On the following day 18 of the animals were tested for the ability of apomorphine to inhibit low dose amphetamine-induced locomotor activity and rearings. Rats received saline or 50 μg/kg apomorphine SC 1 min before receiving 0.5 mg/kg d-amphetamine sulfate SC. Locomotor activity and rearings were measured for 2 1/2 hrs.

The locomotor crossovers and rearings for the control and ECS-treated rats over the dose range of apomorphine investigated are shown in Fig. 1. An overall analysis of variance indicated that apomorphine inhibited spontaneous activity in both the control and ECS-treated groups, $F(3,41)=7.96$, $p<0.01$, and that the ECS-treated group demonstrated lower locomotor activity taken over all condi-

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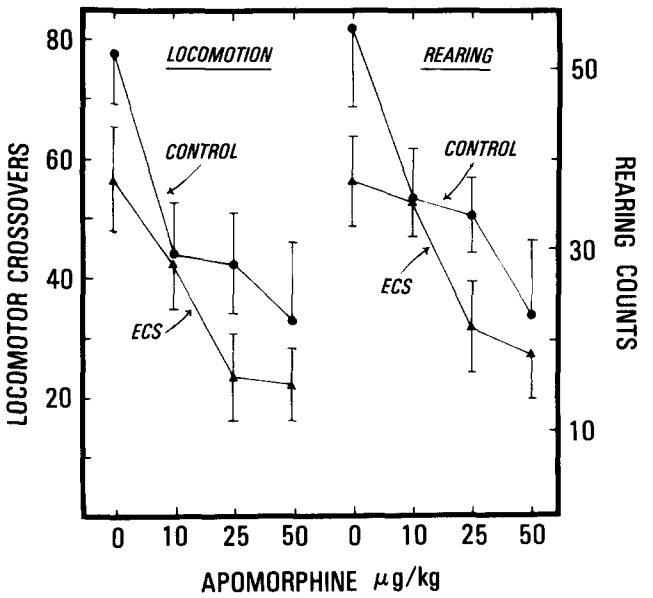

FIG. 1. Effect of a single electroconvulsive shock on spontaneous and apomorphine inhibition of motor activity 7 days later. Locomotor and rearing activity were measured for 30 mins after saline or apomorphine administration.

tions, $F(1,41)=4.48$, $p<0.05$. A similar finding was apparent for rearings activity with apomorphine significantly inhibiting rearing in both groups, $F(3,41)=6.69$, $p<0.01$, and the ECS-treated group showing less rearing activity overall, $F(1,41)=4.080$, $p<0.05$. However, individual comparisons at each dose level of apomorphine revealed no significant differences. Visual observation of sniffing behavior indicated that both groups behaved in a similar fashion.

In the second experiment the ability of apomorphine to inhibit low dose amphetamine-induced locomotor activity and rearings over a 2.5 hr period was investigated. The results are summarized in Table 1. In both the control and ECS groups, although apomorphine was able to substantially inhibit amphetamine-induced locomotor activity and rearings, $F(1,14)=10.39$, $p<0.01$ and $F(1,14)=13.03$, $p<0.01$, respectively, there was no difference between its effects on the ECS and control groups. Analysis of locomotor and rearing activity recorded during the first hour after amphetamine

TABLE 1

EFFECT OF A SINGLE ELECTROCONVULSIVE SHOCK ON APOMORPHINE INHIBITION OF AMPHETAMINE-INDUCED MOTOR ACTIVITY MEASURED 8 DAYS LATER

	Locomotion		Rearings	
	Control	ECS	Control	ECS
Amphetamine (0.5 mg/kg, SC)	557 ± 220 (n=5)	416 ± 50 (n=4)	166 ± 37 (n=5)	179 ± 54 (n=4)
Amphetamine (0.5 mg/kg, SC) + Apomorphine (50 μg/kg, SC)	74 ± 20 (n=5)	75 ± 31 (n=4)	71 ± 20 (n=5)	28 ± 9 (n=4)

administration revealed similar results (data not shown). Visual observation indicated that the reduction in locomotor activity and rearings was not the result of the rats exhibiting enhanced stereotypy but rather to a generalized decrease in all motor activity.

The hypothesized reduction in "autoreceptor" inhibition of spontaneous or drug-induced motor activity derived from the electrophysiological studies of Chiodo and Antelman [4] was not substantiated by these experiments. Although the basal levels of locomotion and rearing are decreased by ECS, the degree of inhibition produced by apomorphine appears to be similar in the control and ECS groups. Therefore, the autoinhibitory effects of apomorphine are unaltered by ECS treatment. Despite the discrepancy between our results and those of Chiodo and Antelman [4], it is clear that a single ECS can have marked long-term effects. Furthermore, since apomorphine and ECS produce a comparable, and possibly additive, decrease in the pattern of spontaneous locomotion, it is conceivable that both effects are mediated through a similar alteration of dopamine neurotransmission.

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