Pharmacology Biochemistry & Behavior, Vol. 6, pp. 363–365.

BRIEF COMMUNICATION

Effects of Apomorphine on Self-Stimulation Behaviour in Dorsal and Ventral Area of Lateral Hypothalamus in Mice

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(Received 4 October 1976)

CAZALA, P., AND B. CARDO. *Effects of apomorphine on self-stimulation behaviour in dorsal and ventral area of lateral hypothalamus in mice.* PHARMAC. BIOCHEM. BEHAV. 6(3) 363–365, 1977. – Intraperitoneal injections of low doses of apomorphine, a dopaminergic receptor agonist, depressed briefly, and then enhanced self-stimulation behaviour in the dorsal area of lateral hypothalamus. In contrast, only depressant effects were observed in the ventral area. These differential effects suggest the presence of a dopaminergic componant in the dorsal hypothalamic self-stimulation system.

Self-stimulation Hypothalamus Apomorphine Mouse C57BL/6

A PREVIOUS experiment from our laboratory has shown that in BALB/c, DBA/2 and C57BL/6 inbred mice, intracranial self-stimulation behaviour (ICSS) in the dorsal part of the lateral hypothalamus (LH) is more enhanced than stimulation of the ventral region by an injection of d-amphetamine [4].

Numerous data seem to show that d-amphetamine acts on dopaminergic mechanisms of the central nervous system [3,6]. The differential effect obtained on ICSS suggests therefore, that some of the neurochemical mechanisms which control this behaviour in the dorsal and ventral LH are different, and specifically that one part of the dorsal ICSS substratum is dopaminergic.

In order to test this hypothesis, we have studied the effects of apomorphine, an agonist of dopaminergic receptors [1] on dorsal and ventral hypothalamic ICSS. This study was carried out using C57BL/6 mice, in which the most clear-cut enhancing effect of amphetamine on ICSS performances has been obtained.

METHOD

Animals and Surgery

Twenty five C57BL/6 Orl male mice, approximately 12 weeks old, were used.

Under deep anesthesia using sodium thiopental (70 mg/kg) the animals were stereotaxically implanted with a bipolar electrode made by tightly twisting two strands of 0.09 mm platinum wire. In twelve animals the electrode was implanted into the dorsal LH. In the other animals the electrode was implanted into the ventral LH. The antero-posterior and lateral coordinates were identical for all mice: +2.00 mm anterior to the interaural plane and ± 1.00 mm lateral to the sagittal line. The vertical coordinates, taken from the surface of the skull, were 5.30 mm for the dorsal group and 5.70 mm for the ventral one.

Apparatus and Experimental Procedure

The equipment, described elsewhere [5], consisted of four cages with two identical levers separated by a small partition. The pressing of one of these levers triggered a central stimulation of 0.2 sec (100 HZ, sinewave), while the other served as a reference for operant behaviour.

After acquisition of ICSS, ICSS thresholds were determined in all animals using 1 μA steps [5]. The performances were then stabilized on one lever [4] at a similar level in the two implantation groups, using suprathresholds intensities (Dorsal group: intensity of stimulation 15 (SEM ± 1) μA; number of presses/20 min 437 (SEM ± 53). Ventral group: intensity of stimulation 23 (SEM ± 2) μA; number of presses/20 min 409 (SEM ± 27).)

The animals self-stimulated only every other day. Twenty minutes after the begining of each ICSS session, 21 mice received an intraperitoneal injection of apomorphine CHl. During the same time, 4 animals were used as controls and

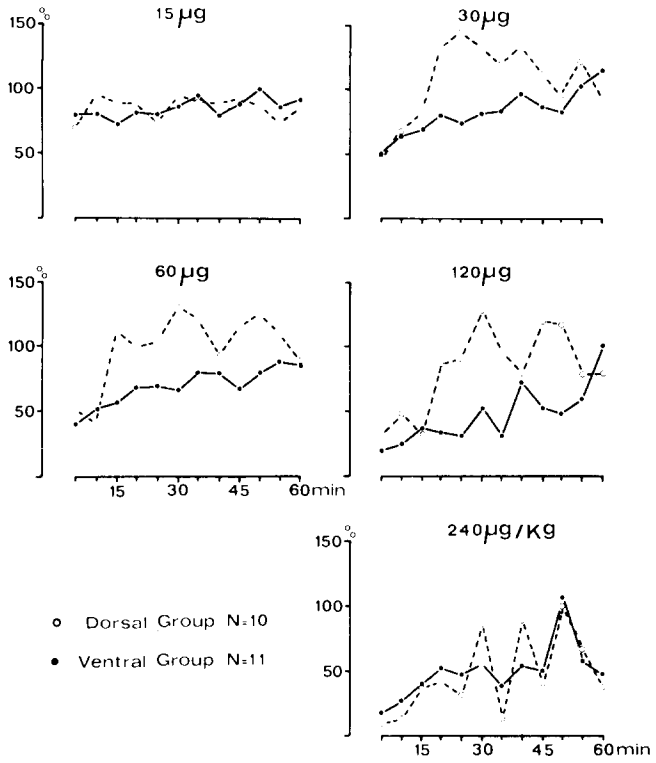

FIG. 1. Effects of injection of increasing doses of apomorphine on dorsal and ventral hypothalamic self-stimulation in C57BL/6 mice strain. Abscissae: the time in min. Ordinate: the mean of lever pressing in 5 min expressed in percentage of the preinjection scores.

received an injection of isotonic NaCl. The increasing doses of apomorphine injected were 15, 30, 60, 120, and 240 µg/kg. The effects of injection on ICSS were studied during a one hour period.

RESULTS

No variation of ICSS was obtained with 15 µg/kg of apomorphine, irrespective of the site of stimulation (Fig. 1).

However, with 30, 60 and 120 µg/kg. two phenomenons were observed: immediately after the injection, ICSS performances were significantly depressed in the two groups. This disruption increased as a function of the dose injected, whereas the control group was not disturbed by NaCl and maintained stable performances.

These decreases were followed by a period when presses on the lever increased. This enhancement was more rapid and more intense in the dorsally implanted mice, which at 30 µg showed only a slight but significant improvement of their performances (t = 3.01, p = 0.02). No similar improvement was observed in the ventral group. The dichotomy between the two groups was confirmed by the trend analysis [11] (60 µg $F(1/20) = 6.34$, $p<0.025$; 120 µg $F(1/20) = 7.97$, $p = 0.01$).

With 240 µg/kg ICSS was highly depressed in all mice, which shown numerous stereotyped movements. Moreover the dorsoventral dissociation disappeared.

Histological control revealed that the two implantation groups were well differentiated. Electrode tips were situated in LH, dorsolaterally and ventrolaterally to the fornix.

DISCUSSION

As it has been already observed [8], the effects of apomorphine on ICSS seem to be dependent upon the location of the stimulated brain area. The various changes in performances we have obtained according to the hypothalamic site, could explain the results of Wauquier *et al.* [10] and Broekkamp *et al.* [2]. These authors report that the same dose of apomorphine improves hypothalamic ICSS in some animals and depress it in the others; moreover Wauquier [10] found that the best performance enhancements are obtained in animals with the lowest ICSS thresholds. In our experiment ICSS performances were improved by 30 µg of apomorphine in the dorsally implanted mice, which showed the lowest ICSS thresholds [5]. This result confirms those obtained with d-amphetamine, and highly suggests that one part of the neurochemical substratum of dorsal LH ICSS is dopaminergic, since apomorphine specifically stimulates these receptors [1].

Dopaminergic neurons of substantia nigra (A9) and mesencephalo-cortico-limbic system (A10) send their fibres through the medial forebrain bundle [7,9]. Dorsal LH ICSS might be mediated by one or both of these dopaminergic pathways; but the role of A9 fibres is not quite clear since substantia nigra ICSS is not increased by apomorphine [8].

When the dose of apomorphine was increased, the dorsoventral variation persisted while the performance level showed time dependent decreases in both groups.

At the highest dose, performance levels remained continually depressed and the dorsal enhancement disappeared. These phenomenons may be the product of a competition between the enhancing and depressant effect of the drug. This hypothesis corresponds with the elicitation of stereotyped movements, often described after injection of high doses of apomorphine [2, 8, 10]. But it is also possible that the repeated injections progressively affected the response of the animals to the drug. This phenomenon perhaps could explain the disappearance of the dichotomy between the dorsal and ventral groups for the 240 µg/kg dose.

ACKNOWLEDGEMENT

We wish to thank Mrs. A. M. Perret for technical assistance. This investigation was supported by the C.N.R.S. (ERA N° 416) and by Grant N° 74.1.171.08 of the Institut National de la Santé et de la Recherche Médicale.

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