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Effects of Lesions in the Ventral Noradrenergic Bundle on Behavior and Response to Psychotropic Drugs in Rats

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JERLICZ, M., W. KOSTOWSKI, A. BIDZINSKI AND M. HAUPTMANN. *Effects of lesions in the ventral noradrenergic bundle on behavior and response to psychotropic drugs in rats.* PHARMAC. BIOCHEM. BEHAV. 9(6) 721–724, 1978.—Bilateral lesions of the ventral noradrenergic bundle (VB) decreased concentration of noradrenaline within the mesendiencephalon but not in the cortex. Lesioned rats showed increased activity measured in the open field test. Cataloptogenic effects of chlorpromazine and haloperidol were almost completely abolished in VB-lesioned animals. The stereotypy induced by both—amphetamine and apomorphine was, however, unchanged. It is supposed that lesions of the VB lead to increased activity in dopaminergic neurons in the brain.

Ventral noradrenergic bundle Noradrenaline Neuroleptics

HISTOCHEMICAL fluorescence studies have demonstrated two major noradrenergic (NA) systems in the brain: the dorsal NA bundle (DB) which originates mainly in the locus coeruleus (LC) and the ventral noradrenergic bundle (VB) which originates more heterogenously from NA cells located within the pons and medulla oblongata and designated by Dahlström and Fuxe [3] as A-1, A-2, A-5 and A-7 groups. There is evidence that LC is important for sleep and waking mechanisms [9] and that fibers from this area make up an important part of the ascending reticular activating system [18]. The role of VB remains, however, unknown. The axonal projection of this system to the variety of basal brain structures associated with the hypothalamus and the limbic system implicates that VB is probably involved in the mediation of motivation and neuroendocrine processes [21, 23, 27].

Recently the involvement of the LC and dorsal NA bundle in regulation of locomotor activity has been emphasized by some authors [13,22]. Unilateral lesions of the LC result initially in ipsilateral rotation which is then replaced by contralateral rotation [22]. Previous studies in our laboratory have shown that bilateral lesions of the LC markedly increased susceptibility to the cataleptogenic effect of neuroleptics and to the apomorphine-induced stereotypy [13]. This phenomena is probably due to decreased impulse flow in the dopaminergic neurons associated with increased sensitivity of dopaminergic receptors [13, 22, 26].

To further evaluate the role of brain NA system in the behavior and action of psychotropic drugs, we have studied the effects of some neuroleptics, amphetamine and apomorphine in VB-lesioned rats. The general activity of animals in the open field was also evaluated.

METHOD

Animals and Operations

Male Wistar rats weighing 180–200 g were housed in macrolon cages 42×24×20 cm (2–3 per cage) at a constant room temperature of 20–22°C, normal light conditions and about 60% humidity. Lab standard chow and water were available ad lib. Rats were anaesthetized with chloral hydrate (400 mg/kg, IP) and electrolytic lesions were produced stereotaxically in VB according to the coordinates of the König and Klippel stereotaxic atlas [10]: A=1.3 mm, L=1.4 mm and H=−2.0 mm (modified after Ungerstedt [25] and Ritter and Stein [23]). The procedure was the same as previously described [13]. In brief, 1.0 mA DC current was passed for 5 sec through an intracranial anode made from stainless steel wire 0.25 mm in. dia., insulated with Epoxylite except for the tip. A stainless steel needle inserted into the tail was the cathode. Sham operated animals were prepared by inserting the electrode 1 mm dorsal to the VB yet not passing a current.

Biochemical and Histological Analyses

At the completion of the experiment the rats were sac-

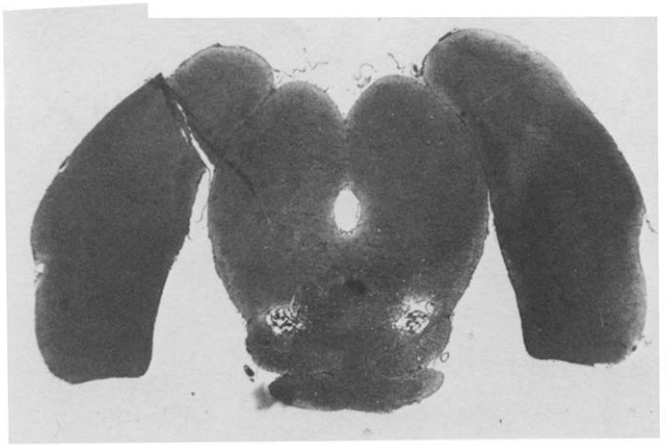

FIG. 1. Frontal section showing bilateral lesion of the ventral noradrenergic bundle.

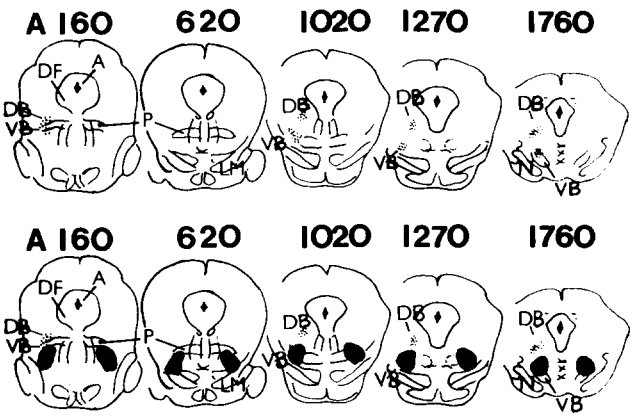

FIG. 2. Placement and size of lesions involving the ventral noradrenergic bundle (composite of 59 lesions). Locations of NA bundles were taken from atlas of Ungerstedt [25]. Numbers: distance in μm anterior to the zero plane of the König and Klippel stereotaxic atlas [10]. Abbreviations: A—cerebral aqueduct, DB—dorsal NA bundle, DF—dorsal longitudinalis fasciculus, LM—medial lemniscus, P—superior cerebellar peduncle, SN—substantia nigra, VB—ventral noradrenergic bundle.

TABLE 1

EFFECT OF VB LESION ON AMINE CONCENTRATION IN BRAIN

Brain Region	Experimental Group	Mean Concentrations ng/g Wet Weight ± SEM			
		5-HT	5-HIAA	NA	DA
Forebrain					
	Sham (n=14)	485 ± 27	442 ± 16	530 ± 28	1210 ± 98
	VB lesion (n=6)	483 ± 31	440 ± 48	465 ± 33	1264 ± 106
Cortex					
	Sham (n=6)	367 ± 41	394 ± 29	247 ± 68	907 ± 116
	VB lesion (n=7)	321 ± 19	364 ± 51	282 ± 43	926 ± 118
Mesen-diencephalon					
	Sham (n=6)	818 ± 42	740 ± 64	844 ± 62	1437 ± 324
	VB lesion (n=7)	924 ± 74	589 ± 83	531 ± 38*	1137 ± 347

*$p<0.01$ with respect to sham lesioned.

rificed by decapitation, their brains were quickly removed and dissected by precollicular section caudally to the hypothalamus for two parts, forebrain and brainstem. The brainstems were checked histologically after fixation in 10% Formalin, the sections were stained with hematoxylin and eosin. Biogenic amine levels were measured 7–8 days after the lesion in two separate groups of untreated rats. In the first group amine levels were measured in the whole forebrain while in the second one amine levels were measured in two parts of the forebrain: cortical (cortex and hippocampus) and mesendiencephalon (hypothalamus, thalamus mesencephalon anterior to the superior colliculus). The extraction and fluorimetric determination of brain amines were carried out basically according to Haubrich and Denzer [7] except that 5-HT was determined after Korf and Sebens [11].

Testing of Animals and Drugs

Seven days after lesion one group of animals was tested in the open field. Three days later the same animals were tested for neuroleptic-induced catalepsy and for stereotyped behavior induced by apomorphine or amphetamine, according to a method previously described [6,12].

The "open field" was a 65×65 square field surrounded by a 30 cm high wall and divided into 16 small squares, 4 "central" and 12 "peripheral". The number of entries into the squares, the number of rearings (the orienting reaction) and groomings as well as the number of immobility periods and feces boli were counted during a 5 min observation period. The grooming episodes as well as the immobility were scored as 5 sec periods (one point was scored for 5 sec).

The following drugs were used: apomorphine hydrochloride (Sandoz), 10 mg/kg IP, d-amphetamine sulphate (Smith, Kline and French), 10 mg/kg IP, haloperidol (Richter), 1 mg/kg IP and chlorpromazine (Polfa), 10 mg/kg IP. All drugs except haloperidol were dissolved in water. All experiments were performed between 9:00 a.m. and 1:00 p.m.

Statistics

Statistical analysis was performed using the Mann-Whitney two-tailed test for unrelated scores (U test). For analysis

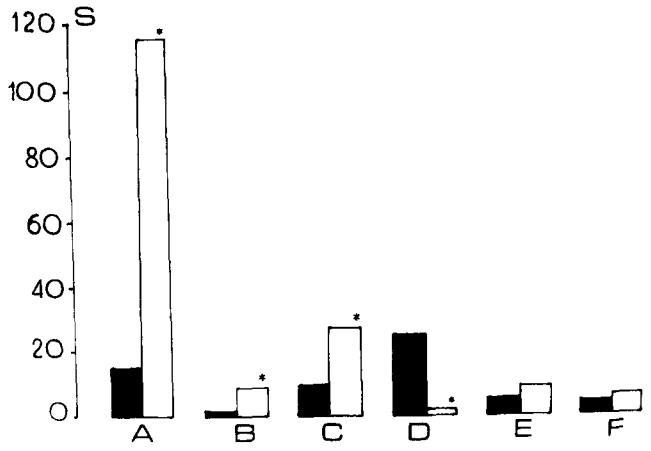

FIG. 3. Behavior of rats in the open field test. Black columns indicate sham-lesioned animals, white columns indicate VB-lesioned animals (mean values of 8–11 animals). Vertical scale indicates the scores (s) of behavioral patterns: A—number of peripheral squares, B—number of central squares, C—rearing, D—periods of immobility, E—grooming, F—number of feces boli (see text for details). x=$p<0.005$ (Mann-Whitney, two-tailed).

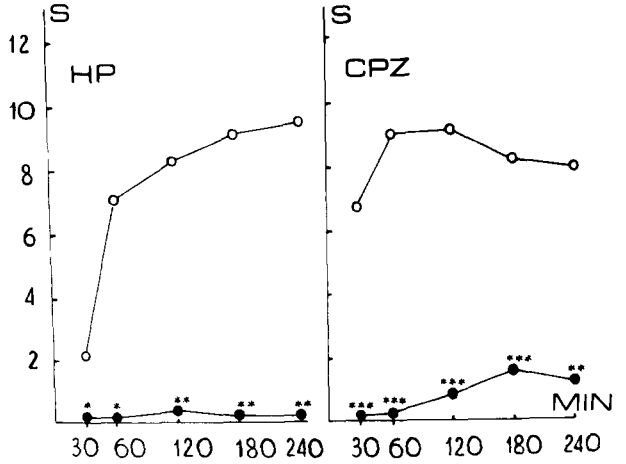

FIG. 4. Cataleptogenic effect of haloperidol (HP) and chlorpromazine (CPZ) in VB-lesioned rats (●- - - -●) and sham-lesioned rats (○————○). Values are means of 9–11 experiments. Ordinate: the intensity of catalepsy (scored, s), abscissa-time after injections in minutes. x=$p<0.025$, xx=$p<0.01$ and xxx=$p<0.005$ in respect to sham-lesioned (Mann-Whitney test, two-tailed).

of biochemical results the two-tailed Student's t-test was used.

RESULTS

Location of Lesions

Histological examination showed that lesions were mainly restricted to the VB and partially involved medial lemniscus and superior cerebellar peduncle in 59 rats (Figs. 1 and 2). In the remaining 8 animals the lesions were not accurately positioned in the VB and involved other structures such as the substantia nigra, the medial lemniscus and the mesencephalic reticular formation. These rats were excluded from the statistical analysis of results.

Biochemical Examinations

Bilateral lesions of the VB slightly but insignificantly decreased NA concentration in the whole forebrain. The NA level was, however, markedly reduced ($p<0.01$) in the mesendiencephalic region. The cortical NA level was unchanged in lesioned rats (see Table 1).

Open Field Test

Rats with lesions involving the VB showed increased activity measured in the open field test. The numbers of both peripheral and central squares passed by animals were significantly increased while the number of immobility periods was decreased. Lesioned animals showed increased number of "rearing" (Fig. 3).

Testing of Drugs

As shown in Fig. 4 lesions involving the VB almost completely abolished cataleptogenic effects of both chlorpromazine and haloperidol. On the other hand these lesions failed to change the intensity of stereotyped behavior after d-amphetamine and apomorphine.

DISCUSSION

The results of our experiments indicate that bilateral lesions of the VB reduce the NA concentration within the mesendiencephalic region of the brain. This finding is compatible with that of Donaldson *et al.* [4] who reported decreased NA concentration in the hypothalamus after unilateral lesion of the VB. In our previous study we also reported decreased mesendiencephalic NA concentration in VB-lesioned rats [14,15].

The present experiments have shown that bilateral lesions of the VB markedly increased locomotor activity as well as exploratory behavior. The finding of particular interest in the present experiments is that cataleptogenic action of some neuroleptic drugs is blocked by bilateral lesion of the VB. The most probable explanation for this phenomenon is that these lesions produce an increase in activity of dopaminergic neurons in the brain. Thus it is possible that impulse flow in the dopaminergic neurons leads to increased amount of released amine available to compete with the neuroleptic drug for receptor sites. Neuroleptics are thought to act primarily by blocking brain dopaminergic and NA receptors and by decreasing the release of dopamine from nerve terminals [1, 24, 28]. It is worthwhile noting that lesions of the LC, the second main NA brain system, produce rather opposite effects to those obtained after lesioning of the VB. Bilateral lesions of the LC have been reported either to reduce the locomotor activity [14] or produce no clear effect [2]. The cataleptogenic action of neuroleptics was significantly potentiated in LC-lesioned rats [13]. Moreover, the stereotyped behavior induced by apomorphine was also enhanced in these animals [13]. On the basis of these findings it has been suggested by us that lesions of the LC produce a decrease in activity of brain dopaminergic neurons as well as hypersensitivity of postsynaptic dopaminergic receptors [13,14].

The mechanism by which VB lesions increase locomotor activity is not clear. There are at least two possibilities which

might explain this phenomenon. One is that VB lesion produces changes in the activity of other brain transmitter systems. The most probable is an increase in activity of dopaminergic neurons since VB lesions blocked the cataleptogenic action of neuroleptics. The sensitivity of dopaminergic receptors seems to be unchanged since no changes in both apomorphine and amphetamine stereotypy have been observed. Amphetamine acts through endogenous catecholamines whereas apomorphine acts directly upon postsynaptic dopaminergic receptors [5,19]. Thus, it seemed likely that increased activity of dopaminergic brain neurons may be responsible for both locomotor hyperactivity and decreased responsiveness to neuroleptic drugs in VB-lesioned animals. Recently Manson and Fibiger [20] have reported that dorsal NA bundle lesions increased in the exploratory behavior in rats. Since these lesions resulted in severe depletion of hypothalamic NA as well as cortical-hippocampal NA concentration it was impossible to say whether this behavioral change was due to destruction of the dorsal NA bundle or the VB. Another facilitating effect on behavior was recently observed in our laboratory. It was reported [16] that bilateral lesion of VB markedly facilitated avoidance acquisition in rats.

The second possible mechanism by which lesions of the VB might influence the locomotor activity and modulate the action of psychotropic drugs is that these lesions result in changes in synthesis and/or release of hypothalamic hormones such as corticotrophin releasing hormone, throtropin releasing hormone, etc. There is evidence that these hormones are under control of catecholaminergic neurons [8, 17, 27].

Recently we postulated that the ventral NA bundle and the dorsal NA bundle might play an opposite role in brain function and that possible interactions of these NA systems with other transmitter systems are different [14]. Thus, it has become apparent that brain NA neurons are not functionally homogeneous. Further research will be required however, to elucidate the function of these brain NA systems.

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