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Behavioral Effects of Lesions of the Central Noradrenergic Bundles in the Rat

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VERLEYE, M. AND F. BERNET. *Behavioral effects of lesions of the central noradrenergic bundles in the rat.* PHARMACOL BIOCHEM BEHAV 19(3) 407–414, 1983.—Rats with bilateral lesions of the dorsal noradrenergic bundle (DB) or of the ventral noradrenergic bundle (VB) were studied in different behavioral test situations. All lesioned animals defecate less than sham operated animals in the open-field (OF) or in the conditioning apparatus described by Henderson [16]. These data suggest a decrease of emotional reactivity in lesioned animals. However, the DB rats' level of exploration was higher than that of VB rats. No effect on the amplitude of the startle response has been shown after lesioning. The lesions of the dorsal noradrenergic bundle induce a decrease in cortical noradrenaline hypothalamic catecholamines. The lesions of the ventral noradrenergic bundle induce a decrease in hypothalamic catecholamines without change in the cortex. These results do not support the postulation [22] that the dorsal bundle and the ventral bundle play an opposite role in behavior. Yet, a selective participation of each bundle is suggested in modulating responses to novel environments and anxiogenic situations.

Dorsal and ventral noradrenergic bundles   Open-field   Conditioned emotional response   Startle response
Brain catecholamines and serotonin   Rat

SEVERAL authors have shown the importance of the central noradrenergic system in different forms of behavior. Schildkraut and Kety [44] induce depression and inactivity in the animal by drugs which interrupt temporarily the activity of aminergic neurons. The use of a neurotoxic drug, the 6-hydroxydopamine, which destroys specifically the noradrenergic pathways [49] has recently enabled Sorenson and Ellison [45], Mason and Fibiger [33] to modify some of the rat's behavior. In this way, after intracerebroventricular injections of 6-OHDA, they report an increase in the number of fecal boli excreted in open-field (O.F.) and a decrease in ambulatory activity. These authors suggest these results to be due to an increase in the emotional reactivity of the animals. Electrolytic destruction of central noradrenergic pathways by Pycok *et al.* [39], Kostowski *et al.* [23], Kostowski [22], revealed the involvement of these structures in the regulation of locomotor activity.

But, the central noradrenergic system does not make up an only anatomical structure. The ascending noradrenergic fibers form two main bundles in the rat: the dorsal bundle (DB), originates in the locus coeruleus area (LC, A6 cell group) and projects mostly to the neocortical area, hippocampus and cerebellar cortex. The second main noradrenergic ascending system, the ventral bundle (VB), projects from disseminated medulla oblongata cells groups (Area, A1, A2, A5, A7) [11] and gives ascending projection to hypothalamus, septum, piriform cortex and other subcortical areas such as amygdala nucleus. Many authors have revealed the opposite effects induced by lesions of the DB and the VB in learning capacity in the rat [24,25].

So, the lesions of the VB increases the acquisition of conditioned two-way avoidance in rats [24,25] but the destruction of the LC or the DB impairs learning capacity.

Jerlicz *et al.* [19] have shown that the bilateral lesions of the VB enhance the ambulatory and exploratory activity, whereas the bilateral lesions of the LC decrease the locomotor activity in the rats [24]. Kostowski [22] postulates that the DB and the VB play an opposite role in behavior and probably interact with other transmitter aminergic systems.

The aim of this study is to evaluate the role of each noradrenergic central bundle in different forms of behavior induced by anxiogenic situations: the open-field, the Henderson test and the startle response. The O.F. test consists in placing the rat an uncovered and brightly lit arena. This situation interferes with photo-and-agoraphobic tendencies of the animal and evokes different reactions, that many authors, since Hall [16] have considered to be emotional.

The Henderson situation make is possible to measure some neurovegetative and somatomotrice responses conditioned by the administration of an intense and inescapable electric shock.

The measurement of the startle response makes it possible to appreciate the reaction of the rat to an exteroceptive stimulus, in this case an acute and very intense sound.

The research of a possible and functional antagonism between these central noradrenergic systems has been effected selectively by destroying one of these bundles by electrolytic lesions. After destroying DB or VB, the brain noradrenaline, dopamine and serotonin levels were measured with the view to firstly indirectly controlling the efficiency of lesions and secondly revealing possible relations, between the modifications of brain amines concentrations and behavioral disturbances.

METHOD

Animals and Operations

The experiments were performed on forty-five male Sprague Dawley IOPS rats weighing 250–300 g at the beginning of the experiment. The animals were housed in propylene cages 43×43×20 cm (5 per cage) on a 12 hr light-dark cycle (light 7.00–19.00), with food and water ad lib.

The animals are anesthetized with Equithesine (0.4 ml/100 g, IP) and immobilized in a stereotaxic apparatus (Precision Cinematographique). The bilateral electrolytic lesions are made by passing a direct current (intensity 1.5 mA for 10 sec) through a bipolar electrode. The stereotaxic coordinates are derived from Ritter and Stein [42], according to the coordinates of the König and Klippel atlas [21]. The skull is flat between bregma and lambda and the lambda is the reference point. The dorso-ventral coordinates are measured from the top of the level skull.

	anterio-posterior	medio-lateral	dorso-ventral
VB rats (n=15)	+0.1 mm	1.8 mm	7.5 mm
DB rats (n=15)	+0.5 mm	1.4 mm	6.5 mm

Sham operated animals are prepared for the same operation, but they do not receive a current. After the operation, the animals operated on return to their home cage until the first passage into the open-field.

Testing of Animals

Open-field behavior. Ten days after lesion, the rats' behavior is tested in an arena or open-field. The appartus consists of a circular floor, 80 cm in diameter, surrounded by a metal wall 40 cm high, with inside surface painted white. It is strongly lit by two 150 W lamps from 150 cm above. The surface of the floor is divided into 19 equivalent sections (12 "peripheral" and 7 "central") so as to better appreciate the quantity of the animal's horizontal activity. The open-field is placed in a soundproof room where a ventilator creates a background continuous noise, which covers eventual noises in the experimental room. The animal is placed in the center of the arena and his behavioral activity is recorded continually over a 3 min period.

Five parameters are in this way recorded: (1) Defecation, measured by the number of fecal boluses excreted; (2) The horizontal activity in the centre and on the outskirts in arbitrary units (each unit corresponds to the movement from one sector where the animal is placed, to the next sector); (3) Number of times the animal stood up on its hind legs (rearing); (4) The time (in seconds) spent in washing itself (grooming).

Each animal is submitted to three analogous tests over three consecutive days, between 8.00 hr and 12.00 hr with a view to limiting the effect of possible nycthemeral variations.

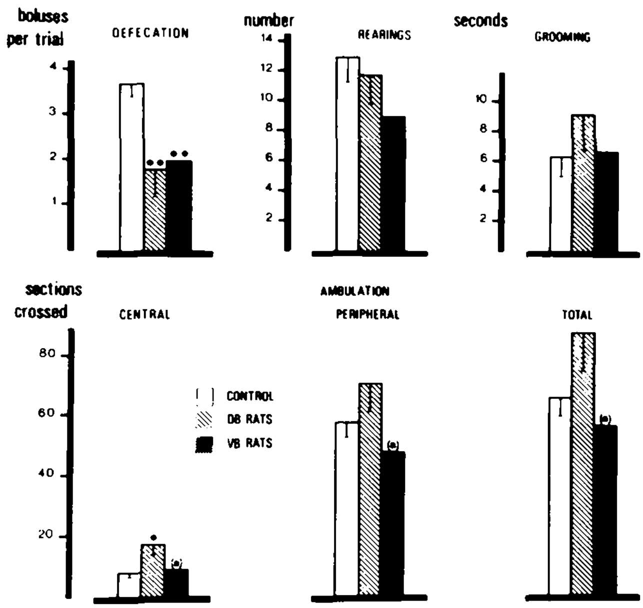

FIG. 1. Mean values of the principal parameters in the O.F. test in sham rats (control) (n=14) and lesioned rats (DB, n=10 and VB, n=9). Each value indicates the mean of three passages in the open-field. Each value is indicated with S.E.M. $^*p<0.05$; $^{**}p<0.01$ between sham and lesioned rats; (a) $p<0.05$ between DB and VB rats.

Between each passage, the floor of the open-field is cleared of the excrement and washed with chlorinated water to eliminate the animal's odour.

Henderson test. This test described by Jaffard [18], according to Henderson [16], is carried out in a rectangular cage of Plexiglas (75×25×32 cm), the floor of which is electrified. The cage is crossed by two photoelectric beams which make it possible to measure the locomotor activity of the animal.

This test consists of four experimental sessions: (1) Each animal is placed gently in the experimental area, where it is free to walk about for a 30 sec period. The animals used are called "Non stimulated" (NS). (2) Twenty four hours later, the animal is again placed in the area for a 3 min period. Three parameters are recorded during this period: the latency of movement expressed in seconds or the time needed to cover the distance from the point where the animal was placed to the furthest infra-red beam; the number of fecal boli excreted during the 3 min period; the ambulation, recorded by the number of times the photocell beams are broken. (3) Twenty four hours after this second passage, the animal is again placed in the area for a 30 seconds period, but this time, an electric shock of 1.5 mA lasting 1 sec is delivered to the cage floor after the 30 seconds. In future references, these animals are called "stimulated" (S). (4) Then, twenty four hours later, the animals are again tested for a 3 min period and the three parameters described (cf., (2)) are recorded.

Startle response. This test is used to evaluate the reaction of the animal to a exteroceptive stimulus [32].

The apparatus used to measure the startle response, consisted of a polypropylene cage (36×16×16 cm), placed on a horizontal support, with one of its extremities moving about a transversal axis and the other connected to a strain-gauge force transducer. The measurement axis of the transducer is

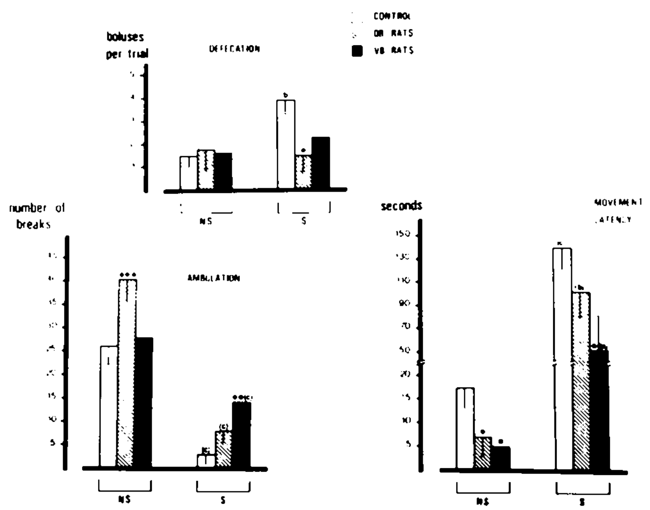

FIG. 2. Mean values of parameters in the Henderson test (sham (control), n=14; rats DB, n=10 and rats VB, n=9), after passage without electric shock (NS) and after passage with electric shock (S). Each value is indicated with S.E.M. *$p<0.05$; **$p<0.01$; ***$p<0.001$ between sham and lesioned rats, (a) $p<0.05$; (b) $p<0.01$; (c) $p<0.001$ between NS and S animals of the same groups.

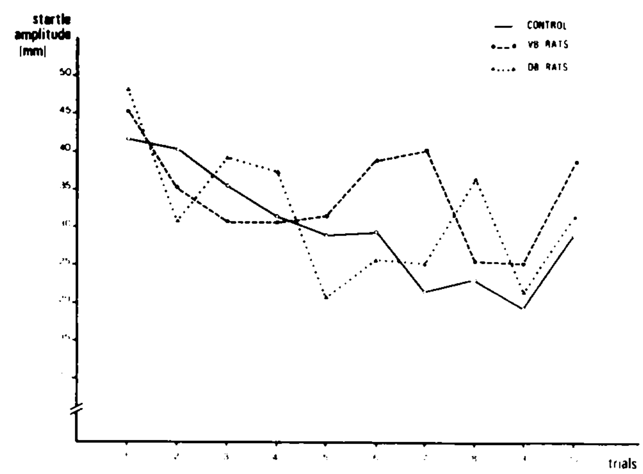

FIG. 3. Mean amplitude startle responses in sham rats (control) (n=14) and in lesioned rats (DB, n=10 and VB, n=9) to an auditory stimulus (4,000 Hz; 120 dB (A); 90 msec), presented 10 times in a haphazard way.

vertical. The vertical force-component applied to the cage and support are measured by this transducer. The error due to the dynamic response of the transducer is very low and is therefore ignored. The vertical forces developed by the animal during startle response are recorded on graphic recorder (Offner of type R. Beckman).

After an adaptation period of 5 minutes in the cage, ten sounds at a frequency of 4,000 Hz, lasting 90 msec and at an intensity of 120 dB (A) are haphazardly delivered over a 3 min period by a loud-speaker mounted approximately 40 cm above the animal.

Biochemical and Histological Analyses

At the completion of the experiment, the rats are sacrificed by decapitation. Their brains are quickly removed and dissected into four parts according to the method of Glowinski and Iversen [13]: the cerebral cortex, hypothalamus, mesendiencephalon and medulla oblongata. These cerebral parts are frozen in isopentane (−160°C). Following this rapid freezing (15 sec), the parts are then stored in a refrigerator (−20°C) until the extraction and fluorimetric determination of brain amines [17].

A histological control was carried out on DB and VB rats, to ascertain the exact location and extent of the lesions. After fixation in 10% Formalin, and freezing the brain, the 50 μm sections are stained with cresyl violet.

Statistics

Statistical analyses are performed using Student's "t"-test for independant and paired groups and the r of Bravais-Pearson.

RESULTS

Open-Field Test

The results are shown in Fig. 1: (1) The DB rats defecate significantly less than the sham rats ($p<0.01$) and ambulate more, particularly in the central sectors of the O.F. ($p<0.05$). (2) The VB rats defecate significantly less than the sham rats ($p<0.01$) but ambulate identically. (3) The DB rats ambulate significantly more than the VB rats in the peripheral and central sectors of the O.F. ($p<0.05$). (4) The number of rearings and the time of washing in lesioned rats are identical for sham rats.

Henderson Test

The results of behavioral scores measured during the second and the fourth passage are shown in Fig. 2.

(1) NS animals. The number of fecal boli excreted by lesioned animals is identical to these of sham rats. Ambulation in DB rats is greater than for sham rats ($p<0.001$) or VB rats ($p<0.01$). The movement latency of lesioned animals is shorter than that of sham rats ($p<0.05$).

(2) S animals. The lesioned S rats defecate less than sham S rats, however the difference between sham rats and DB rats is statistically significant ($p<0.05$). The lesioned S rats ambulate more than sham S rats, but only the VB rats ambulate significantly more than sham rats. Correlatively, the movement latency of lesioned S rats is shorter than that sham S rats, but only the difference between sham and VB rats is statistically significant ($p<0.05$).

(3) Comparison of NS animals and S animals. The sham S rats compared with sham NS rats show an increased defecation ($p<0.01$), a longer movement latency ($p<0.001$) and a decreased ambulation ($p<0.001$). Similarly, the lesioned S animals ambulated significantly less than the lesioned NS animals ($p<0.001$) and wait longer before ambulating. On the other hand, there is no significant difference between these two groups of lesioned rats.

Startle Reflex

The mean startle response amplitude in DB and VB rats, for each trial, do not differ to that of sham rats (Fig. 3). It is observed that the repetitive presentation of an auditory stimulus brings out a habituation behavior in the sham rats.

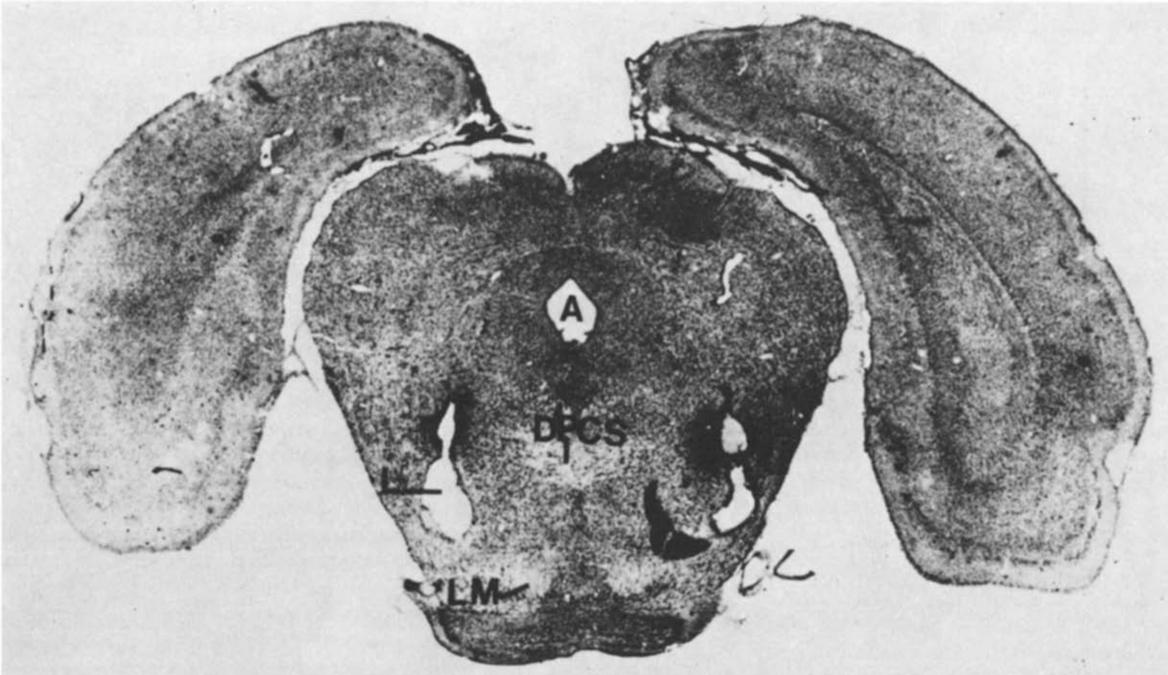

FIG. 4. (Left side). Mesencephalic frontal section showing bilateral lesions of the dorsal noradrenergic bundle (DB) (right) and of the ventral noradrenergic bundle (VB) (left). A: cerebral aqueduct; DPCS: decussation superior cerebellar peduncle; L: lesion of DB or VB; LM: medial lemniscus; CC: corpus cerebri.

TABLE 1

NORADRENALINE, DOPAMINE AND SEROTONIN CONCENTRATION IN DIFFERENT BRAIN REGIONS IN SHAM AND LESIONED (DB AND VB) RATS

Brain region	Experimental group		NA	DA	5 HT
Medulla-oblongata	Sham	(n=9)	540 ± 37	45 ± 15	864 ± 34
	DB lesion	(n=9)	480 ± 45	22 ± 10	898 ± 132
	VB lesion	(n=9)	537 ± 64	45 ± 36	870 ± 81
Mesendiencephalon	Sham	(n=8)	460 ± 47	285 ± 55	999 ± 85
	DB lesion	(n=9)	374 ± 35	252 ± 103	802 ± 50
	VB lesion	(n=9)	403 ± 57	337 ± 128	950 ± 92
Hypothalamus	Sham	(n=9)	2,165 ± 326	535 ± 152	1,526 ± 320
	DB lesion	(n=8)	1,283 ± 132*	123 ± 67*	969 ± 96
	VB lesion	(n=9)	1,100 ± 174†	28 ± 19†	1,166 ± 179
Cerebral cortex	Sham	(n=9)	252 ± 14	633 ± 87	565 ± 42
	DB lesion	(n=9)	164 ± 26†	606 ± 69	525 ± 67
	VB lesion	(n=9)	221 ± 42	513 ± 96	540 ± 43

The amine concentrations are expressed in $ng \cdot g^{-1}$ fresh tissue (Mean ± SEM) *$p<0.05$ and †$p<0.01$ with respect to shams.

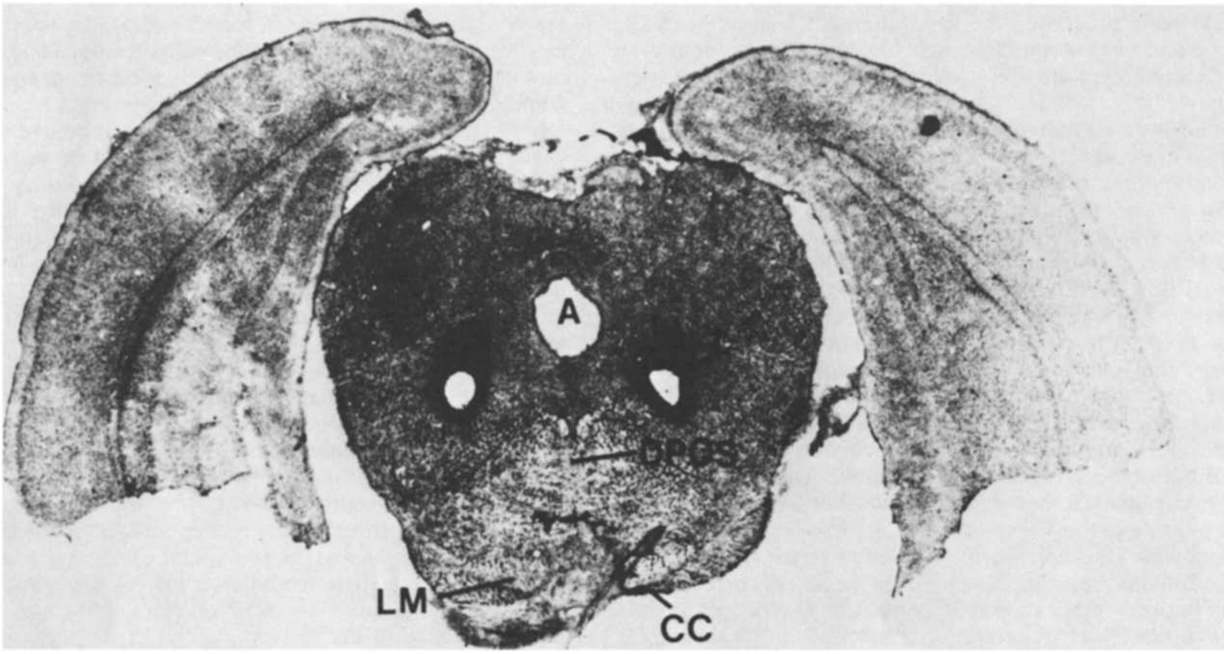

FIG. 4. (Right side). See legend to left side.

Biochemical Examinations

After lesions, catecholamine concentrations decreased in some parts of the brain (Table 1).

Bilateral lesions of VB decreased the noradrenaline level in hypothalamus ($p<0.05$), whereas bilateral lesions of DB decreased the cortical and hypothalamic noradrenaline level ($p<0.01$ and $p<0.05$) at the same time. Consequently, the lesions of DB and VB show a significant decrease in the dopamine level in hypothalamus ($p<0.05$ and $p<0.01$).

The brain serotonine level is unchanged in lesioned rats.

Location of Lesions

Because it is impossible to carry out at the same time a biochemical dosage and a histological control in the same rat, we examined first of all the location of mesencephalic lesions in a rat whose O.F. behavior is representative of each group, secondly in the animals whose behavior after lesions is comparable with that of sham animals.

Fig. 4 shows the lesions which correspond to the regions described by Ungerstedt [50], involving the fibres of DB and VB.

In five VB rats, other structures, such as the substantia nigra or the medial lemniscus were destroyed by lesions. In four DB rats, the ventrolateral region of the periaqueductal gray matter was lesioned. These 9 animals were excluded from the statistical analysis of the results.

DISCUSSION

The decrease in cortical NA level after bilateral lesions of DB is compatible with the results obtained by many authors, who reported that all areas of cortical cortex receive large fibres projections of DB, originating in locus coeruleus [29, 31, 36, 50].

The reduction of the hypothalamic NA level in these same animals, already observed by Mason and Fibiger [33], can be due to lesions of the ascending fibres of the intermediate noradrenergic bundle, which are situated ventrally in relation to DB [31], Olson and Fuxe [37], Maeda and Schimizu [31], Olson and Fuxe [38] have shown that the subcoeruleus nucleus and the anterior portion of the locus coeruleus, at the origin of this pathway, project mostly to the hypothalamus.

The NA depletion in hypothalamic neurons consecutive to the bilateral lesions of VB, already reported by Kostowski *et al.* [24], Bellinger *et al.* [4], supports the argument for the projection of this pathway on the hypothalamus.

Many assumptions can explain the decrease in the hypothalamic DA level after the lesions of DB and VB: (1) A possible transfer between the intrahypothalamic dopaminergic pathways the presence of which has been shown by Lindvall and Björklund [29], with the collaterals of the ascending noradrenergic fibres of DB and VB [20, 28, 47] could explain the secondary or indirect effects of noradrenergic bundle lesionings, on the working of these dopaminergic neurons [10]. (2) The hypothesis of the united lesions of Area A8 and A9 (substantia nigra), in the mesencephalic region, is excluded given the choice of stereotaxic coordinates used to reach the fibres of DB or VB [42]. However, the lesions of dopaminergic fibres, originating in A8 and A9 (substantia nigra) and travelling with the ascending noradrenergic fibres can explain the DA depletion in the hypothalamus: the region which receives the projections of these bundles.

This hypothesis is supported by the data which was recently contested by Milon and Mc Rae-Degueurce [35], of Versteeg *et al.* [51], who reveal that 25% of catecholaminergic neurons, originating in LC, are dopaminergic.

The unchanged brain, serotonine level after lesioning of the noradrenergic bundle does not make it possible to show the interaction, proposed by Kostowski [22], between these bundles and the serotonergic neurons.

The use of 6-OHDA would have provoked without doubt more effective and more specific lesions of noradrenergic neurons, but the spread which is with difficulty checkable would have prevented the separations of lesionings of the dorsal and ventral noradrenergic bundles. This is the reason that has justified the use of electrolytic lesions in this experiment.

The novel stimuli (open-field, brightly lit), that is the O.F. situation, evokes a pattern of neurovegetative, endocrine and somatomotrice responses in the animal [8].

In general, the animals, characterized by a hyperreactivity to novelty or neophobia, present an increased defecation and reduced ambulatory activity during an open-field test. But, if this locomotor activity can interpret many forms of behavior, it has been reported according to Hall [14], Broadhurst [9], Whimbey and Denenberg [52], Bernet [5], Bernet and Denimal [6] that the importance of defecation in a novel environment is a valid index of emotional reactivity. It is therefore possible to think that the lesioned rats have became "less emotional," as shown by a decreased number of fecal boluses excreted in the open-field. The comparison of the two lesioned animal groups shows that the DB rats ambulate more than the VB rats, whereas these latter are inclined to ambulate less than shams. According to the calculation of r by Bravais Pearson, a significant negative correlation is seen between defecation and ambulation ($r=.67$; $p<0.05$) in the DB rats. Such a correlation is not seen in the shams. On the other hand, the correlation is positive in the VB rats ($r=.82$; $p<0.01$). To understand these differences, it should be remembered that, as said by Boissier and Simon [7], Denenberg [12], ambulation in a novel enviornment, such as the O.F. situation, measures the emotional reactivity and the exploratory behavior. The rapid raising of the inhibiting processes, generated by this novel situation, could explain the increase in the DB rats exploration.

In the VB rats, ambulation and rearings, relatively unfrequent, could be an indicator for a high "emotionality" in this situation, if they were correlated with an increase in defecation. The hypoactivity of VB rats can be attributed to a modification of the emotional state of the animal, in the direction of emotional hyporeactivity, without increasing the exploratory behavior as in the DB rats.

In the open-field, the fact that the lesions effect the ambulation more than rearings underlines a difference as to their behavioral significance. Lát [26], then Soubrie and Boissier [46] suggest that the rearing could reflect the wakefulness level of the animal.

During the Henderson test, the sham NS defecate significantly less than in the O.F. ($p<0.01$), for an identical period of time. This observation emphasizes the less anxiogenic character of this situation. Furthermore, the comparison of NS animals does not reveal any difference between the defecation of shams and that of lesioned rats, on the other hand the defecation in lesioned NS rats is not different to that of lesioned rats in the O.F. situation. These data are further proof of the emotional hyporeactivity of lesioned rats in the O.F.

The behavioral pattern of sham rats after being administered an intensive electric shock is characterized by a decrease in the ambulation activity, an increase in the movement latency and defecation. The behavioral inhibition, which is represented by freezing brought on by this intense stimulus is a predominant element in the rats defensive behavioral system [2,40]. The emotional hyporeactivity of the DB rats in O.F. is shown in the Henderson test, for the stimulated animals by a significantly lower rate of defecation to that of the shams ($p<0.05$) and an identical rate to that of the non-stimulated animals. However, the values of the motor activities (locomotion, movement latency) of the DB S rats hardly differs to those of the sham S rats. The somatic-motor inhibition of these animals, in reply to an intense stimulus does not appear to be changed by the lesions of the DB. On the contrary the VB rats seem less inhibited than the sham animals by the electric shock received the day before, as they move about more and after a shorter delay period. Their tendency to defecate hardly at all together with this diminished inhibition of the motor activity probably corresponds to a conditioned emotional response which is smaller than that of the shams.

In the startle test, the bilateral lesions of DB and VB do not affect the response amplitude in spite of the NA depletion in some brain parts. The genesis of the startle response seems to be situated at an adjacent level to that of the lesions more precisely at the bulbopontine reticular formation [27]. Roberts *et al.* [43] have pointed out the importance of the influence of LC on the spinal cord, showing that NA depletion in the spinal cord raised the threshold for the startle response an electric shock. Furthermore, after injections of NA agonist substances in the spinal cord, Astrachan and Davis [3] revealed the modualtion role of this structure on the startle amplitude. The question can now be asked about the importance of the chosen parameter for measuring the rat's reactivity because according to Hansen and Hard [15], the duration of the animal's immobility in reply to a sudden auditory stimulus seems more appropriate.

The lesions of the main central noradrenergic pathways confirms the hypotheses of Redmond [41], who suggests that the activation of central noradrenergic systems, such as the LC, plays a role in the apparition of a behavior, which is characteristic of the state of "fear" primates. The comparison of the effects of the dorsal and ventral noradrenergic bundle lesions does not confirm the hypothesis of Kostowski [22], by which the two central noradrenergic bundles appear to be a functional antagonism in behavioral expression. Indeed whether in the O.F. situation or in Henderson's test, the lesioned rats present behavioral modifications which can be interpreted as a drop in their emotional reactivity which could be induced by catecholamines depletion in the hypothalamus. However, there are differences between the two groups of lesioned animals. The DB rats, which have less NA in the cerebral cortex also explore more in novel situations which are less "anxiogenic": for example open-field, the Henderson test without shock, when the VB rats are characterized by an ambulation more typical of the expression of emotional behavior; positive correlation with the O.F. defecation (negative in DB rats); and finally an increase in the horizontal activity in the Henderson test, only seen in shocked animals. Moreover we cannot exclude a selective involvement of each bundle in novel situations which are more or less "anxiogenic," in controlling and expressing behavior. The O.F. test, the Henderson test and the startle reflex test correspond to different "anxiogenic" situations. Many authors [1, 34, 48] have shown that the quality, the intensity and the duration of a "stressful" stimulus are multiple variables influencing the neurovegetative and behavioral responses.

In conclusion, this study indicates that the electrolytic lesions of central noradrenergic bundles induce behavioral modifications, which interpret a decrease in emotional reactivity. These results have not revealed a functional duality between the two systems, but the selective participation of these according to the 'stressful" stimuli in controlling and expressing behavior.

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