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BRIEF COMMUNICATION

Opposed Effects of Locus Coeruleus and Substantia Nigra Lesions on Social Behavior in Rat Colonies[1]

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EISON, M. S., A. D. STARK AND G. ELLISON. *Opposed effects of locus coeruleus and substantia nigra lesions on social behavior in rat colonies.* PHARMAC. BIOCHEM. BEHAV. 7(1) 87–90, 1977. Rats were observed in enriched colony environments following radio-frequency lesions of the locus coeruleus (LC), zona compacta of substantia nigra (SN), or control operations. LC-lesioned animals were initially inactive, stayed in the burrows, and fell when climbing ropes and ramps. SN-lesioned rats were opposite to LC animals in many ways. They were hyperactive, had minimal motor disturbances, and were hyperaggressive. SN animals self-isolated and were not social-groomers, whereas LC rats socially-groomed and mounted other animals more than controls. These results provide evidence that the dopaminergic nigrostriatal pathway and the noradrenergic fibers innervating the cerebral cortex and limbic forebrain exert opposed effects upon behavior.

Locus coeruleus Substantia nigra RF lesions Social behavior Norepinephrine Dopamine

CONSIDERABLE evidence indicates that the catecholamines (CA), dopamine (DA), and norepinephrine (NE) mediate important central functions. NE has been implicated in diverse processes such as arousal [5], feeding [1], and affective mood [15], while alterations in brain DA have been found to influence motor activity [14], feeding behavior [19], and are implicated in the etiology of Parkinson's disease [11].

Although much significance has been attributed to the actions of these neurotransmitters, pharmacological investigations of their precise role in behavior have been hampered by the fact that DA and NE are closely related compounds. Anatomically, however, the cell bodies responsible for much of CA synthesis are discretely located in several brain nuclei. The cell bodies of origin for NE projections to the cerebral cortex and limbic forebrain lie in the locus coeruleus (LC), and the DA synthesizing cell bodies of the nigrostriatal pathway are found in the zona compacta of substantia nigra (SN) [18]. Electrolytic lesions of these nuclei result in specific CA depletions in these terminal areas [2, 9, 13]. The present study compared the effects of radio-frequency (RF) lesions of these nuclei on social and other behaviors in rat colonies.

METHOD

Animals

The study was run in two replications. In each, 34 young male Long-Evans rats weighing 160–180 g were raised in enriched colony environments for 60 days. The animals were then collected, assigned to one of three groups balanced for body weight, and anesthetized with Equithesin. They were marked in one of three stripe patterns with a fur dye and returned to the colony for twelve days prior to surgery.

Surgery

The animals were anesthetized with Equithesin and RF lesions were made bilaterally using a Grass LM-3 lesion maker in the LC group at A −1.8, L ± 0.9, D −2.4 (incisor bar 5 mm above interaural line) by passing 10.5 mA rms current for 60 sec through the 1 mm bare tip of a 0.5 mm diameter stainless steel electrode. The SN lesion was made with electrodes angled at 45° to the midsaggital plane at two AP levels by passing 9 mA for 60 sec. Two lesions were made 1 mm anterior to SN where DA fibers are maximally disrupted [18]. One lesion was A +3.8, L +1.7, D −1.3; a

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second 1 mm dorsolateral along the 45° plane. A single additional lesion was made in the center of SN zona compacta at A + 2.8, L + 2.0, D 1.1. These coordinates were determined prior to surgery by fluorescence microscopy using the rapid glyoxylic acid method [21] and later confirmed using cresyl violet. Half the controls received sham LC lesions and half sham SN lesions.

Collection of Behavioral Data

The colony enclosure was a 4 × 3 × 2 m area with separate burrows, a behavioral arena, and a feeding area [8] maintained on a 12 hr reversed day-night cycle. In the first run of this study the animals were observed during the middle 5 hr of the night phase for 40 days; they were observed 7 hr daily for 15 days in the replication. Trained observers recorded the frequency of various spontaneous behaviors described elsewhere [8]. A census was taken every half hour. All data was subjected to two-way analyses of variance ($df = 2,42$).

RESULTS

Following lesioning, LC animals stayed in the burrows while SN rats were out in the arena more than controls (both $p < 0.05$); this trend was still present 40 days after lesioning. These differences in census location were correlated with differences in activity levels (Fig. 1). The LC rats ran least often in activity wheels and the SN animals most often ($p < 0.001$); again this effect was still present 40 days after lesioning. Throughout the study, SN animals climbed more on ropes and ramps than did control or LC rats ($p < 0.05$). The LC animals were observed to walk with a waddling or lumbering gait and were clumsy in that they fell more during climbs than any other group ($p < 0.001$). SN rats had minimal motor disturbances as reflected in number of falls.

The LC rats were active participants in positive social interactions (Fig. 1), socially-grooming and mounting other animals more than any other group (both $p < 0.01$). Conversely, SN rats self-groomed more often and for longer periods of time ($p < 0.001$ and < 0.05, respectively) than either control or LC rats. An antisocial pattern of behavior in SN rats was further seen across three measures of aggression (Fig. 2). They fought more, and LC rats less, than controls as reflected in stand and box ($p < 0.05$), broadsiding, and violent fights (both $p < 0.001$). Many of the violent fights initiated by SN rats were directed toward LC animals, and in two separate incidences LC rats were observed to be killed in unyielding violent attacks by SN animals. Control rats were never seen to kill or engage in as prolonged violent episodes as did SN rats. In the 40 day replication, the most violent SN animal developed a compulsive habit of biting the tails of other rats resulting in frequent blood-letting and tail mutilations.

SN dominance was further observed during the feeding hour (Fig. 2) in that they fought more for the possession of food ($p < 0.05$) and won more of these contests ($p < 0.001$) than any other group. However, LC rats spent more time on the feeding tray ($p < 0.05$) and gained more weight after lesioning ($p < 0.05$) than either other group.

At the conclusion of the study, the animals were collected, perfused with Formalin, and frozen sections were cut and stained with cresyl violet. There were circular LC lesions 0.5 mm in diameter under the dorsolateral edge of

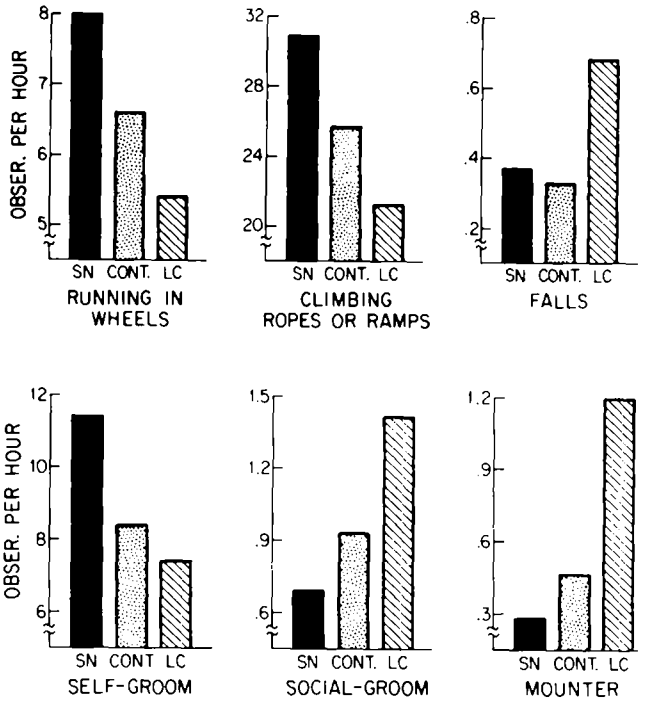

FIG. 1. Mean number of times various behaviors were recorded per hour of observation. Top half: Activity measures. SN-lesioned rats became hyperactive after surgery, and had minimal motor disturbances as reflected in their number of falls. LC-lesioned rats were conversely inactive and fell frequently. Bottom half: Opposed social proclivities in the two lesioned groups. These opposite patterns of social behavior persisted 40 days after lesioning.

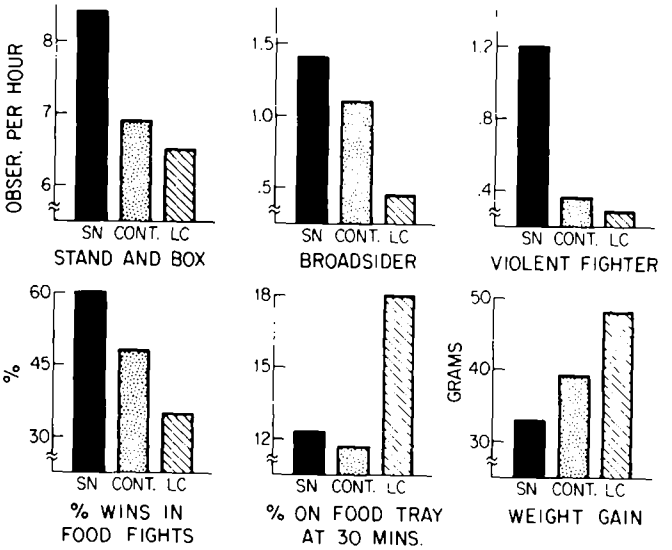

FIG. 2. Top half: mean number of times per hour that animals were observed in 3 different kinds of aggressive encounters. Whereas LC-lesioned rats fought less than Controls, SN-lesioned animals gradually became hyperaggressive and violent. Bottom half: While SN rats won more fights for the possession of food than did either other group, LC-lesioned animals spent more time on the feeding tray and gained more weight between lesioning and sacrifice.

the IV ventricle extending from the dorsal tegmental nucleus to the mesencephalic nucleus of the trigeminal nerve. There were few remaining cell bodies in the LC. In the SN-lesioned animals, glial scars 1.8 mm long and 0.5 mm wide were found ventral to the medial lemniscus, penetrating the zona incerta along a 45° plane to terminate 0.5 mm dorsomedial to the ventral tip of the cerebral peduncle. When examined with fluorescence microscopy, few swollen catecholamine cells were observed in the area between the two lesions. These cells showed the enhanced fluorescence characteristic of axonimized CA cells [18].

DISCUSSION

Opposed behavioral syndromes were observed following RF lesions of the locus coeruleus, which contains the cell bodies that give rise to the NE fibers innervating cerebral cortex and limbic forebrain, and of the zona compacta substantia nigra, which gives rise to the DA nigrostriatal pathway. Compared to the controls, LC-lesioned animals tended to stay in the burrows, were inactive when out on the arena floor, and often fell during the performance of motor tasks. Conversely, SN-lesioned rats were most often out of the burrows, were hyperactive, and had minimal motor disturbances. The LC rats socially-groomed and mounted other animals, whereas SN rats avoided positive social interactions and self-groomed. While LC animals were less violent than controls, SN rats gradually became hyperaggressive after lesioning. These findings provide behavioral evidence that these noradrenergic and dopaminergic systems exert opposed actions on the central nervous system, a conclusion consistent with other evidence that NE and DA have opposite effects on behavior [3] and that LC and SN lesions have opposed effects on central glucose metabolism [16].

There are a number of similarities between the behavioral syndromes of the LC-lesioned animals of this study and those of rats observed in a previous colony study following small, multiple intraventricular injections of 6-hydroxydopamine (6-OHDA) [8]. Both LC and 6-OHDA rats tend to stay in burrows, are inactive out in the arena, and are poorly coordinated. Also, both mount other animals and become dominated in aggressive encounters. While intraventricular 6-OHDA produces widespread central depletions of NE, including spinal cord, LC lesions predominantly deplete NE in cerebral cortex, limbic forebrain, hypothalamus, and thalamus [4,13]. It is interesting to note that although the patterns of NE depletion achieved with these manipulations may differ, they result in similar behavioral syndromes. However, unlike 6-OHDA injected rats who show both decreased food consumption and weight gains [8], LC-lesioned rats gained significantly more weight than controls. It is unlikely that these weight gains merely reflect reduced energy expenditure in the inactive LC rats, as 6-OHDA rats were likewise inactive. Furthermore, hyperphagia can also be observed following local injections of 6-OHDA into the midbrain NE bundles [1].

SN-lesioned rats, however, were unique among other monoamine depleted rats studied in previous rat colonies in their avoidance of positive social interactions (such as mounting and social grooming) and their tendency to self-isolate, engage in single-animal activities such as wheel running, and their hyperreactivity to other animals who approached them. They were sometimes unyielding in violent attacks and persevered in other behavioral sequences once begun, such as grooming and wheel running.

Although this hyperactive and hyperaggressive pattern of behavior which we observed following RF lesions of the substantia nigra is discrepant with reports of inactivity and hypophagia following local injections of 6-OHDA into the SN [19], it is consistent with other reports of hyperactivity without aphagia following RF lesions of the SN [10,12]. It could be argued that the increased activity seen following RF lesions of SN was a paradoxical effect, perhaps supersensitivity, for such lesions do not deplete caudate dopamine extensively [12]. However, in previous studies we have found that supersensitive behavioral phenomenon are characterized by an initial deficit followed by exaggerated recovery [17], whereas the behavioral changes in both lesioned groups of the present study were stable over time. Furthermore, in studies to be published elsewhere, we have found that these same SN-lesioned animals showed attenuated stereotypy following d-amphetamine administration, a result which is not consistent with a supersensitivity argument. A more likely explanation of these discrepant findings is that the catecholamine depletions found following local injections of 6-OHDA into the substantia nigra are not solely confined to dopamine, but also involve extensive depletions of cortical and hypothalamic norepinephrine [7] due to leakage of 6-OHDA along the injecting cannula.

A variety of evidence indicates that animals with central norepinephrine depletions can model aspects of human depression [15]. The present results are consistent with this for LC-lesioned animals are inactive and dominated in a social environment. Rats with RF lesions of the dopaminergic nigrostriatal pathway behave very differently. Surprisingly, in some ways they resemble animals with caudate lesions: both are hyperactive, persevere in behavioral sequences once begun [20] and show increases in dominance [6]. Their antisocial pattern of behavior is a novel finding which merits further study.

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