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Behavioral and Biochemical Alterations in Median and Dorsal Raphe Nuclei Lesioned Cats

M. KOPROWSKA AND A. ROMANIUK[1]

Department of Neurophysiology, University of Łódź, 90-222 Łódź, Poland

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KOPROWSKA, M. AND A. ROMANIUK. *Behavioral and biochemical alterations in median and dorsal raphe nuclei lesioned cats.* PHARMACOL BIOCHEM BEHAV **56**(3) 529–540, 1997.—Ten days after 5, 7-dihydroxytryptamine (5,7-DHT) administration into the median (MRN) and dorsal (DRN) raphe nuclei, preceded by nomifensine IP, an increase of post-carbachol growling response occurred. There were no differences in the amount of locomotor activity on any post-lesion day. In predatory test in a competitive situation for paired cats ten and fifteen days after 5,7-DHT administration into the MRN and DRN of submissive cats, formerly submissive animals, engage in the fight for domination after lesions. HPLC analysis showed in all lesioned groups a significant reduction of 5-HT and 5-HIAA in the hypothalamus, midbrain, amygdala and hippocampus after the MRN lesion and in the hypothalamus, amygdala, hippocampus and frontal cortex after the DRN lesion. After the MRN and DRN lesion no spontaneous aggressive behavior occurred in any cat. The results indicate that both raphe nuclei participate in the central regulation of affective and predatory aggression in the cat.

5,7-DHT Nomifensine Nuclei raphe Brain monoamines HPLC Affective and predatory aggression Cat

IT IS well documented that various manipulations leading to the lowering of 5-HT level in the brain as well as blocking of serotonergic transmission bring about an increase in general emotional arousal, in locomotor activity and enhanced irritability and aggression. Thus so, the serotonergic system is considered to inhibit many forms of emotional behaviors, including offensive and defensive aggression as well as predation [for review see (33)] .Yet one has to observe the fact that the serotonergic system is differentiated into two main systems: mesolimbic which originates from the median raphe nucleus (MRN) and mesocortical which originates from the dorsal raphe nucleus (DRN) projecting partially to different forebrain structures (21). Simultaneously it has to be pointed out that these two systems innervate the same structures of the forebrain, and it is only the degree of innervation in particular structures provided by each of the systems that is different (20,21).

The fact that there are anatomical differences in the projections from the MRN and DRN suggests that different raphe nuclei are involved in the control of different aspects of behavior. This outlook is supported by the results of tests conducted on rats which reveal that various behavioral and neurochemical effects were obtained after electrolytic or neurotoxic lesions of the MRN and DRN. Fundamental differences consist in the fact that the destruction of the MRN potentiates locomotor activity and does not produce aggressive behavior whereas lesions to the DRN produce muricide in non-killing rats, increase in pain elicited aggression, and are without effect on locomotor activity (7,8,12,14,15,19,24,25,34). In the studies in which neurochemical changes were also analysed it was demonstrated that lesions to the MRN and DRN resulted in a similar fall in the level of 5-HT in the hypothalamus, striatum and cerebral cortex (15), in the striatum and substantia nigra (7), however, it is different in the hippocampus. The DRN lesion produced non-significant reduction in the hippocampal 5-HT level, while the MRN lesion caused a significant reduction (7,15). Jacobs et al. (15) attributes an increase in locomotor activity to the said decrease of 5-HT level in the hippocampus. There are also data indicating that after lesions to both

[1]Requests for reprints should be addressed to Dr. Andrzey Romaniuk, Department of Neurophysiology, University of Łódź, 66 Rewolucji 1905 r. St., 90-222 Łódź, Poland.

the DRN and MRN a similar decrease of 5-HT in the cat's hippocampus occurs (23).

In our previous investigations performed on cats (26,28) we found that 5,6-dihydroxytryptamine (5,6-DHT) administrations to the DRN and MRN resulted in a similar increase in the carbachol-induced emotional-defensive behavior. Lesions to the DRN resulted in a decrease of 5-HT, 5-HIAA and NA in the hypothalamus, midbrain and amygdala. Lesions to the MRN resulted in a decrease of 5-HIAA and DA in the hypothalamus, midbrain and amygdala but 5-HT level remained unchanged. Consequently, we did not observe a functional differentiation of the MRN and DRN in the central regulation of carbachol-induced defensive behavior in the cat. The present study was aimed at investigating the role of the MRN and DRN in the regulation of locomotor activity, affective and predatory aggression and at clarifying the underlined neurochemical processes. We used experimental models which reflected the natural behavior of the cats such as defensive and predator behavior. These behaviors partly rely on different motivation systems (36,37). As a model of affective aggression the response evoked by intrahypothalamic carbachol injection was used. This response consisted of intensive autonomic activation (the increase of heart rate, blood pressure and respiration, pupil dilatation and piloerection), threatening posture and characteristic vocalization manifested by regular growling which is a quantitative indicator precisely reflecting the dynamics and intensity of defensive excitation (5,27). Predatory aggression expressed without autonomic activation as quiet biting includes a complex behavioral sequence of stalking approach to the prey followed by a rapid attack directly on the back of the neck (18). It is also worth mentioning that in our models the interference due to the presence of the experimenter was negligible and no pain stimuli were applied to evoke behavioral response. In order to obtain as much information as possible on neurochemical processes we determined the concentrations of monoamines (NA, DA, 5-HT) and their metabolites (MHPG, DOPAC, HVA, 5-HIAA) in the key areas (anterior and posterior hypothalamus, midbrain central grey matter, amygdala, hippocampus and frontal cortex) forming the neuronal systems which participate in the central regulation of various forms of defensive behavior (1,22). The animals were treated with the dopamine re-uptake inhibitor nomifensine before injecting 5,7-DHT in the MRN or DRN. This procedure prolongs and enhances the action of catecholamines and therefore minimizes the effect of the neurotoxin on the cells other than the serotonergic ones. In this respect the lesions we performed can be considered "relative selective" for serotonergic neurons.

METHOD

Subject

The experiments were performed on forty adult cats of either sex. The animals were housed in individual wire mesh cages and maintained in the temperature controlled room (22 ± 2°C) on 12 L : 12 D cycle with food (cereal with meat and milk) ad lib.

The behavioral recordings took place between 0900 and 1200. The animals were divided into six groups.

Surgery

Twenty cats (Groups 1, 2, 3, and 4, each $n = 5$) had two cannulas chronically bilaterally implanted in the anteriomedial hypothalamus according to the stereotaxic coordinates of Snider and Niemer's atlas (30): A = 13.0, L = 1.5, H = −3.0. Ten cats had additionally one cannula implanted in the median raphe nucleus (MRN): P = 2.0, L = 0.0, H = −4.5 (Groups 1 and 2), other ten cats in the dorsal raphe nucleus (DRN): P = 1.0, L = 0.0, H = −1.0 (Groups 3 and 4). The cats of Group 5 (5 dominant and 5 submissive) had implanted one cannula only in the MRN, and in Group 6 (5 dominant and 5 submissive) one cannula only in the DRN. The cannula was inserted into the MRN at an angle of 33° and into the DRN at an angle of 40° at the horizontal plane after appropriate trigonometric calculations. Stereotaxic operations were performed in semi-sterile conditions, under barbiturate anesthesia (hexobarbital, 90 mg/kg IP). The animals got penicillin IM to prevent infection. The guide steinless steel cannulas (1.0 mm outer and 0.6 mm inner diameter) were fixed to the skull with self-polimerizing methacrylate resin (Duracryl Special, Spofa, Prague). The outer openings of the cannulas were plugged with cotton swabs soaked with 0.9% NaCl solution and sealed with wax. The chronically implanted cannulas served as guides for an injection cannula (0.5 mm outer and 0.2 mm inner diameter) which was directly connected with a microinjector (E. Zimmermann, Leipzig). Drug solutions were injected into the brain mannually at a rate of about 0.1 μl/s.

Drugs

Carbachol (carbachol puriss, Koch-Light) was dissolved in a 0.9% NaCl solution and injected bilaterally at the dose of 4 μg/1μl /site into each part of the hypothalamus. 5,7-DHT (5,7-dihydroxytryptamine creatine sulfate, Sigma) was dissolved in a 0.2% ascorbic acid (AA) in saline at 4°C and injected at the dose of 10 μg/2 μl into the MRN and DRN. To prevent catecholamines depletion, 40 min before 5,7-DHT injection all animals (all six groups) were treated with dopamine uptake inhibitor nomifensine (nomifensine maleate, RBI) at the dose of 15 mg/kg IP in a volume of 2 ml. A control group received nomifensine and 40 min later 2 μl AA into the MRN and DRN. All drugs were dissolved immediately before use.

Experimental Procedure

Locomotor activity. In Groups 1, 2, 3 and 4 registration of locomotor activity was carried out in a chamber measuring 95 × 95 × 65 cm. Four movable tiles measuring 45 × 45 cm each were the floor. Each time the animal pressed the tile an electric impulse was produced and registered by digital frequency meter. This system of registration reflected a general locomotor activity (motility) consisting in the movements within one particular tile as well as crossing to another tile. This method of measuring turned out to be the most proper one since the movements within one tile were of locomotor nature. Locomotor activity was assessed during 30 min experimental sessions. The first test was recorded 12 days after surgery and the second one 19 days after surgery. The mean value of the two tests was considered to be the baseline. Six days after the second locomotor activity test (25 days after surgery) the animals were administered nomifensine IP and after 40 min 5,7-DHT was injected into the MRN (Group 2) and DRN (Group 4). Locomotor activity was then measured 10 and 15 days after neurotoxin injection. In the control groups this procedure was identical, only AA was injected into the MRN (Group 1) and DRN (Group 3). The registering equipment, TV screen and experimenter were in a separate room.

Group 1, 2, 3 and 4 cats were subject to recording for

both locomotor activity and growling response induced by intrahypothalamic injections of carbachol. Locomotor activity was always registered first, and then immediately carbachol-induced response followed. These two behaviors were recorded in two different chambers in a separate room.

Carbachol-induced growling response. In Groups 1, 2, 3 and 4 registration of growling response evoked by intrahypothalamic carbachol injection was carried out in a chamber measuring 110 × 80 × 60 cm. The intensity of the growling response was evaluated by recording the latency to the first growl, the number of growls, the total time spent growling, and the duration of growling period, i.e., from the first to the last growl. A set of telephone digital counters operated manually allowing simultaneous measurements of the number of growls as well as time spent growling was used. Pressing of one switch of the apparatus (immediately at the beginning of growling) initiated counting of two different counters. One of them recorded the number of growls and the other the time spent growling in seconds. The response was considered completed if a growl was not followed by another within 3 min. All cats (Groups 1, 2, 3 and 4) were tested twice before 5,7-DHT or vehicle injections into the MRN or DRN. The first test for carbachol-induced growling response was recorded 12 days after surgery and the second one 19 days after surgery. The mean value of the two tests was considered to be the baseline. Further procedure was identical as in locomotor activity test.

Predatory test for a single cat (PS Test). This test was intended to eliminate animals which did not prey spontaneously (spontaneous non-killers). The test was performed in an experimental chamber (180 × 180 × 120 cm), in which the cats were able to freely move, jump and catch a mouse. The animal, after 24 h food deprivation, was placed in the chamber for 5 min. After this time a freely moving white mouse (body wt. 25–30 g) was dropped into the chamber through a port in the upper wall. Three such tests were performed during one session, i.e. three mice were dropped, one at a time, each after consumption of the previous mouse. Each cat participated in three sessions. In the course of these experiments three times were measured, namely: the time in which the cat actually bit a mouse to death (latency of affective attack), the time in which it started devouring the dead mouse and the time in which the cat devoured the mouse (consumption time).

Predatory test in a competitive situation for paired cats (PC Test). The cats selected in the previous test were paired. The base of pairs selection was the same sex, approximate weight and killing latency. The paired cats after 24 h food deprivation were introduced at the same time into the experimental chamber for 5 min, and then a freely moving white mouse was dropped into the chamber. The interpartner relationship of the cats was observed, and only the pairs with marked dominance of one of the paired cats were used in the experiment. In these pairs the established dominance was stable during three successive sessions, i.e. a dominant cat always caught, killed and ate each mouse, while a submissive cat never preyed for a mouse in the presence of its partner. Ten experimental sessions (performed from 11 to 20 days after surgery) consisting of three tests each were carried out after establishing the dominance in all pairs used, in order to consolidate the established hierarchy. After these sessions 21 days after surgery the submissive cats were treated with nomifensine IP, and 40 min later 5,7-DHT was injected into the MRN (Group 5S) and into the DRN (Group 6S). The dominant cats were treated with nomifensine IP, and 40 min later AA was injected into the MRN (Group 5D) and into the DRN (Group 6D). Next, 10 and 15 days after neurotoxin and vehicle injections into the MRN and DRN paired cats were tested in a PC Test in the same way as before neurotoxin and vehicle injections.

Biochemical analysis. The concentrations of NA, DA, 5-HT and respective metabolites, MHPG, DOPAC, HVA and 5-HIAA were measured in the selected brain regions using high-performance liquid chromatography with electrochemical detection (HPLC-ED).

All animals were killed by decapitation 24 h after the last tests of behavioral experiments, between 1100–1200. Their brains were quickly removed and selected regions, i.e. the anterior hypothalamus (AH), posterior hypothalamus (PH), midbrain central grey matter (CG), hippocampus (HC), amygdala (AM) and the prefrontal cortex (CTX) were separated and kept frozen at −70°C until analysed (29). Each frozen brain region was weighed and homogenized with an ultrasonic cell disruptor (Vibracell 72434, 50 W, Bioblock) in 1 ml 0.1 M perchloric acid containing 0.4 mM sodium metabisulphite. The samples were then centrifuged at 10,000 × g for 25 min at 4°C and supernatants were filtered through 0.22 μm filter (Sigma) and 20 μl filtrates were injected into the HPLC system.

The HPLC system consisted of a delivery pump Model HP 1050 (Hewlett-Packard), a sample injector Model 7125 (Rheodyne, Berkeley), and an analytical column ODS2, 250 × 4.6 mm, particle size 5 μm (Hewlett-Packard) protected by a guard column ODS2, 20 × 2.1 mm, particle size 5 μm (Hewlett-Packard). 1.4 ml/min flow rate column temperature of 30°C were used. An electrochemical detector Model HP 1049 A (Hewlett-Packard) with glassy carbon working electrode was used at a voltage setting of +0.65 V vs an Ag/AgCl reference electrode. The detector response was plotted and measured using chromatointegrator (Esoft, Łódź). The concentrations of monoamines and their related metabolites in each sample were calculated from the integrated chromatographic peak area and expressed as ng/g wet tissue. The mobile phase comprised a 0.15 M sodium dihydrogen phosphate, 0.1 mM EDTA, 0.5 mM sodium octanesulphonic acid, 10–12% methanol (v/v) and 5 mM lithium chloride. The mobile phase was adjusted to pH 3.4 with phosphoric acid, filtered through a 0.22 μm filter (Sigma) and degassed with helium.

All chemicals were obtained from Sigma (St. Louis, MO) except for methanol (for HPLC), which was obtained from Serva (Heidelberg). The experimental procedures are in agreement with European Communities Council Directive of 25 November 1986 (86/ 609/ EEC).

Statistics

The results were elaborated statistically with the two-way ANOVA followed by the *a priori test.*

RESULTS

The Effects of 5,7-DHT Injection into the Median or Dorsal Raphe Nuclei

Locomotor activity. ANOVA demonstrated no differences between the groups (AA and 5,7-DHT) as well as between time period (baseline and 10 and 15 days after AA or 5,7-DHT treatment) for locomotor activity after 5,7-DHT or AA administration both into the MRN or DRN (Fig. 1A and 1B).

Carbachol-induced growling response. Carbachol-induced growling response parameters, i.e. latency to first growl, number of growls, total time spent growling and duration of growling period after AA and 5,7-DHT injections into the MRN are presented in Fig. 2A. ANOVA demonstrated that there

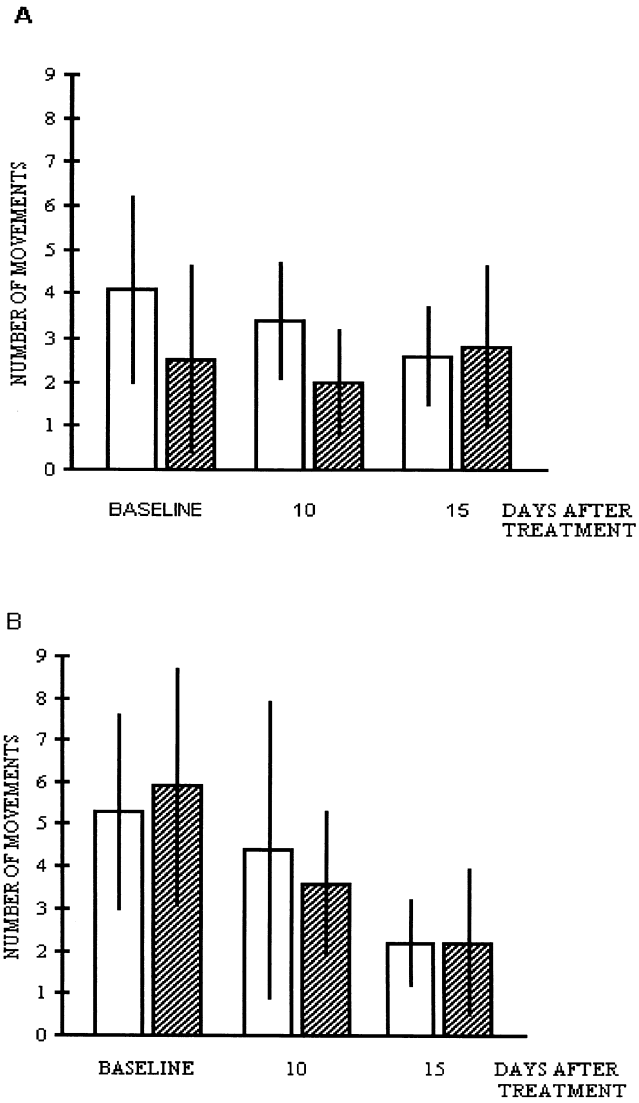

FIG. 1. The effects of ascorbic acid (white bars) and 5,7-DHT (shaded bars) injections into the MRN (A) and DRN (B) on the number of movements (mean ± SEM). Two-way ANOVA (repeated measures) demonstrated NS differences between the groups (5,7-DHT vs vehicle) and within subjects (baseline and 10 and 15 days after 5,7-DHT or vehicle treatment).

were no differences between time period (baseline and 10 and 15 days after AA or 5,7-DHT tretment) for latency to first growl and for duration of growling period but significant differences occurred for a number of growls, $F(2,16) = 7.13$, $p < 0.01$, and for total time spent growling, $F(2,16) = 7.07$, $p < 0.01$. Further analysis by means of *a priori test* showed a significant increase in the number of growls in 5,7-DHT treated group after 10 days vs baseline ($p < 0.05$) and decrease after 15 days vs 10 days ($p < 0.01$). Furthermore, *a priori test* showed a significant increase in the total time spent growling in 5,7-DHT treated group after 10 days vs baseline ($p < 0.05$) and decrease after 15 days vs 10 days ($p < 0.05$). ANOVA demonstrated significant differences between the groups (AA and 5,7-DHT) for the total time spent growling, $F(1,8) = 6.99$, $p < 0.05$, and for duration of growling period, $F(1,8) = 7.18$, $p < 0.05$.

Carbachol-induced growling response parameters after AA and 5,7-DHT injections into the DRN are presented in Fig. 2B. ANOVA demonstrated that there were no differences between the time period (baseline and 10 and 15 days after AA or 5,7-DHT treatment) for latency to the first growl and for number of growls but significant differences occurred for the total time spent growling, $F(2,16) = 8.73$, $p < 0.01$, and for duration of growling period, $F(2,16) = 8.58$, $p < 0.01$. Further analysis by means of *a priori test* showed a significant increase in total time spent growling in 5,7-DHT treated group after 10 days vs baseline ($p < 0.05$) and decrease after 15 days vs 10 days ($p < 0.05$). Also *a priori test* showed a significant increase in duration of growling period in 5,7-DHT treated group after 10 days vs baseline ($p < 0.01$) and decrease after 15 days vs 10 days ($p < 0.05$). ANOVA demonstrated significant differences between the groups (AA and 5,7-DHT) for number of growls, $F(1,8) = 13.69$, $p < 0.01$, for the total time spent growling, $F(1,8) = 12.77$, $p < 0.01$) and for duration of growling period, $F(1,8) = 10.15$, $p < 0.05$).

Biochemical data. Regional brain concentrations of monoamines and metabolites after AA (Group 1) and 5,7-DHT (Group 2) injections into the MRN are presented in Table 1.

In Group 2 a marked decrease of 5-HT level occurred in PH by 52.7% and in CG by 43.8%. Also in Group 2, 5-HIAA level decreased in PH by 55.6% and in CG by 53.1%. ANOVA demonstrated statistically significant differences between the groups in the contents of 5-HT, $F(1,8) = 15.80$, $p < 0.01$, and of 5-HIAA, $F(1,8) = 8.98$, $p < 0.05$, and *a priori test* showed that the level of 5-HT was lower in PH ($p < 0.001$) and in CG ($p < 0.05$) in Group 2 vs Group 1. The 5-HIAA level was lower in PH ($p < 0.01$) and in CG ($p < 0.01$) in Group 2 vs Group 1. No significant differences occurred between the groups in the contents of NA, DA, MHPG, DOPAC and HVA.

Regional brain concentrations of monoamines and metabolites after AA (Group 3) and 5,7-DHT (Group 4) injections into the DRN are presented in Table 2.

In Group 4 a marked decrease of 5-HT level occurred in CTX by 62.5% and in HC by 40.9%. The level of 5-HIAA also decreased in Group 4 in AH by 35.4%, in PH by 41.2%, in CTX by 72.3% and in HC by 47.4%. ANOVA demonstrated statistically significant differences between the groups in the contents of 5-HT, $F(1,8) = 38.14$, $p < 0.001$, and of 5-HIAA, $F(1,8) = 69.36$, $p < 0.001$, and *a priori test* showed that the level of 5-HT was lower in CTX ($p < 0.001$) and in HC ($p < 0.001$), and also 5-HIAA level was lower in AH ($p < 0.05$), in PH ($p < 0.05$), in CTX ($p < 0.001$) and in HC ($p < 0.001$) in Group 4 vs Group 3. No significant differences occurred between the groups in the contents of NA, DA, MHPG, DOPAC and HVA.

The Effects of 5,7-DHT Injection into the Median or Dorsal Raphe Nuclei in Submissive Cats

Predatory test in a competitive situation for paired cats (PC Test). Once the hierarchy in the paired cats was established, the dominant cat was taking the initiative to attack a mouse in the middle of the chamber close to the place of preying. When the mouse was let into the chamber it was immediately caught by the cat, killed and devoured. At the same time the submissive cat was sitting motionless in the corner of the experimental chamber and was observing its partner's behavior. After the submissive cat was injected 5,7- DHT into the MRN or DRN its behavior changed completely. The submissive cat, first passive and submissive in relation to its partner, became very active, undertook competition and fought for dominance. This led to a reverse of hierarchy or a significant

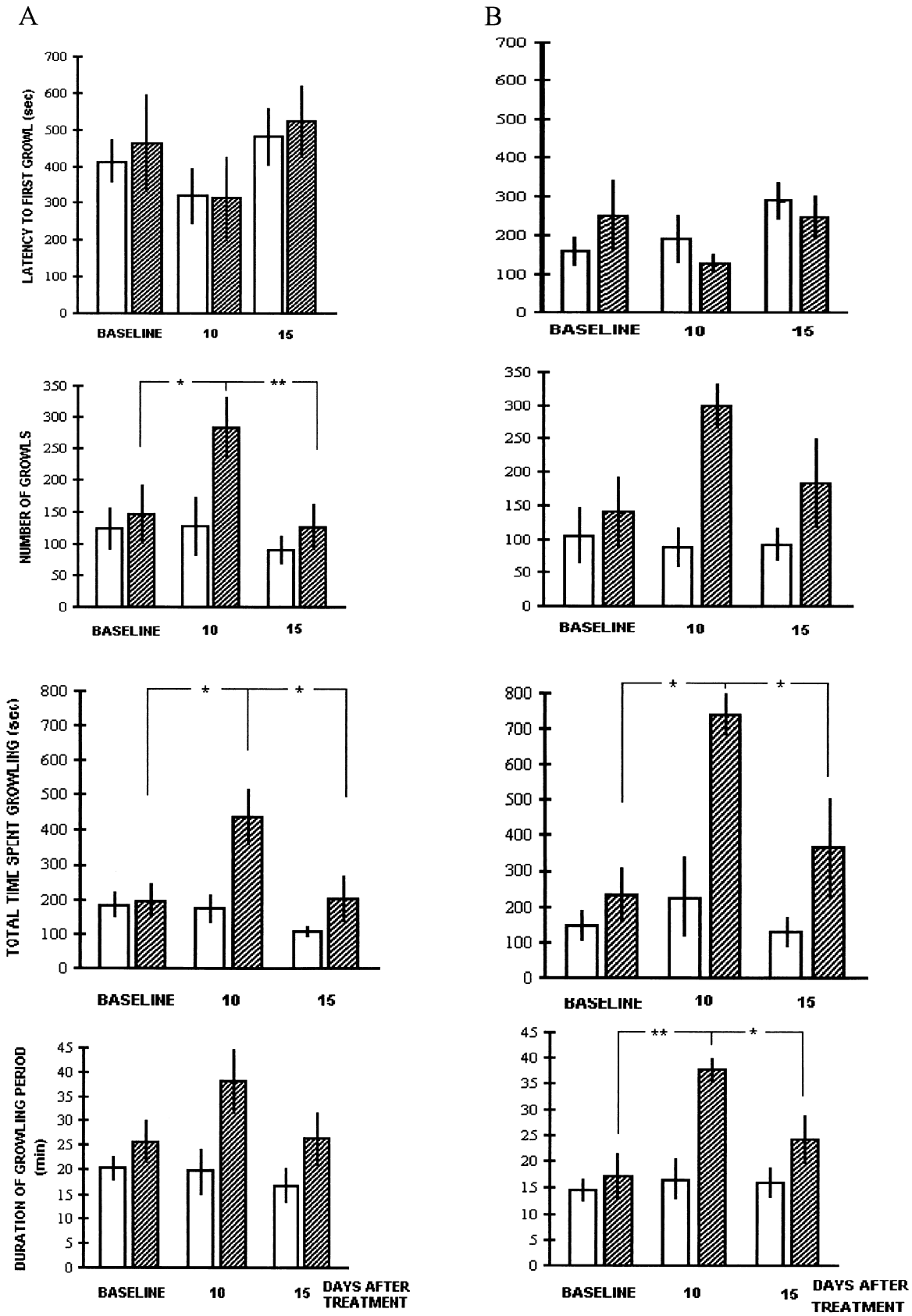

FIG. 2. The effects of ascorbic acid (white bars) and 5,7-DHT (shaded bars) injections into the MRN (A) and DRN (B) on the growling response evoked by intrahypothalamic carbachol injections. Mean latency to first growl, mean number of growls, mean total time spent growling and mean duration of growling period ± SEM. *$p < 0.05$ and **$p < 0.01$ *a priori test.*

TABLE 1

REGIONAL BRAIN CONCENTRATIONS OF NA, DA, 5-HT, MHPG, DOPAC, HVA AND 5-HIAA AFTER 5,7-DHT INJECTION INTO THE MRN

		Monoamine and Metabolite Content in ng/g Wet Tissue						
Group	Brain Region	NA	DA	5-HT	MHPG	DOPAC	HVA	5-HIAA
1. Control	AH	589.3 ± 43.4	126.8 ± 59.0	674.4 ± 46.3	74.6 ± 19.8	51.0 ± 15.9	280.0 ± 37.9	332.2 ± 27.0
2. 5,7-DHT		695.7 ± 117.4	102.0 ± 23.6	533.7 ± 80.1	115.8 ± 20.5	69.4 ± 13.3	247.7 ± 31.6	260.1 ± 34.2
		NS	NS	NS	NS	NS	NS	NS
1. Control	PH	519.4 ± 50.2	56.2 ± 5.4	1254.1 ± 102.7	64.2 ± 5.6	30.6 ± 4.6	186.5 ± 15.2	448.1 ± 38.7
2. 5,7-DHT		492.9 ± 96.2	53.6 ± 11.1	593.8 ± 82.0	61.8 ± 16.5	32.6 ± 5.7	140.4 ± 16.1	199.4 ± 33.2
		NS	NS	$p < 0.001$	NS	NS	NS	$p < 0.01$
1. Control	CG	699.0 ± 107.8	71.4 ± 31.4	2176.8 ± 366.7	71.8 ± 14.1	37.3 ± 13.3	405.4 ± 71.3	927.3 ± 118.9
2. 5,7-DHT		634.2 ± 58.3	90.5 ± 14.0	1225.2 ± 84.8	79.1 ± 20.0	40.5 ± 4.7	360.0 ± 94.0	435.3 ± 61.5
		NS	NS	$p < 0.05$	NS	NS	NS	$p < 0.01$
1. Control	AM	423.6 ± 59.9	409.0 ± 36.6	1667.1 ± 273.6	56.1 ± 11.2	102.6 ± 18.9	341.8 ± 40.0	480.8 ± 103.5
2. 5,7-DHT		486.3 ± 52.3	479.7 ± 51.0	1248.6 ± 129.6	39.2 ± 9.2	110.2 ± 16.3	300.1 ± 54.8	430.7 ± 69.9
		NS	NS	NS	NS	NS	NS	NS
1. Control	CTX	416.6 ± 56.5	130.5 ± 12.7	680.0 ± 131.6	59.1 ± 9.3	52.7 ± 7.9	77.8 ± 18.1	290.9 ± 84.4
2. 5,7-DHT		371.9 ± 48.1	145.6 ± 12.9	465.2 ± 44.8	52.6 ± 17.2	57.6 ± 7.0	79.1 ± 11.1	155.6 ± 21.7
		NS	NS	NS	NS	NS	NS	NS
1. Control	HC	289.2 ± 30.1	89.3 ± 26.0	742.1 ± 79.1	52.5 ± 10.1	39.9 ± 5.3	139.1 ± 16.8	276.1 ± 32.7
2. 5,7-DHT		198.7 ± 53.0	133.7 ± 64.2	670.4 ± 136.0	39.7 ± 13.5	59.1 ± 16.4	228.5 ± 41.7	208.5 ± 34.1
		NS	NS	NS	NS	NS	NS	NS

Values are mean ± SEM. $n = 5$ for each group.
Statistical significance: *a priori test.*

TABLE 2

REGIONAL BRAIN CONCENTRATIONS OF NA, DA, 5-HT, MHPG, DOPAC, HVA AND 5-HIAA AFTER 5,7-DHT INJECTION INTO THE DRN

		Monoamine and Metabolite Content in ng/g Wet Tissue						
Group	Brain Region	NA	DA	5-HT	MHPG	DOPAC	HVA	5-HIAA
3. Control	AH	590.9 ± 90.0	188.4 ± 40.2	913.3 ± 86.1	94.1 ± 16.4	57.3 ± 5.8	405.5 ± 81.8	649.4 ± 71.6
4. 5,7-DHT		714.8 ± 63.7	70.2 ± 8.3	747.2 ± 50.6	77.3 ± 17.7	45.2 ± 2.6	291.6 ± 28.4	420.0 ± 8.3
		NS	NS	NS	NS	NS	NS	$p < 0.05$
3. Control	PH	388.1 ± 59.7	72.6 ± 14.6	1564.1 ± 205.5	103.7 ± 12.3	37.5 ± 6.8	213.6 ± 34.0	693.3 ± 109.4
4. 5,7-DHT		426.9 ± 32.5	68.9 ± 9.7	1149.8 ± 155.6	92.0 ± 57.1	37.7 ± 4.4	207.8 ± 35.8	408.2 ± 20.4
		NS	NS	NS	NS	NS	NS	$p < 0.05$
3. Control	CG	326.9 ± 23.8	59.3 ± 12.3	1419.8 ± 76.1	86.9 ± 31.7	41.4 ± 8.4	139.8 ± 24.2	645.4 ± 45.6
4. 5,7-DHT		328.6 ± 32.7	64.1 ± 10.6	1460.2 ± 145.8	104.7 ± 26.0	31.6 ± 3.5	290.6 ± 38.8	628.2 ± 55.3
		NS	NS	NS	NS	NS	NS	NS
3. Control	AM	325.8 ± 18.1	437.9 ± 62.5	1462.1 ± 75.9	112.2 ± 26.9	100.9 ± 9.3	340.1 ± 43.3	496.8 ± 27.5
4. 5,7-DHT		281.2 ± 98.3	534.6 ± 75.5	1300.4 ± 158.0	199.7 ± 61.6	105.9 ± 18.9	399.5 ± 73.0	452.9 ± 62.9
		NS	NS	NS	NS	NS	NS	NS
3. Control	CTX	357.4 ± 33.7	122.5 ± 23.0	760.6 ± 92.0	190.1 ± 32.4	57.6 ± 8.0	77.4 ± 19.3	263.9 ± 53.6
4. 5,7-DHT		239.0 ± 25.3	77.6 ± 5.7	285.9 ± 27.0	129.0 ± 53.7	33.2 ± 5.4	51.1 ± 22.5	73.2 ± 8.0
		NS	NS	$p < 0.001$	NS	NS	NS	$p < 0.001$
3. Control	HC	207.7 ± 43.5	103.0 ± 42.8	776.9 ± 60.6	188.5 ± 43.6	40.0 ± 6.4	93.4 ± 18.2	357.5 ± 51.0
4. 5,7-DHT		136.4 ± 16.7	116.1 ± 57.9	459.6 ± 100.4	129.2 ± 36.3	37.7 ± 5.8	84.8 ± 29.6	188.4 ± 39.9
		NS	NS	$p < 0.001$	NS	NS	NS	$p < 0.001$

Values are mean ± SEM. $n = 5$ for each group.
Statistical significance: *a priori test.*

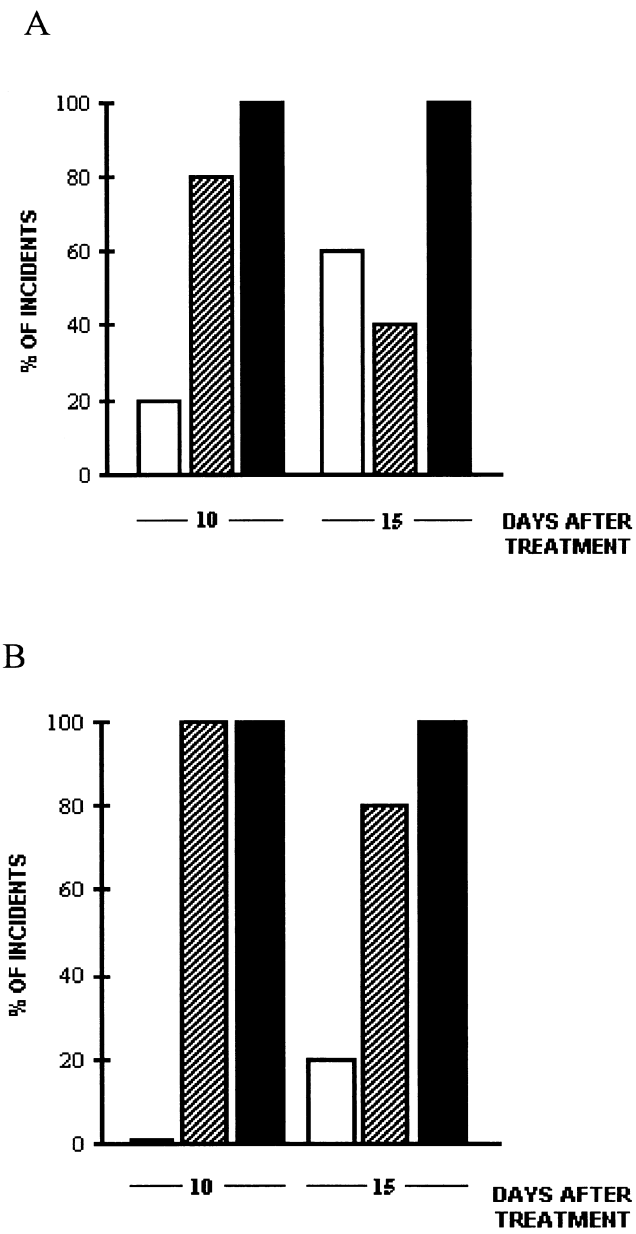

FIG. 3. Histogram expressed as percentage of the total number of incidents of behavioral categories (5 cats × 3 tests per session = 100%) observed in previously submissive cats after 5,7-DHT injection into the MRN (A) and DRN (B). Total reversal of hierarchy (white bars), attempts to take the mouse already caught by a dominant cat (shaded bars), fight for taking a better position in relation to the place in which mouse is put (black bars).

weakening of a position of the dominant cat. Even if the hierarchy was not completely reversed, the cats which were earlier submissive fought against their partners for getting a good position to attack a mouse and made attempts to take the mouse which was already the partner's prey. Quantitative data referring to particular categories of these behaviors in submissive cats 10 and 15 days after 5,7-DHT injections into the MRN (Group 5) and DRN (Group 6) were shown in Fig. 3A and 3B.

Biochemical data. Regional brain concentrations of monoamines and metabolites are presented in details in Table 3 (Group 5D and Group 5S) and in Table 4 (Group 6D and Group 6S).

In Group 5S a marked decrease of 5-HT level occurred in AH by 55.8% and in HC by 53.7%. Also 5-HIAA level decreased in Group 5S in AH by 56.5%, in PH by 58.0%, in AM by 35.4% and in HC by 55.4%. ANOVA demonstrated significant differences between the groups in the content of 5-HT, $F(1,8) = 20.75$, $p < 0.01$, and of 5-HIAA, $F(1,8) = 16.37$, $p < 0.01$), and *a priori test* showed that the level of 5-HT was lower in AH ($p < 0.001$) and in HC ($p < 0.001$) in Group 5S vs Group 5D. The 5-HIAA level was lower in AH ($p < 0.001$), in PH ($p < 0.001$), in AM ($p < 0.05$) and in HC ($p < 0.01$) in Group 5S vs Group 5D. No significant differences occurred between the groups in the contents of NA, DA, MHPG, DOPAC and HVA.

In Group 6S a decrease of 5-HT level occurred in AH by 53.5%, in AM by 29.1% and in CTX by 39.4%. 5-HIAA level decrease in Group 6S in AH by 36.1%, in AM by 33.2% and in CTX by 55.2%, and DA decrease in Group 6S in AH by 88.9%. ANOVA showed significant differences between the groups in the contents of 5-HT, $F(1,8) = 15.56$, $p < 0.01$, of 5-HIAA, $F(1,8) = 8.62$, $p < 0.05$, and of DA, $F(1,8) = 21.04$, $p < 0.01$, and *a priori test* demonstrated that the level of 5-HT was lower in AH ($p < 0.001$), in AM ($p < 0.05$) and in CTX ($p < 0.01$) in Group 6S vs Group 6D. The 5-HIAA level was lower in AH ($p < 0.05$), in AM ($p < 0.05$) and in CTX ($p < 0.001$) in Group 6S vs Group 6D. DA level was lower only in AH ($p < 0.001$) in Group 6S vs Group 6D. No significant differences occurred between the groups in the contents of NA, MHPG, DOPAC and HVA.

It should be pointed out that 5,7-DHT administration alone into the MRN and DRN did not produce growling behavior in cats.

DISCUSSION

After 5,7-DHT administration into the MRN or DRN the locomotor activity of the cats in both cases was not subject to significant changes. Growling response evoked by intrahypothalamic carbachol injections, whose quantitative parameters precisely reflect the intensity of an affective aggression (5), significantly increased (Groups 2 and 4). Moreover, after the MRN or DRN lesions, cats previously labelled as submissive in the PC Test (Groups 5S and 6S) violated the established hierarchical pair system. They fought for domination and in a few cases obtained a complete reversal of the hierarchy.

Our results, contrary to experiments performed on rats, indicate that there is no functional differentation of the MRN and DRN and both nuclei participate in the regulation of affective and predatory aggression, their function being inhibitory. The results obtained on rats indicated that only DRN participates in the regulation of defensive behavior (25). In our study the animals were treated with nomifensine IP before injecting 5,7-DHT into the MRN or DRN to prevent catecholamines depletion. In this respect the lesions we performed can be considered as "relative selective for serotonergic neurons." In the rat studies the MRN or DRN lesions were performed either electrolytically or with 5,7-DHT non preceded by nomifensine administration (8,12,14,15,34). In both cases lesions resulted in being less "selective" than the ones produced by us. The "selectivity" of the lesion on 5-HT neurones is very important since in the cat's MRN only 35% and in the DRN 70% of the total number of cells presented are 5-HT

TABLE 3

REGIONAL BRAIN CONCENTRATIONS OF NA, DA, 5-HT, MHPG, DOPAC, HVA AND 5-HIAA AFTER 5,7-DHT INJECTION INTO THE MRN IN SUBMISSIVE CATS

		Monoamine and Metabolite Content in ng/g Wet Tissue						
Group	Brain Region	NA	DA	5-HT	MHPG	DOPAC	HVA	5-HIAA
5. Domin.	AH	826.9 ± 79.9	582.0 ± 187.1	1272.2 ± 117.5	91.6 ± 5.9	83.4 ± 13.4	640.5 ± 94.5	433.2 ± 26.3
5. Subm.		864.3 ± 84.8	490.5 ± 223.3	563.5 ± 118.2	130.2 ± 32.8	57.2 ± 16.9	325.3 ± 57.6	188.8 ± 45.3
		NS	NS	$p < 0.001$	NS	NS	NS	$p < 0.001$
5. Domin.	PH	749.6 ± 112.6	145.4 ± 13.1	1645.2 ± 160.3	109.7 ± 31.4	49.5 ± 5.3	242.8 ± 27.8	636.5 ± 93.7
5. Subm.		712.7 ± 135.0	121.5 ± 11.4	1296.3 ± 237.1	83.9 ± 35.6	38.5 ± 6.7	183.9 ± 20.3	267.9 ± 41.6
		NS	NS	NS	NS	NS	NS	$p < 0.001$
5. Domin.	CG	537.2 ± 82.2	79.2 ± 10.2	1572.6 ± 122.3	89.7 ± 20.6	33.5 ± 3.5	178.3 ± 26.4	506.4 ± 25.3
5. Subm.		644.9 ± 78.0	99.1 ± 20.0	1571.6 ± 187.2	77.1 ± 24.8	53.5 ± 6.0	245.1 ± 42.6	364.2 ± 75.7
		NS	NS	NS	NS	NS	NS	NS
5. Domin.	AM	554.4 ± 100.0	699.2 ± 107.5	1811.4 ± 85.4	101.8 ± 24.4	111.1 ± 14.5	282.5 ± 32.6	362.3 ± 43.4
5. Subm.		492.4 ± 143.1	783.3 ± 67.7	1544.9 ± 116.8	57.6 ± 17.1	107.6 ± 11.7	336.6 ± 9.5	234.1 ± 48.7
		NS	NS	NS	NS	NS	NS	$p < 0.05$
5. Domin.	CTX	367.8 ± 86.2	122.1 ± 19.6	619.0 ± 107.4	130.4 ± 44.0	37.2 ± 2.6	82.6 ± 10.7	119.2 ± 26.2
5. Subm.		327.6 ± 80.9	130.5 ± 14.0	410.0 ± 56.2	153.9 ± 48.5	45.2 ± 8.6	84.8 ± 11.2	83.3 ± 16.6
		NS	NS	NS	NS	NS	NS	NS
5. Domin.	HC	213.9 ± 37.3	324.0 ± 92.5	1415.5 ± 216.8	44.6 ± 13.0	59.8 ± 13.7	155.4 ± 33.5	304.3 ± 62.1
5. Subm.		256.4 ± 75.4	186.3 ± 34.9	655.5 ± 103.1	67.5 ± 22.6	43.6 ± 2.8	104.1 ± 6.1	135.9 ± 204.1
		NS	NS	$p < 0.001$	NS	NS	NS	$p < 0.01$

Values are mean ± SEM. $n = 5$ for each group.
Statistical significance: *a priori test.*

TABLE 4

REGIONAL BRAIN CONCENTRATIONS OF NA, DA, 5-HT, MHPG, DOPAC, HVA AND 5-HIAA AFTER 5,7-DHT INJECTION INTO THE DRN IN SUBMISSIVE CATS

		Monoamine and Metabolite Content in ng/g Wet Tissue						
Group	Brain Region	NA	DA	5-HT	MHPG	DOPAC	HVA	5-HIAA
6. Domin.	AH	1760.4 ± 149.3	1134.7 ± 308.0	2319.3 ± 126.3	30.4 ± 4.4	184.1 ± 32.4	572.2 ± 106.0	435.3 ± 39.7
6. Subm.		1046.3 ± 190.3	126.9 ± 39.8	1080.2 ± 84.1	48.3 ± 10.7	53.8 ± 13.0	233.6 ± 46.3	278.2 ± 43.6
		NS	$p < 0.001$	$p < 0.001$	NS	NS	NS	$p < 0.05$
6. Domin.	PH	846.8 ± 143.2	168.7 ± 20.2	1454.7 ± 205.1	24.5 ± 3.3	51.3 ± 3.6	182.1 ± 19.9	342.3 ± 30.5
6. Subm.		654.7 ± 76.9	120.8 ± 8.2	1288.2 ± 202.2	54.6 ± 11.4	54.2 ± 8.4	230.4 ± 38.1	255.9 ± 18.3
		NS	NS	NS	NS	NS	NS	NS
6. Domin.	CG	597.5 ± 51.8	155.5 ± 25.5	1539.7 ± 98.1	27.3 ± 4.7	51.7 ± 9.5	211.7 ± 30.1	366.4 ± 31.9
6. Subm.		776.9 ± 82.5	81.0 ± 6.4	1615.7 ± 234.3	61.1 ± 17.7	52.5 ± 4.8	281.5 ± 19.8	470.3 ± 47.9
		NS	NS	NS	NS	NS	NS	NS
6. Domin.	AM	861.2 ± 176.9	622.7 ± 82.5	2159.5 ± 274.0	25.1 ± 7.9	122.0 ± 27.7	333.7 ± 81.2	430.7 ± 60.2
6. Subm.		603.0 ± 74.0	706.3 ± 65.1	1532.5 ± 97.7	30.2 ± 5.7	121.8 ± 22.3	345.5 ± 38.0	288.1 ± 44.8
		NS	NS	$p < 0.05$	NS	NS	NS	$p < 0.05$
6. Domin.	CTX	630.7 ± 55.2	161.0 ± 16.4	690.8 ± 83.9	77.9 ± 23.7	48.6 ± 5.8	55.8 ± 9.2	159.8 ± 46.6
6. Subm.		503.0 ± 52.5	127.9 ± 18.0	419.2 ± 40.5	28.2 ± 5.9	36.3 ± 7.3	42.2 ± 8.0	71.7 ± 15.7
		NS	NS	$p < 0.01$	NS	NS	NS	$p < 0.001$
6. Domin.	HC	383.4 ± 40.7	204.1 ± 90.6	1254.4 ± 75.3	25.7 ± 7.3	61.7 ± 8.1	156.4 ± 15.0	262.5 ± 27.3
6. Subm.		338.1 ± 34.2	161.1 ± 52.3	1044.7 ± 73.1	44.3 ± 11.6	61.8 ± 6.3	137.6 ± 18.0	236.1 ± 16.0
		NS	NS	NS	NS	NS	NS	NS

Values are mean ± SEM. $n = 5$ for each group.
Statistical significance: *a priori test.*

neurons (35). This means that a high percentage of cells are non-5-HT neurons. This percentage might be even higher in the rat raphe nuclei. Descaries et al. (6) reported that 70% of the total number of cells in the rat DRN are non-5-HT neurons. Consequently, the possibility of affecting neurons other than serotonergic ones when performing neurotoxic lesions is a crucial variable that has to be considered. Besides, a doubt is put forward whether it is possible to perform, in rats, lesions limited only to the MRN or only to the DRN since the two nuclei are much smaller than in the cat and to some extent overlap (4).

Different experimental models are used to investigate defensive responses in rats and cats. The two models used in the present study were designed to reproduce the natural behavior of the cat (18). The interference due to the presence of the experimenter was minimized and the use of nociceptive stimuli to elicit defensive behavior response was avoided because it was considered non-physiological. On the contrary, the emotional-defensive responses showed in rats were often induced by painful and stressful stimuli (25,33).

Interspecies differences may also play a role in the divergency of the results between cats and rats studies. Cats usually live and prey individually while rats live in groups and do not present a predator behavior comparable to that of cats. Consequently the aggressive behavior induced in cats and rats may rely in part on different anatomo-functional circuits.

Finally, in the present study we want to underline that neither MRN nor DRN lesions increased spontaneous aggressiveness and such a response appeared only in the experimental situation.

The neurochemical analysis performed in the cats labelled as submissive in the PC Test (groups 5S and 6S), showed interesting results. The submissive cats which after the MRN or DRN lesions fought for domination had a lower level of 5-HT and 5-HIAA in the structure examined. This evidence is consistent with the theory that 5-HT inhibits aggressive behavior (25,33). More surprisingly, the content of NA and MHPG did not significantly differ from the contents observed in the dominating cats (groups 5D and 6D). The latter observation is very important since in earlier studies it consistently emerged that NA metabolism is increased in submissive animals (13,17,31,32), and it is decreased in aggressivly behaving animals (16,38). Therefore, in the present study the NA metabolism should be higher in the submissive cats than in the dominant animals. The lack of these results suggests that following the MRN or DRN lesions not only 5-HT/5-HIAA levels are decreased, but also the level of NA might have dropped to the values normally present in the dominant animals. If this hypothesis was true, the violation of the established hierarchy after the lesions might be related on the one hand to the increase of aggressiveness due to a drop in 5-HT metabolism and on the other hand to a reduction of fear due to a drop of NA metabolism. Nevertheless we are aware that this hypothesis is speculative since there is no direct evidence in this paper of a higher level of NA in submissive cats before the MRN or DRN lesions.

In conclusion the biochemical findings suggest that affective aggression and predatory aggression both appear to rely on similar neurochemical processes since the two responses are equally affected by lesions of the MRN or DRN. Nevertheless, the two types of aggression are clearly differentiable on the basis of their behavioral patterns (18) and neuroanatomical underlined systems (2,3,9,10,11).

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