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THE PARTICIPATION OF SEROTONINERGIC SYSTEM IN THE REGULATION OF EMOTIONAL-DEFENSIVE BEHAVIOR EVOKED BY INTRAHYPOTHALAMIC CARBACHOL INJECTIONS IN THE CAT

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Abstract. The influence of bilateral injections of serotonin (5-HT) and methysergide (MET) to antero-medial hypothalamus (HA) on carbachol-induced emotional-defensive behavior was investigated. Earlier (15 min) stimulation of 5-HT receptors in HA region by 5-HT injections evoked a decrease in the level of vocal response (number and time of growling), while previous blocking of these receptors by means of MET brought about a considerable increase of vocalization level evoked by carbachol (Cch) injections (10 μg) to the same loci of HA. Intrahypothalamic injections of 5-HT alone or MET did not evoke any observable changes in the animals' behavior. The alterations of the level of Cch-induced vocal response 3 to 35 days after chemical damage of 5-HT neurons in HA or in the middle forebrain bundle (MFB) in posterolateral hypothalamus caused by 5,7-dihydroxytryptamine were examined. Local neurotoxin injections both to MFB and to HA evoked a long-lasting increase in the level of Cch-induced vocalization, which began on the 5th-7th day after lesioning and lasted till the completion of the experiment (35 days). Results data indicate that the 5-HT system exerts an inhibiting influence on the emotional-defensive behavior induced by the cholinergic system.

INTRODUCTION

Acetylcholine (Ach) or carbachol (Cch) injections to various structures of the limbic system and to the hypothalamus in cats evoke the syndrome of characteristic vegetative and behavioral symptoms which are well-integrated emotional-defensive behavior (2, 12, 21, 29, 34, 36). Later experiments proved this behavior to be a warning threat equivalent to a natural response of the cat in a dangerous situation and according to the external situations it may evoke either aggressive or defensive behavior (5, 9, 11).

Neurochemical correlates of emotional-defensive behavior have been carefully investigated recently. This behavior can be induced exclusively by intracerebral cholinomimetics injections, while a direct stimulation of noradrenergic (NA), dopaminergic (DA) and serotoninergic (5-HT) neurons does not evoke the emotional-defensive response (1–3, 13, 14, 19, 30, 34, 37, 41). In the light of the obtained data it is doubtless that the cholinergic mechanism evoking emotional-defensive behavior is in a close functional correlation to the other neurotransmitter systems, since numerous reports indicate a significant participation of monoaminergic neurons in the final integration and expression of this behavior (1, 2, 6, 7, 14, 16, 18, 20, 26, 32–35, 37, 42). It is probable that aminergic systems stimulated through the cholinergic neurons influence this behavior not by isolated activity changes in one system but by mutual inter- or counteractions (2, 32, 34).

The aim of the present experiments was to examine the interaction of the 5-HT system with the cholinergic system in the central regulation of emotional-defensive behavior. The carbachol-induced emotional-defensive response of well-defined quality and accurately measured quality carbachol-induced emotional-defensive response (which is the best representative of the cat's behavior in natural conditions after being exposed to threat) was used as a model response (9, 10, 14, 43).

On the basis of the data obtained on various animals and from different experimental approaches, the opinion that suggests it self is that the 5-HT system inhibits animals' activity as well as various forms of emotional-defensive behavior. This opinion can be supported by the following facts: (i) 5-HT synthesis blocking evoked by para-chlorophenylalanine (PCPA) administration increases aggressive behavior of cats (16, 20), these symptoms can be reduced by 5-hydroxytryptophan administration, (ii) the blocking of 5-HT receptors by methysergide (MET) increases the carbachol-induced vocal response (1), (iii) peripheral administration of l-tryptophan brings about the inhibition of carbachol-induced emotional-defensive response (1). Beleslin and Samardzić (7) report that the

5-HT system in the cat facilitates the affective expression of emotional behavior induced by stimulation of the cholinergic brain system.

In the present paper we refer to experiments performed mostly on cats and only in some cases to results obtained on other animals. Such an approach seems to be justified by the following reasons: (i) biological environment and regimen of cats and rats (which are mostly subjects of investigations) are different. Forms of behavior and external symptoms of emotional responses have so little in common that they cannot be compared, (ii) neurochemical investigations stated the presence of significant functional differences between species (30), (iii) there are some data suggesting that various types of defensive responses possess different neurochemical mechanisms (32).

MATERIAL AND METHODS

Subjects and surgery. The experiment was performed on 27 cats of both sexes, of 2.0 to 3.2 kg body weight. All cats had chronically bilaterally implanted cannulas to the anterio-medial hypothalamus (HA) according to the stereotaxic coordinates of Jasper and Ajmone-Marsan's atlas (23): A = 13.0, L = 1.5–2.0, H = −3.5. Additionally, in cats of experimental group II (subgroups 1 and 3) cannulas were bilaterally implanted to the middle forebrain bundle (MFB) in the postero-lateral hypothalamus according to the following coordinates: A = 10.0, L = 3.0, H = −4.5. Other details of the operation and microinjections procedure were described in earlier works (11, 36).

Chemical compounds. Intracerebral injections of chemical compound solutions were administered bilaterally. Doses of each compound (as a free base) which are presented below, refer to the values administered unilaterally. Carbachol (choline chloride carbamate, Koch-Light) 5 μg in 1 μl, serotonin (serotonin creatinine sulphate, Merck) 5 μg in 1 μl, methysergide (methysergide maleate, Sandoz) 10 μg in 2 μl, 5,7-DHT (5,7-dihydroxytryptamine, Sigma) 10 μg in 2 μl, 0.2% solution of ascorbic acid (AA) in 0.9% NaCl — 2 μl. 5,7-DHT was dissolved just before use in 0.2% AA in physiological saline solution at a temperature of 4 °C and other compounds were dissolved in 0.9% NaCl at 20 °C.

Experimental procedure. The emotional-defensive behavior was evoked by bilateral Cch injections to HA. The intensity of this response was evaluated by recording the number of growls and the duration of growling during a 30 min experimental session (for exact procedure see 10). The animals were divided into two experimental groups. In group I ($n=6$) the influence of 5-HT system activity on emotional-defensive vocal response induced by Cch injections to HA was the subject

of investigations. Successive sessions were held at 7 day intervals. The control level of Cch-induced response was established as a mean numbers of growls and mean time of growling during 30 min determined at two successive sessions. Next, the level of vocal response evoked by Cch injections to HA (to which 5-HT was injected 15 min earlier) was measured in two successive sessions and compared to the level of control response. When the control level was evaluated again, it was compared to the level of response evoked by Cch injections administered 15 min after intrahypothalamic MET injections (in the way mentioned above). Group II was divided into 4 subgroups. In the first two subgroups the effect of decreasing 5-HT system activity in the hypothalamus on Cch-induced emotional-defensive behavior was examined. In animals of subgroup 1 ($n=5$) 5-HT neurons in MFB, and in animals of subgroup 2 ($n=6$) 5-HT neurons in HA were damaged. The level of Cch-induced emotional-defensive response evoked on the 3rd, 5th, 7th, 13th, 17th, 21st, 28th and 35th day after 5,7-DHT administration was compared to the level of control response evaluated in three successive sessions before 5,7-DHT injections. In subgroups 3 and 4 in identical time periods as in subgroups 1 and 2, the measurements were taken of the vocal response evoked by Cch injections to HA after an earlier single administration of AA to MFB (subgroup 3, $n=5$) and to HA (subgroup 4, $n=5$). The level of Cch-induced response was compared to the level of control response which was determined in three successive sessions held before AA injections. Subgroup 3 and 4 served as controls for subgroups 1 and 2, respectively.

Histology. At the end of the experiments the cats were killed by hexobarbital overdose and their brains fixed in 4% formalin. Paraffin sections 20 μm thick were stained with cresyl violet and subsequently the injections points were localized histologically.

Statistics. The results were statistically analysed by means of the analysis of variances, Type AS for group I and Type I for group II (27), and next by means of Duncan's test (15).

RESULTS

Group I. A histological analysis of brain sections showed that cannulas had been implanted, according to previous assumptions, in HA area between frontal planes A = 12.0–13.0 (Fig. 1). Cch injections to HA evoked the characteristic emotional-defensive behavior described in detail in our previous papers (36, 37). The level of this behavior measured by means of time duration of growling and the number of growls (control level) is illustrated in Fig. 2. Intrahypothalamic injections both

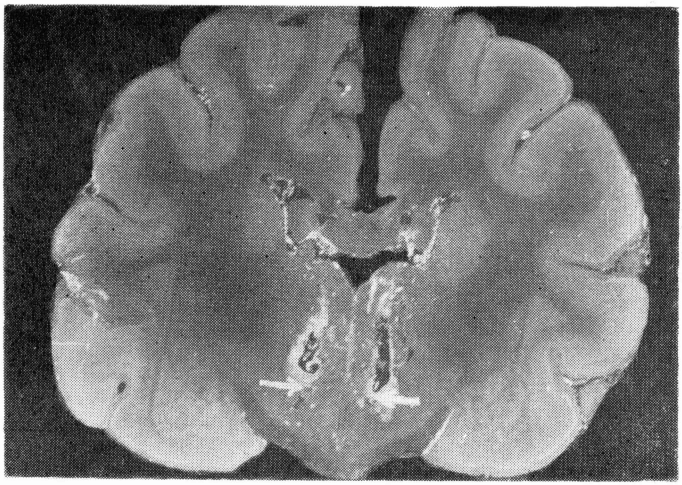

Fig. 1. Photomicrograph of the representative frontal section of the cat's brain showing the localization of injection sites (arrows) in the anterio-medial hypothalamus in Group I.

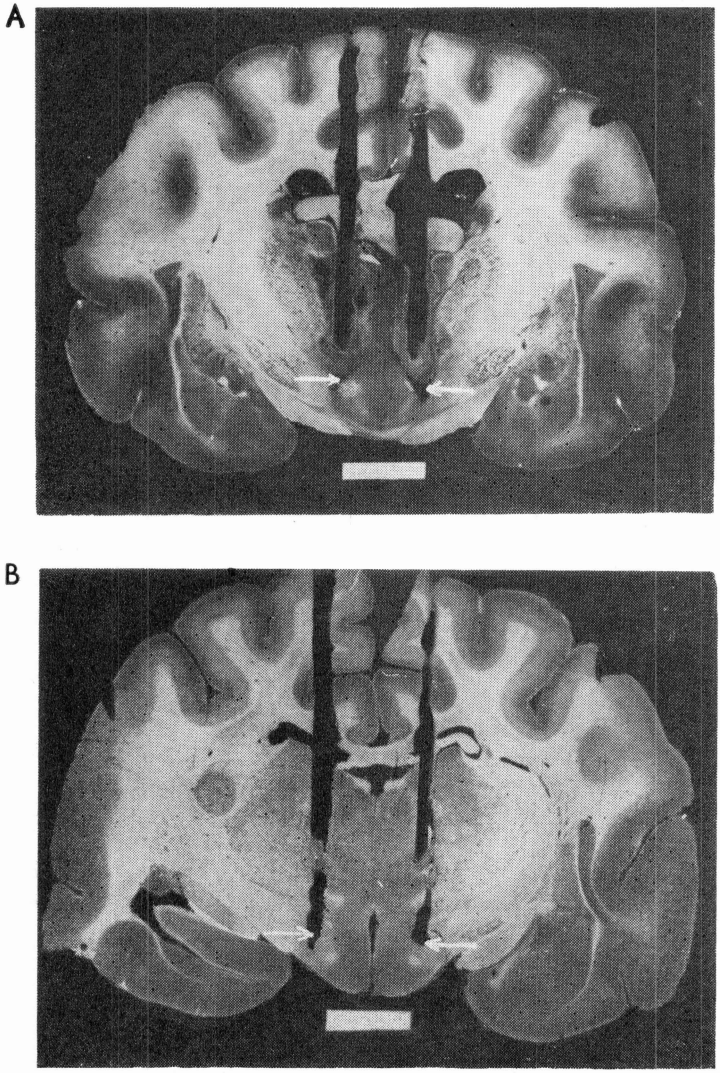

Fig. 3. Photomicrograph of the representative frontal section of the cat's brain showing the localization of injection sites in HA (A) and in MFB (B) (arrows) in Group II. The white strip located on the bottom of the photograph is a scale 5 mm in length.

of 5-HT and MET did not evoke any observable changes in the cats' behavior during 15 min. Following intrahypothalamic Cch injections performed 15 min after 5-HT administration to this area, a significant decrease of vocal response ($P<0.001$ for time duration of growling and number of growls) was observed. However, the previous blocking of 5-HT receptors in HA by means of MET injections brought about a considerable rise in Cch-induced vocal response ($P<0.001$ for number of growls

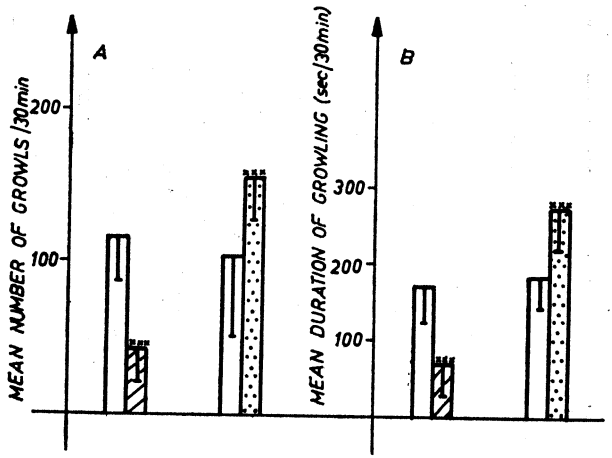

Fig. 2. Mean number of growls (A) and mean time duration of growling (B) ± SEM evoked by injection of Cch into HA (control level, white bars) and Cch acting on the background of compounds influencing the activity of the serotoninergic system: 5-HT (dashed bars) and MET (doted bars) injected 15 min earlier into the same hypothalamic loci. Data are means from 5 cats and two sessions. *** $P<0.001$ as compared to the control data, Duncan's test.

and time duration of growling) evoked from this area 15 min later (Fig. 2). ANOVA (AS type) showed that the sequence of injected compounds (factor A) had a significant influence on the level of vocalization: $F_{2,6} = 45.64$, $P < 0.001$ for the number of growls, $F_{2,6} = 37.18$, $P < 0.001$ for the time duration of growling.

These results indicate that the stimulation of 5-HT system in HA previous to Cch injections to this area decreases the Cch-induced emotional-defensive behavior, while the earlier blocking of this system increases it.

Group II. A histological analysis of brain sections proved cannulas to be implanted in HA area between frontal planes A = 12.5–13.5 and in MFB in frontal planes A = 9.5–10.5 (in subgroups 1 and 3) (Fig. 3). After the delineation of the control level of Cch-induced vocalization, 5-HT neurons were damaged by single 5,7-DHT bilateral injections to MFB (subgroup 1) and to HA (subgroup 2), and on definite days the

emotional-defensive response was evoked by intrahypothalamic Cch injections. The level of Cch-induced vocal response was examined in an identical way after AA administration to MFB (subgroup 3) and to HA (subgroup 4). With the use of Duncan's test it was proved that the Cch-

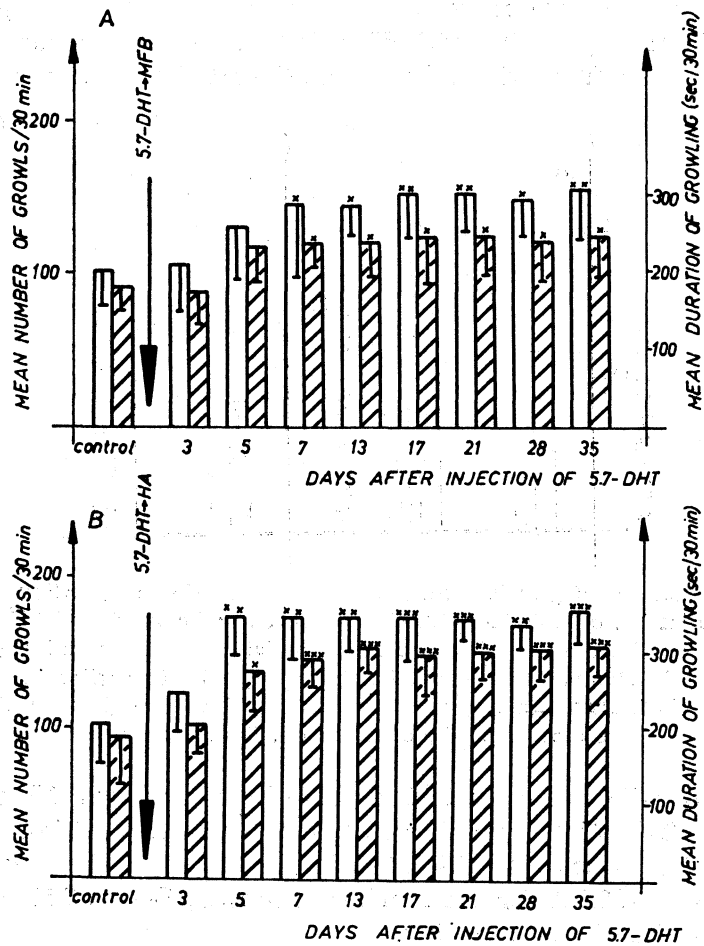

Fig. 4. Mean number of growls (white bars) and mean time duration of growling (dashed bars) ± SEM evoked by injection of Cch into HA (control level) and by Cch acting on successive days after injection of 5,7-DHT to MFB (A) or to HA (B). *** $P<0.001$, ** $P<0.01$, * $P<0.05$ as compared to the control data, Duncan's test.

induced vocal response — the number of growls as well as the time duration of growling — evoked from HA after 5-HT neurons damage in MFB was considerably raised in comparison to control one. This rise appeared on the 7th day after neurotoxine injection and lasted till the end of the experiment i.e. 35 days. The increase of Cch-induced vocal

response (number of growls and time duration of growling) was observed also after 5-HT neurons damage in HA i.e. in the area of evoking emotional-defensive behavior, on the 5th day after neurotoxine administration and it lasted till the completion of experiment (Fig. 4). Duncan's test indicates that the level of Cch-induced vocal response evoked on

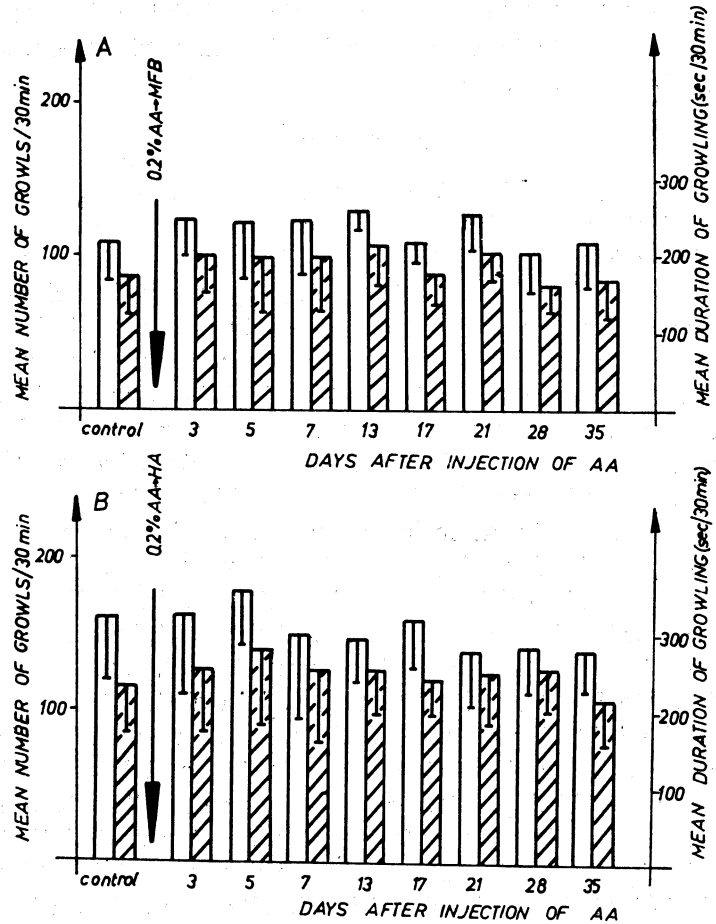

Fig. 5. Mean number of growls and mean time duration of growling ± SEM evoked by injection of Cch into HA (control level) and by Cch acting on successive days after injection of AA to MFB (A) or to HA (B). Other explanations as in Fig. 4.

successive days after AA administration both to MFB and to HA was not statistically different from the level of control response (Fig. 5). ANOVA have proved that the place and type of injected compounds (5,7-DHT to HA, 5,7-DHT to MFB, AA to HA and AA to MFB — factor B) and the time period which passed after the administration of this compounds (factor A) exerted a statistically significant influence on the

number of growls and the time duration of growling. For the number of growls the values of statistic were: factor A: $F_{8,136} = 4.27$, $P < 0.001$; factor B: $F_{3,17} = 4.14$, $P < 0.05$; AB interactions: $F_{24,136} = 2.28$, $P < 0.005$, and for the time duration of growling: factor A: $F_{8,136} = 5.33$, $P < 0.001$; factor B: $F_{3,17} = 6.0$, $P < 0.005$; AB interactions: $F_{24,136} = 2.27$, $P < 0.025$.

From the obtained data one may conclude that the decrease of 5-HT system activity results in a considerable increase of Cch-induced emotional-defensive behavior.

DISCUSSION

The performed experiment proved that although the intrahypothalamic microinjections of 5-HT and MET did not evoke any changes in the emotional-defensive behavior in cats, which is in agreement with previous reports by other authors (19, 40), they exerted a significant influence on the intensity of emotional-defensive response induced by the cholinergic system. It was stated that earlier stimulation of 5-HT receptors induced by 5-HT intrahypothalamic injections significantly decreases the Cch-induced emotional-defensive behavior evoked from this region, while a previous blocking of these receptors by MET injections to HA considerably increases this response. This led to a conclusion that the 5-HT system exerts, at least, a suppressing influence on the emotional-defensive behavior of cats. Yet, the results obtained after the chemical damage of 5-HT neurons in HA and in MFB area supply further data confirming the hypothesis about an inhibiting role of the 5-HT system in emotional behavior regulation (2, 32). Local 5,7-DHT injection both to MFB and to HA resulted in a statistically significant increase in the intensity of emotional-defensive response. This rise appeared on the 5th-7th day after the lesioning and lasted till the end of the experiment (35 days). This result, may be ascribed to the decrease of 5-HT system activity, since Jacobs et al. (22) reported that a single 5,7-DHT injection to MFB in rats evoked a decrease of 5-HT level in the forebrain to 1/3 of the initial 5-HT level. File et al. (17), after 5,7-DHT injections to amygdala in rats, reported a 55–80% decrease of 5-HT level in this structure. The experiments conducted on cats (16, 20) and on rats (4, 28, 38, 39) seem to support this hypothesis, for after the blocking of 5-HT synthesis by means of PCPA, the rise of aggression and irritability in the animals was evoked. The relation of the results of biochemical investigations to our experiment allows to assume that the drop of 5-HT level caused a significant and long-lasting rise of intensity of the Cch-induced emotional-defensive behavior, which in our experiment was recorded after the break of serotoninergic transmission in MFB or/and in HA.

The obtained data are controversial to the investigations of Beleslin and Samardžić (6), who after a chemical lesion of 5-HT neurons in the cat's brain performed by intraventricular 5,6-DHT injections, observed a decrease of vocal response evoked by intraventricular injections of cholinomimetics. Similar effects were also achieved after a decrease of 5-HT level evoked by peripheral PCPA administration, while other autonomic and somatic symptoms characteristic for emotional-defensive behavior were prevalent. Since vocalization disappeared after both 5,6--DHT and PCPA injections and was not recovered after intraventricular 5-hydroxytryptophan administration, Beleslin and Samardžić concluded that the decrease of vocal response could not be consequent only upon 5-HT neurons damage, the more so that similar effects were obtained after intraventricular 6-hydroxydopamine administration (7). On this basis, the authors suggest that the 5-HT system facilitates the expression of only one component of the emotional-defensive behavior, i.e. vocalization. This thesis seems hardly acceptable. It should rather be considered that their results are a consequence of damage which was not very specific owing to the use of very high doses of 5,6-DHT (125 μg) which causes damages of various neuronal elements in the neurotoxin diffusion area (8, 31), as well as extensive damages of paraventricular brain regions, including the periventricular midbrain area which is the vocalization "center" (24, 25).

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