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ADRENERGIC MODULATION OF THE HYPOTHALAMIC CHOLINERGIC MECHANISM IN THE CONTROL OF EMOTIONAL-DEFENSIVE BEHAVIOR IN THE CAT

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Abstract. Effects of drugs influencing the activity of the hypothalamic noradrenergic system on the carbachol-induced emotional-defensive response were investigated. Intrahypothalamic injections of noradrenalin, amphetamine and reserpine did not produce any changes in cats' behavior. Injections of carbachol into the same hypothalamic loci, following the injections of noradrenalin, amphetamine or reserpine evoked all the characteristic symptoms of emotional-defensive behavior. However, a strong decrease in the number of growls and the duration of growling was observed when reserpine injections preceded the injections of carbachol into the same hypothalamic areas. Adrenergic α and β agonists (methoxamine and isoprenaline) as well as antagonists (phentolamine and oxprenolol) when injected alone had no influence on the cats' behavior. Their effect on vocal responses evoked by subsequent injections of carbachol was not statistically significant. Results show that emotional-defensive behavior cannot be triggered by an activation of the hypothalamic noradrenergic system. However, emotional-defensive behavior induced by cholinergic stimulation of the hypothalamus may be modified by changes in the activity of the hypothalamic noradrenergic system.

INTRODUCTION

In physiological and pharmacological literature the opinion prevails that the central regulation of emotional-defensive behavior is mediated mainly through the adrenergic system. This viewpoint is based on the fact that the emotional behavior is usually accompanied by numerous symptoms reflecting an activation of the sympathetic system (pupil

dilatation, piloerection, increase in blood pressure, acceleration of heart and respiratory rates). Some recent neurochemical investigations however, question the validity of this opinion.

The hypothalamus is one of the key links in the emotional system of the brain. It consists of a highly differentiated neurochemical mosaic composed of a set of neural systems containing different neurotransmitters. Adrenalin (Ad), noradrenalin (NA), dopamine (DA), acetylocholine (Ach) and serotonin (5-HT) are the main ones. In studies on the distribution of NA and DA in the brain, Versteeg et al. (54) have found comparatively large quantities of these amines in hypothalamic nuclei. A significant amount of catecholamines has been found in the hypothalamus of the rat (22), cat (13), and monkey (20, 21). Numerous studies performed with the aid of the histochemical fluorescence method have revealed an abundance of axon terminals in the hypothalamus containing NA and DA (10, 14, 36, 51) as well as 5-HT (14, 29, 37, 51). A high Ad content has been reported by Van der Gugten et al. (52). Indirect evidence suggesting the presence of NA and DA in the rat hypothalamus has also been obtained after intraventricular injections of ^{3}H-6-hydroxydopamine (47). It was observed in these experiments that among other brain areas the hypothalamic region was the most heavily labelled.

Brownstein et al. (8) have found a significant decrease in NA, DA and 5-HT contents in the hypothalamus after a surgical isolation of this area from the rest of the brain. It might suggest that the bodies of neurons synthesizing these neurotransmitters are located outside the hypothalamus. On the other hand, they have observed that the choline acetylase content decreases only in some hypothalamic areas after such an operation, thus allowing one to suppose that at least a considerable portion of Ach is synthesized within the hypothalamus itself.

The above data concerning the distribution of different neurotransmitter systems in the brain are the basis for the studies on the participation of these systems in the central regulation of emotional-defensive behavior. Investigations carried out in many laboratories on different animal species and with the use of different experimental models have shown that well integrated emotional-defensive behavior, usually of an aggressive character, develops in response to cholinergic stimulation of different brain areas, mainly the hypothalamus and the midbrain (1, 3, 5–7, 9, 15, 17, 42, 43, 45). Thus, the participation of the cholinergic system acting as a triggering mechanism in the control of emotional-defensive behavior, seems to be unquestionable. The participation of other systems in this process has not been sufficiently documented and the proposed hypotheses need to be verified experimentally.

The participation of the adrenergic system in the control of emotional-defensive behavior has been investigated intensely. The obtained results, however, do not account for the role of this system in the regulation of emotional behavior. It is well known that intracranial injections of adrenergic substances into the same places from which emotional-defensive reactions may be evoked by cholinergic stimulation, produce a decreased locomotion, subsidence, placidity, and sometimes, somnolence or cataleptic states (2, 3, 7, 16, 17, 26, 35, 41, 44). To the contrary, Eichelman et al. (19) have found increased aggression in rats after intraventricular injections of 6-hydroxydopamine (6-OHDA), disrupting the adrenergic system. There are also some data showing that quiet and placid animals became aroused and aggressive and reacted vigorously to tactile stimuli after intracranial injections of adrenergic substances (4, 27, 40). Reis (40) maintains that aggressive behavior depends on an activation of the adrenergic system. He has presented some data showing a decrease in the NA content in the brain after a long-lasting aggression (3 h) produced by stimulation of the hypothalamus or amygdalar nuclei. This result suggests that NA is utilized during such a stimulation and that the resynthesis of this neurotransmitter can not balance its expenditure. The DA and 5-HT contents did not change during this experiment. Opposite results have been obtained in experiments where the influence of a pharmacological blockade of different adrenergic receptors on emotional-defensive behavior was studied. Allikmets (3) has found that the administration of α-adrenergic blocking drugs inhibits the aggressive behavior evoked by intrahypothalamic injections of Ach, whereas the administration of β-adrenergic blockers has no effects. To the contrary, Johansson et al. (30) have found that the blockade of α-adrenergic receptors causes an increased aggressiveness and the blockade of β-adrenergic receptors does not change animals' behavior. The data obtained, however, are not unequivocal and are frequently contradictory. Therefore, further experimental verifications are needed.

In this paper we shall present the results concerning the influence of some drugs which are known to affect the activity of the adrenergic system, and the influence of some antagonists and agonists of adrenergic receptors on the carbachol-induced emotional-defensive behavior in cats.

METHODS

The experimental procedure has been reported previously (45), therefore, only the necessary details are given.

The experiments were performed on 16 cats of both sexes, of 3.0

to 3.5 kg body weight. Stainless steel chronic cannulas were implanted bilaterally into the anterio-medial hypothalamic area in all cats according to the following coordinates of Snider and Niemer's stereotaxic atlas (50): A = 13.0, L = 2.0, H = —2.0.

All the substances used were dissolved in 0.9% NaCl with the addition of NaH_2PO_4 - Na_2HPO_4 buffer to maintain the pH = 7.0 to 7.3. The drugs were injected bilaterally in volume of 1.0±0.1 µl into each hemisphere. The following substances were used: carbachol (carbamylcholine chloride, Koch-Light) in a 2×5.0 µg dose, levarterenol bitatrate (l-noradrenaline, Fluka-Buchs) in a 2×5.0 µg dose, d,l-amphetamine (psychedrinum, Polfa) in a 2×15.0 µg dose, reserpine (serpasil, Ciba-Geigy) in a 2×2.5 µg dose, methoxamine hydrochloride (vasoxine, Burroughs) in a 2×7.5 µg dose, isoprenaline hydrochloride (Ciech-Polfa) in a 2×6.0 µg dose, oxprenolol hydrochloride (trasicor, Ciba-Geigy) in a 2×7.5 µg dose and phentolamine hydrochloride (regitine, Ciba-Geigy) in a 2×10.0 µg dose.

The animals were divided into two groups: Group I ($n = 10$) in which the influence of drugs changing the activity of noradrenergic system on the carbachol-induced emotional-defensive response was studied, and Group II ($n = 6$) — which served for studying the influence of the noradrenergic agonists and antagonists on the carbachol-induced emotional response.

All substances were injected into the same hypothalamic loci at 7 to 14 days intervals according to the following experimental schedule:

Group I. 1. injection of noradrenalin (NA) followed 15 min later by an injection of carbachol (C); 2. injection of amphetamine (A) followed 15 min later by an injection of C; 3. injection of A followed 90 min later by an injection of C; 4. injection of A followed 120 min later by an injection of C; 5. injection of reserpine (R) followed 90 min later by an injection of C.

Group II. 1. injection of methoxamine (M) followed 15 min later by an injection of C; 2. injection of isoprenaline (I) followed 15 min later by an injection of C; 3. injection of phentolamine (P) followed 15 min later by an injection of C; 4. injection of exprenolol (O) followed 15 min later by an injection of C.

Each experiment with the double injection was preceded by a control injection of carbachol alone.

Upon completion of the experiments the animals were killed with an overdose of hexobarbital. Their brains were removed and fixed in 4% formaline and embedded in paraffin. Coronal, 20 µm thick sections

were cut and stained with cresyl violet. Then, the sections were analyzed in order to verify the cannula placements within the brain.

An analysis of variances (Lindquist ABS design, 32) and Duncan test (18) were applied for statistical evaluation of the data obtained.

RESULTS

Histology. The cannula placements were within 11.0 to 13.5 frontal planes in the hypothalamic area. Typical example of the cannula placements is presented in Fig. 1.

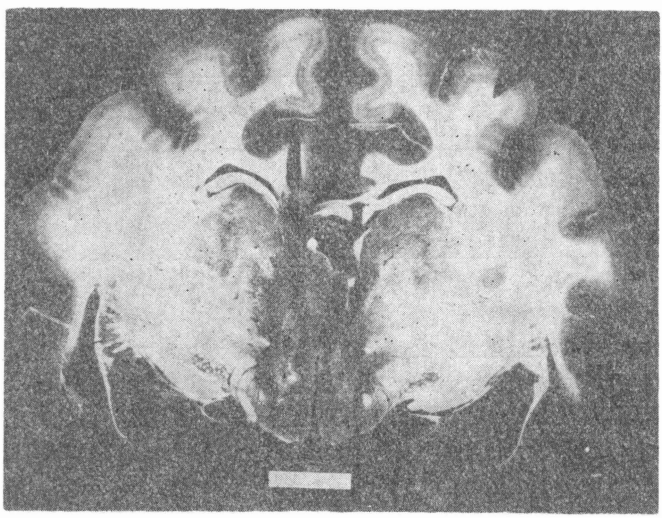

Fig. 1. Representative photomicrograph of the frontal section of the cats' brain showing the cannula tract endings from which the carbachol-induced response was obtained. The white strip located on the bottom of photograph is a scale 5 mm in length.

Effects of drugs influencing the activity of the noradrenergic system on the carbachol-induced emotional-defensive behavior. The intensity of the emotional-defensive behavior induced by intrahypothalamic injections of carbachol was estimated by recording the number and total duration of growls. In all cats ($n = 10$) injections of noradrenalin, amphetamine or reserpine alone did not evoke any changes in behavior. The following injections of carbachol produced a characteristic set of symptoms, typical for the emotional-defensive behavior. This set of symptoms has been described in detail previously (9, 42, 45). Measure-

TABLE I

Mean number of growls evoked by intrahypothalamic injection of carbachol alone (control level) and by carbachol acting on the background of drugs influencing the activity of the noradrenergic system, injected into the same hypothalamic loci. (Counting time = 30 min, starting immediately from the injection of carbachol)

Sequence of drugs	Type of carbachol treatments	
	Carbachol alone (control level)	Drug + carbachol
1. C, NA + C (15 min)	240.3	200.4
2. C, A + C (15 min)	202.5	122.3
3. C, A + C (90 min)	138.5	193.5
4. C, A + C (120 min)	214.7	188.0
5. C, R + C (90 min)	213.3	64.0
Source of variation	***df***	**Values of *F* statistics**
A, sequence of drugs	4, 36	1.83
B, type of carbachol treatment	1, 9	18.04*
AB, interaction	4, 32	4.08*

* $P < 0.01$

ment of the number and the duration of growling has shown that noradrenalin caused a decrease in the intensity of this vocal response though the difference was not statistically significant. Injections of amphetamine performed 120, 90 or 15 min before the injections of carbachol also did not evoke significant changes in the carbachol-induced behavior. Injections of reserpine to the same hypothalamic areas did not cause any qualitative changes in the carbachol-induced response. They did cause, however, a significant decrease ($P < 0.01$) in the number of growls and their duration when injection of carbachol were performed 90 min after reserpine injection. As shown in Table I, the analysis of variance concerning the number of growls revealed that the effect of sequence of drugs (factor A) was not significant. The effect of type of carbachol treatments (factor B) was statistically significant, and the AB interaction was also statistically significant. Further a Duncan test showed that only the difference between the control response and that evoked on the background of reserpine was statistically significant ($P < 0.01$). The analysis of variance concerning the duration of growling (Table II) revealed a significant effect of the sequence of drugs a significant effect of the drug used and a significant AB interaction. Further a Duncan test showed the existence of statistically significant

TABLE II

Mean duration of growling evoked by intrahypothalamic injection of carbachol alone (control level) and by carbachol acting on the background of drugs influencing the activity of the noradrenergic system, injected into the same hypothalamic loci. (Counting time = 30 min, starting immediately from the injection of carbachol)

Sequence of drugs	Type of carbachol treatments	
	Carbachol alone (control level)	Drug + carbachol
1. C, NA + C (15 min)	457.8	382.7
2. C, A + C (15 min)	211.5	242.9
3. C, A + C (90 min)	321.7	428.4
4. C, A + C (120 min)	384.9	378.9
5. C, R + C (90 min)	439.7	128.6
Source of variation	***df***	**Values of *F* statistics**
A, sequence of drugs	4, 36	3.29*
B, type of carbachol treatment	1, 9	34.93***
AB, interaction	4, 32	4.59**

* $P < 0.025$; ** $P < 0.01$; *** $P < 0.001$

differences only between the control response and the response evoked on the background of the action of reserpine ($P < 0.01$).

Thus, the direct as well as indirect activation of the hypothalamic noradrenergic system by noradrenalin or amphetamine does not produce any signs of emotional-defensive behavior. It may cause however, some changes in the carbachol-induced emotional-defensive behavior. A decrease in the NA, DA and 5-HT levels by injections of reserpine causes a statistically significant attenuation in the carbachol-induced response.

Effects of the noradrenergic agonists and antagonists on the carbachol-induced emotional-defensive behavior. The hypothalamic α and β adrenergic receptors were stimulated. Intrahypothalamic injections of methoxamine and isoprenaline were given 15 min before the injections of carbachol into the same loci. The microinjections of these noradrenergic agonists did not influence behavior in all six cats subjected to this treatment. Injections of carbachol, given 15 min later, evoked the typical emotional-defensive behavior. In the further part of the experiment the α and β adrenergic receptors were blocked with the use of intrahypothalamic injections of phentolamine and oxprenolol. The injections of these antagonists alone also had no effect. When 15 min later carbachol was injected into the same loci it produced a well expressed

TABLE III

Mean number of growls evoked by intrahypothalamic injection of carbachol alone (control level) and by carbachol acting on the background of noradrenergic agonists and antagonists injected into the same hypothalamic loci. (Counting time = 30 min, starting immediately from the injection of carbachol)

Sequence of drugs	Type of carbachol treatments	
	Carbachol alone (control level)	Drug + carbachol
1. C, M + C (15 min)	197.2	243.2
2. C,I + C (15 min)	132.0	183.8
3. C, P + C (15 min)	223.2	197.8
4. C, O + C (15 min)	210.3	238.5
Source of variation	*df*	Values of *F* statistics
A, sequence of drugs	3, 15	1.97
B, type of carbachol treatment	1, 5	0.85
AB, interaction	3, 15	0.62

emotional-defensive behavior. As shown in Table III and in Table IV, the analysis of variance revealed neither statistically significant effects of the sequence of drugs and type of carbachol treatments nor significant interaction of these two factors. Thus, there are no statistically significant effects of a stimulation or blocking of α and β adrenergic

TABLE IV

Mean duration of growling evoked by intrahypothalamic injection of carbachol alone (control level) and by carbachol acting on the background of noradrenergic agonists and antagonists injected into the same hypothalamic loci. (Counting time = 30 min, starting immediately from the injection of carbachol)

Sequence of drugs	Type of carbachol treatments	
	Carbachol alone (control level)	Drug + carbachol
1. C, M + C (15 min)	449.2	468.2
2. C, I + C (15 min)	282.3	401.5
3. C, P + C (15 min)	508.8	440.5
4. C, O + C (15 min)	474.0	478.5
Source of variation	*df*	Values of *F* statistics
A, sequence of drugs	3, 15	1.61
B, type of carbachol treatment	1, 5	0.84
AB, interaction	3, 15	1.08

receptors on the number of growls and their duration induced by carbachol injected into the same hypothalamic areas.

DISCUSSION

The results have shown that intrahypothalamic injections of substances which activate directly the noradrenergic system (noradrenalin, methoxamine and isoprenaline) produce no symptoms typical of emotional-defensive behavior. Instead, all these chemicals may cause a well-marked (though not statistically significant) decrease in the number and the duration of growls, if they are injected 15 min before the injection of carbachol. Thus, Reis' hypothesis (40) suggesting that aggressive behavior depends on the activation of the noradrenergic system has not been confirmed. Numerous data obtained by other authors on different species and on different experimental models (2, 3, 7, 16, 17, 35, 44) also failed to support this hypothesis. A secondary role of the noradrenergic system in the control of emotional-defensive behavior is also suggested by the data obtained with the use of α and β adrenergic blocking substances. Intrahypothalamic injections of phentolamine as well as oxprenolol, given 15 min before the carbachol injections, caused an increase, although not statistically significant, in the intensity of the carbachol-induced vocal response. Nevertheless, the fact that there was no inhibition or even a slight decrease in the carbachol-induced changes in behavior, seems to be very important. It shows distinctly that, as Allikmets suggested (1, 3) the mechanism triggering the emotional-defensive behavior is a cholinergic and not an adrenergic one.

The data with the use of drugs having a multiple way of action on the activity of the noradrenergic system — amphetamine and reserpine — require a more detailed analysis. Amphetamine affects mainly the noradrenergic system showing no influence on the DA (23) and 5-HT (33, 39) levels in the brain. It may raise the NA level through: (i) facilitation of the outflow of this neurotransmitter from presynaptic endings, (ii) inhibition of reuptake and (iii) inhibition of the monoamine-oxidase activity (11, 24, 25). Moreover, it is very likely that amphetamine can exert a direct stimulatory action on noradrenergic receptors (49, 53). It should also be emphasized that amphetamine has a biphasic action on the NA level in the brain. In the first phase, immediately following the injection, a rapid increase in the NA level occurs due to the facilitated NA outflow from presynaptic endings. It is followed by the second phase characterized by a decreased NA content resulting from an exhaustion of this neurotransmitter (25, 34).

Our results showed that if injections of carbachol were preceded

15, 90 or 120 min by injections of amphetamine the characteristic vocalization showed only slight and statistically insignificant changes. It suggests that the activation of the noradrenergic system had no influence on the emotional-defensive behavior evoked by cholinergic stimulation of the hypothalamus. The changes evoked by amphetamine, although they did not attain the level of statistical significance, had a well marked bidirectional character which seemed to be dependent on the amount of time elapsing between the amphetamine and the carbachol injections. At the short interval (15 min) the carbachol-induced response seemed to be diminished. A slight increase in this response was observed when long (90 and 120 min) intervals were used. The biphasic action of amphetamine mentioned above suggests that 15 min after intrahypothalamic injection of this drug the NA level was raised, whereas 90 or 120 min after the injection it was lowered. It is likely that the increased activity of the noradrenergic system counteracts the activity of the cholinergic one. But if the noradrenergic activity is lowered, the processes dependent on the cholinergic activity prevail. This supposition is supported by an identical character of changes (though in this case they did not attain statistical significance either) observed after the administration of α and β adrenergic agonists and antagonists. It might appear that the highly significant decrease in the carbachol-induced vocal response which was found 90 min after the administration of reserpine contradicted this line of reasoning. According to the above suppositions an increase in the carbachol-induced emotional-defensive behavior should have been expected. It is known, however, that apart from lowering the NA level (12) reserpine may cause a decrease in the DA and 5-HT levels (12, 38, 46, 48). Levitt and Krikstone (31) maintain that reserpine produces a kind of chemical lesion through the reduction of the catecholamines and indole amine levels leading in this way to a general decrease in the central nervous system activity. Thus, the dramatic decrease in the carbachol-induced emotional-defensive response cannot be considered exclusively as a result of the decreased noradrenergic activity and depends probably, on the decrease in other neurotransmitter levels. It shows at the same time that, although the initiating mechanism seem to be cholinergic, the cooperation of other neurotransmitter systems is necessary for a normal course of the emotional-defensive behavior. Our results suggest that changes in the noradrenergic activity may modulate the emotional-defensive behavior evoked by stimulation of the hypothalamic cholinergic system.

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