CHANGES IN THE NORADRENALIN CONTENT AND NUCLEAR RNA SYNTHESIS IN THE RAT BRAIN DURING DISTURBANCE OF EMOTIONAL AND CONDITIONED-DEFENSIVE BEHAVIOR

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Exhaustion of the noradrenalin (NA) reserves in the rat brain caused by administration of reserpine or dopamine-β-oxidase blockers (disulfiram, diethyldithiocarbamate) is accompanied by a decrease in nuclear RNA synthesis and disturbances of emotional and conditioned-defensive behavior. During the accumulation of cerebral NA (following injection of iproniazid or imipramine) the rate of synthesis of nuclear RNA rises. Prevention of the exhausting effect of reserpine by preliminary injection of iproniazid also prevents the disturbance of nuclear RNA synthesis.

KEY WORDS: noradrenalin; nuclear RNA synthesis; rat brain; mechanisms of memory; emotional and conditioned-defensive behavior.

During an intensive study of the problem of the neurochemical mechanisms of specific brain functions, the role of catecholamines (CA) in the formation of emotional responses [5, 18] and the role of nucleic acids in processes of learning and memory [6, 12, 14] have been actively studied and discussed. There is no doubt that the multicomponent neurophysiological structure of complex forms of behavior corresponds to a relatively complex neurochemical organization, including mechanisms of relations between different brain systems. It was shown previously that pharmacologically induced changes in CA metabolism affect not only emotional but also conditioned-defensive behavior and the processes of formation and recall of memory traces [2, 15-17].

The object of this investigation was to study the possible biochemical mechanisms of these effects, taking into account the data on connections between nucleic acids and CA that have accumulated in the literature [4, 19].

EXPERIMENTAL METHOD

Experiments were carried out on 172 male Wistar rats. Most of the animals were aged 3-4 months and one group consisted of rats aged 12-18 months. As pharmacological agents influencing different aspects of CA metabolism, reserpine (0.5 mg/kg) and iproniazid (100 mg/kg) were injected subcutaneously and disulfiram (100 mg/kg), sodium diethyldithiocarbamate (200 mg/kg), and imipramine (12.5 mg/kg) were injected intraperitoneally. The brain CA concentration was determined by a trihydroxyindole method [1, 10] and the rate of RNA synthesis from the incorporation of P^{32} (orthophosphate), with isolation of cytoplasmic (ribosomal, transfer) RNAs and nuclear RNA (n-RNA) [3]. Conditioned-defensive behavior was investigated in a two-compartment cage as described previously [2]. The formation of a conditioned-defensive avoidance reflex (CDAR) and the reproduction of a previously well-consolidated reflex were studied, using as the quantitative criterion an avoidance index (AI), namely the number of times the animal ran away as a percentage of the total number of presentations of the conditioned stimulus; changes in emotional behavior, especially the onset of experimental depression, were judged by means of the generally accepted indices (spontaneous and evoked motor activity, the animal's posture, the presence of ptosis, diarrhea, etc.).

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EXPERIMENTAL RESULTS AND DISCUSSION

As Table 1 shows, 18 h after the injection of reserpine, which exhausts the cerebral reserves of noradrenalin (NA), a marked decrease in the incorporation of P^{32} into brain n-RNA was observed, in the absence of any significant changes in the cytoplasmic RNAs. The animals' behavior was characterized by the development of a typical picture of "reserpine depression" and a sharp decrease in CDAR performance, which reached a maximum after 18-24 h. After administration of disulfiram and diethyldithiocarbamate, inhibitors of dopamine-β-oxidase, changes in behavior developed earlier than after administration of reserpine: the maximal inhibition of CDAR (AI = 20%) was observed as early as 2 h after injection of the inhibitors. In this same period a decrease in the NA concentration in the brain was observed, accompanied by a decrease in the rate of RNA synthesis; as in the experiments with reserpine, this was most marked for the brain n-RNA.

The disturbances of emotional and conditioned-defensive behavior caused by the blocking of NA storage and synthesis were effectively prevented by preliminary administration of the monoamine oxidase (MAO) inhibitor iproniazid which, as the writers showed previously [2], also stimulates the formation of CDAR in animals with spontaneous or induced "inability" to learn. At the height of the inhibitory action of iproniazid – 18 h after injection – the accumulation of cerebral NA was accompanied by an increase in P^{32} incorporation into brain n-RNA in the absence of any changes in the cytoplasmic RNAs. This coordination of changes in the NA content and synthesis of brain n-RNA was not found in animals of "presenile" age (12-18 months), in which, despite a marked increase in the brain NA concentration, the rate of n-RNA synthesis, like that of cytoplasmic RNA synthesis, remained unchanged. A considerable increase in n-RNA synthesis (by 30%; $P < 0.01$) was found when the reverse process of neuronal NA uptake was blocked (90 min after injection of imipramine), i.e., in the presence of a selective increase in the synaptic functionally active form of the mediator.

These investigations thus revealed a similarity in the direction of changes in the NA concentration and the rate of n-RNA synthesis in the brain. The character of the pharmacological procedures used, being aimed at processes of CA metabolism, suggests that changes in the NA concentration are the factor that determines the relationship thus established. Since the concentration not only of NA, but also of dopamine and serotonin, is modified by reserpine and MAO inhibitors, the results of investigations in which a decrease in n-RNA synthesis was found after administration of dopamine-β-oxidase inhibitors, i.e., in the presence of a disturbance of NA synthesis against the background of dopamine accumulation and in the absence of any appreciable changes in the serotonin concentration, are evidently essentially important. The dependence of the changes in n-RNA synthesis on the level of noradrenergic but not of dopaminergic activity also is stressed by the results of experiments in which an increase in n-RNA synthesis was observed following administration of imipramine, which blocks the reassimilation of synaptic NA, but not after administration of dopamine. These results assume particular significance in connection with the theory of the synaptic action of neurotropic substances [8], and they point to a possible mediator regulation of the genetic apparatus of the cell and to a role of NA-RNA relationships in the mechanisms of adrenergic reception.

A communication according to which DNA, when previously treated with NA, activates RNA-polymerase [19] is of particular interest when compared with the results of the present experiments showing an increase in n-RNA synthesis during the accumulation of NA in the brain. The functional role of this link between changes in the NA concentration and n-RNA synthesis in the brain can be examined to begin with from the standpoint of neurochemical mechanisms of learning and memory processes, considering that in the first hypotheses associating biochemical aspects of memory with the function of the brain nucleic acids [13, 14] and in subsequent conceptual schemes of the neurochemical mechanism of mnemic functions [9, 12] a definite role was ascribed to NA. The parallel between the character of the changes in CA metabolism and the processes of formation and recall of memory traces has been emphasized on several occasions [2, 15-17]. The relationship discovered in the present experiments between NA metabolism and n-RNA synthesis in the brain is in agreement with the postulated role of an emotional component in the mechanisms of memory and the supposed functional organization of "emotional memory" [6]. Intensive liberation of NA taking place at a time of emotional stress is evidently a factor that determines the high velocity of the processes of consolidation and recall of information – a characteristic feature of "emotional memory." The connection between NA metabolism and n-RNA synthesis in the brain can also be looked at in the light of the information theory of emotions [11]. If the mechanism of information recall incorporates an increase in central noradrenergic activity, should information be deficient an intesnive liberation of NA could take place, and this in turn could change the state of the mechanisms controlling emotional behavior.

TABLE 1. Effect of Reserpine and Inhibitors of Dopamine-β-oxidase and Monoamine Oxidase on Noradrenalin Concentration and Rate of RNA Synthesis in Rat Brain (M ± m)

Series No.	Conditions	Noradrenalin (μg/g)				RNA (counts/min/mg P_i)				Emotional behavior	Conditioned-defensive avoidance reflex
		number of animals	hypothalamus	brain stem	hemispheres	number of animals	nuclear	transfer	ribosomal		
I	Intact	12	1,32±0,11	0,50±0,05	0,32±0,03	27 (control to series II and V)	39,6±1,4	7,5±0,5	4,4±0,9		
						12 (control to series III and IV)	40,0±1,7	4,9±0,8	2,9±0,3		
II	Reserpine 0,5 mg/kg after 18 h	10	0,26±0,03*	0,18±0,04*	0,14±0,03*	8	28,4±2,3*	5,6±0,9	4,9±0,6	Depression	Inhibition of reproduction
III	Disulfiram 200 mg/kg after 2 h	6	0,63±0,09*	0,30±0,04‡	0,22±0,03†	12	29,7±0,9*	5,3±0,4	2,5±0,3	Depression	Inhibition of reproduction, inhibition of formation
IV	Diethyldithiocarbamate 100 mg/kg after 2 h	10	0,67±0,10*	0,24±0,03*	0,17±0,02*	21	30,5±1,2*	4,7±0,4	3,2±0,2	Depression	Inhibition of reproduction
							51,6±3,7‡	5,9±0,6	4,0±0,3	Prevention of depression, agressiveness	Stimulation of formation but resistance to learning
V	Iproniazid 100 mg/kg after 18 h	8	1,72±0,10†	0,63±0,04	0,60±0,04*	12					

* $P < 0.001$.
† $P < 0.05$.
‡ $P < 0.01$.

The link between changes in the NA concentration and n-RNA synthesis in the brain may thus be an essential factor in the neurochemical organization of complex forms of behavior, emotions, and memory, especially as a link between these higher functions of central nervous mechanisms.

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