# VARIATIONS IN THE ACTION OF ADRENALIN ON THE CORTICAL EEG OF DOGS WITH AGE

(UDC 612.825.014.423.4.014.46 : 615.361.452 : 612.66-019)

V. D. Rozanova

Laboratory of Age Physiology and Pathology (Head, Professor A. I. Arshavskii),
Institute of Normal Pathological Physiology (Director, Professor V. V. Parin,
Academy of Medical Sciences of the USSR), Moscow
(Presented by Active Member of the Academy of Medical Sciences of the USSR, V. V. Parin)
Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 61, No. 5,
pp. 11-15, May, 1966
Original article submitted August 31, 1964

A series of investigations in the author's laboratory [2-7, 14, 15] has shown that in puppies aged from 1 to 18-20 days an activation reaction may be absent from the cortical EEG in response to the action of acoustic, tactile, and nonciceptive stimuli, and desynchronization may not be found in the encéphale isolé preparation. Animals of this age do not show the periodic change of rhythm on the EEG when sleep changes to waking and vice versa. In both states activity of low amplitude and frequency is found. In inhibition associated with sleep and narcosis, and also during the action of chlorpromazine and in the encéphale isolé preparation, the slow high-amplitude activity typical of adult dogs does not develop in the cortical EEG.

The intravenous injection of adrenalin into adult animals produces transient desynchronization of the bioelectrical activity, followed by a long phase characterized by the appearance of slow high-amplitude activity in the cerebral cortex [18, 19, 21-23, 25, 26]. Because the mechanism of action of adrenalin has not been fully explained [11], the investigation of its action on young animals is interesting in connection with reports of the discovery of a high content of catecholamines in the brain stem [13], the incomplete development of the blood-brain barrier [19], and also the distinctive pattern of the reactions of the pressure receptors of the carotid sinus [1, 20] at this age. The above-mentioned factors are known to be of essential importance to the understanding of the mechanism of the action of adrenalin on the cerebral cortex as revealed by the EEG.

Because of these findings, it appeared interesting to investigate the variations of the cortical EEG of dogs with age in association with the action of adrenalin.

## EXPERIMENTAL METHOD

The EEG of the sensory, parietal, and occipital cortex was recorded on a four-channel VNIOMIO oscillography by means of bipolar needle electrodes implanted into the cranial bones. The ECG in lead II and, in some experiments, the respiration also were recorded. The experiments were conducted without anesthesia and fixation. Adrenalin was injected intravenously in doses of between 10 and 800 μg/kg body weight. The period of observation varied from a few hours to 1 day after injection of the drug.

Experiments were carried out on 22 dogs of three age groups: group 1) puppies aged from 5 to 13 days; 2) puppies aged from 20 days to 2 months; and 3) adult dogs and puppies over 2.5-3 months old.

## RESULTS

The experiments on the adult dogs mainly confirmed the data described in the literature. The activation reaction on the cortical EEG and restlessness of the animals developed after injection of adrenalin, not only in small doses (10-25 μg/kg), but also moderate and large doses (75-800 μg/kg). The period of desynchronization length-

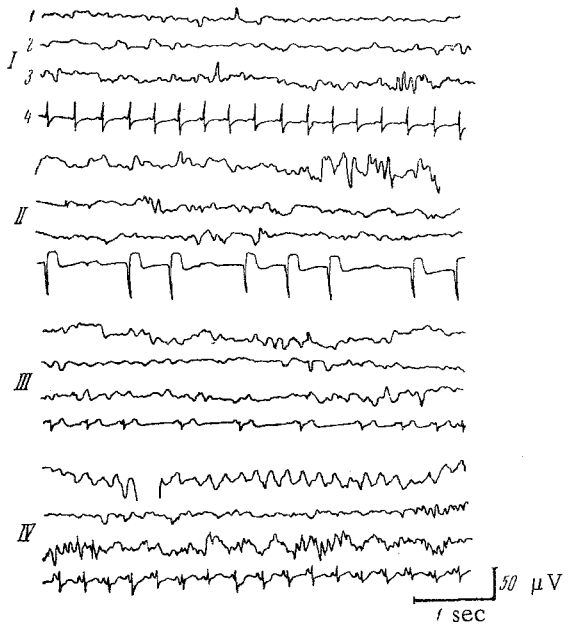


Fig. 1. Cortical EEG of a 6-day old puppy in frontal (1), parietal (2), and occipital (3) leads and ECG in lead II (4). I) Initial EEG and ECG; II) 1 min after intravenous injection of adrenalin in a dose of 25 μg/kg body weight; III) 5 min after; IV) 10 min after injection.

ened from 3-5 to 30 min when the dose was increased from 10 to 75 μg/kg, and with a further increase in the dose it shortened to 10-5 min. Later, slow high-amplitude potentials appeared on the EEG, the dog became quiet, it lay on its side and went to sleep. To judge by the animal's behavior and the indices of the EEG, the state of sleep lasted several hours.

In the young puppies (aged from 5 to 13 days) adrenalin in doses of between 10 and 200 μg/kg did not produce the biphasic reaction typical of adult dogs. Both desynchronization and the subsequent synchronization of the electrical activity of the cortex were absent. The basic electrical activity characteristic of the animals of this age was essentially unchanged, whereas the effect of adrenalin on the heart was present (Figs. 1 and 2). A marked bradycardia was present, as observed earlier by S. I. Enikeeva [8] in her experiments. An increase in the dose to 400 μg/kg and above likewise did not produce desynchronization on the EEG but, on the other hand, it led to a distinctive and reversible depression of the electrical activity, expressed as a decrease in the amplitude of the potentials without any appreciable change in their frequency (Fig. 2, III). The puppy's behavior changed and its movement and cry ceased. The initial EEG and motor activity were restored after 10-15 min. With an increase in the doses of adrenalin to 800 μg/kg (see Fig. 2, IV) the electrical activity almost completely disappeared. During the period of recovery of the EEG the amplitude of the cortical potentials increased and their frequency also rose slightly (Fig. 2, V).

In the puppies of the second group (aged from 20 days to 2 months) the reaction to the injection of adrenalin was similar to the reaction of adult dogs. Initially a transient desynchronization appeared, and the respiration and heart rates rose. This reaction was replaced by slow, high-amplitude potentials on the EEG and a slowing of the respiration and heart rates (Fig. 3). The puppy fell asleep. Initial desynchronization during the action of adrenalin appeared in the puppies at an age when an activation reaction during sensory and nociceptive stimulation appeared in intact animals, and also in the experiments on the encéphale isolé preparation. At the age of 18-20 days the puppies were able to assume a standing posture and several exteroceptors began to function. The activating function of the ascending system of the reticular formation of the brain stem appeared for the first time, as also did signs of its blocking during sleep and narcotic inhibition and also in response to the action of chlorpromazine [2-7, 14, 15].

The results obtained, showing absence of desynchronization in the first phase of the action of adrenalin in the young puppies (under 18 days old), confirm the conclusion drawn from earlier investigations in the author's laboratory that their ascending reticular system is immature.

After the investigations of Bonvallet, Dell, and co-workers [21-25], and of Rothballer [27] and others, the mechanism of the activation reactions has been associated with the adrenergic substratum of the reticular formation of the brain stem.

The facts presented in this paper, demonstrating the absence of the activation reaction in the cortical EEG during the action of adrenalin on young puppies despite the high content of catecholamines in their brain stem and the high permeability of their blood-brain barrier, are evidence that the presence of an adrenergic substratum in the reticular formation alone is inadequate to bring about the activation reaction.

The data indicating the importance of the rostral portion of the brain stem in the mechanism of the activation reaction, especially during the action of sympatheticomimetic drugs, and concerning the blocking of this reaction by muscarine-like cholinolytics [9, 10, 12, 26] demonstrate that the cholinergic neurons of the rostral portion of the reticular formation of the brain stem must participate in the mechanism of this reaction.

In a previous investigation [16, 17] the author showed that the activity of the true cholinesterase of the rostral portion of the reticular formation of the mesencephalon, corresponding to the level of the anterior colliculi in adult

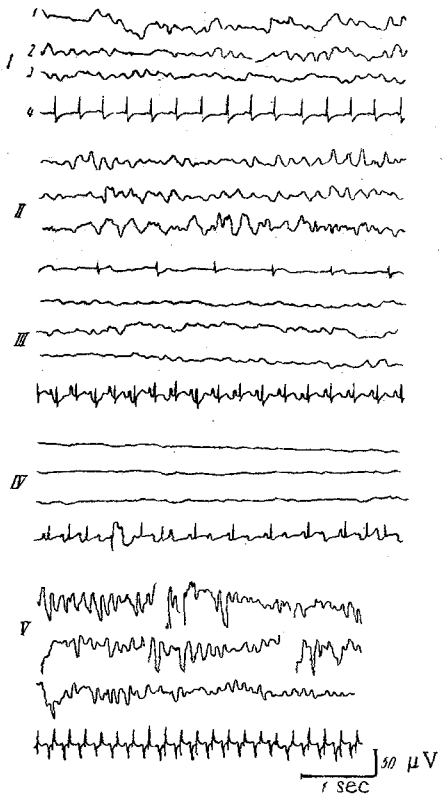


Fig. 2. Cortical EEG and ECG of an 8-day old puppy. I) Initial EEG and ECG; II) 5 min after intravenous injection of adrenalin in a dose of 75 μg/kg; III) 3 min after injection of adrenalin in a dose of 400 μg/kg; IV) 1 min after; V) 18-20 h after injection of adrenalin in a dose 800 μg/kg body weight.

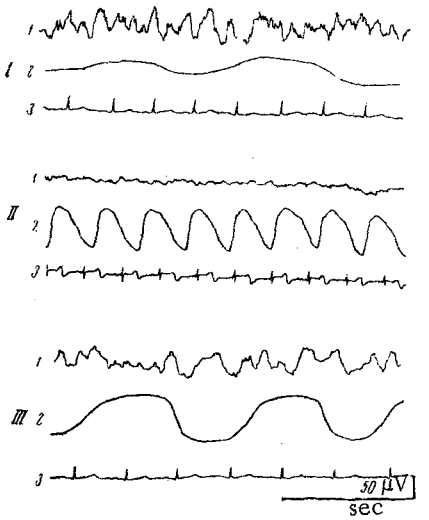


Fig. 3. Cortical EEG (1), respiration (2), and ECG (3) of a 25-day old puppy. I) Before injection II) 10 min after; III) 30 min after injection of adrenalin in a dose of 200 μg/kg.

dogs, is much higher than in the medial thalamus and in the reticular formation of the mesencephalon corresponding to the level of the posterior colliculi. Data indicating the heterogeneity of the biochemical characteristics of these portions of the brain have confirmed the suggestion [2, 3] that the rostral portion of the reticular formation of the brain stem is a distinctive and complex intermediate link in relation to the thalamocortical system, of great importance in the mechanism both of the phase activation reactions and of the reactions of inhibition.

In young puppies (under 18-20 days old) there is no difference between the cholinesterase activity of the rostral portion of the mesencephalon, the medial thalamus, and the more caudal portion of the reticular formation.

The immaturity of the cholinergic neurons in this portion, confirmed in experiments with acetylcholine and atropine, explains the absence of the activation reaction during the action of adrenalin at an early age.

The absence of synchronization in the cortical EEG of young puppies in the second phase of the action of adrenalin may be explained by the immaturity of the functions of the pressure receptors of the carotid sinus [1, 20].

In puppies at the age of 18-20 days there is a sharp increase in the cholinesterase activity of the rostral portion of the reticular formation of the brain stem. A difference appears between the characteristics of this division, and those of the medial thalamus and the more caudal portion of the mesencephalon. It may be considered that the sharp increase in cholinesterase activity is a condition necessary for the realization of the mediator function of acetylcholine in the cholinergic neurons of the rostral portion of the brain stem in bringing about the phased excitation in the period of the arousal reaction appearing for the first time at this age.

## SUMMARY

Data obtained on the absence of the adrenalin effect in puppies of a young age (up to 18 days) confirm the conclusions of the immaturity of their ascending activating system drawn at our laboratory earlier from the results of several studies. Nonrepresentation of desynchronization in the first phase of adrenalin action at an early age is accounted for by the functional immaturity of the intermediate cholinergic link in the rostral part of the reticular formation of the brain stem. The absence of synchronization of the EEG in the second phase of the adrenalin action is associated with the immaturity of the function of the sinocarotid zone baroreceptors.

At the age of 18-20 days puppies develop a typical adult two-phase reaction under the action of adrenalin in connection with maturation of the functions of the ascending activating system, in particular, the intermediate cholinergic link in its rostral part. At the same age, the function of the baroreceptors of the sinocarotid zone appears.

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