CORTICAL COORDINATION IN DOGS WITH EXPERIMENTAL ATHEROSCLEROSIS

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The object of the present research was to investigate the cortical activity in dogs with experimental atherosclerosis, the plan being to study the influence of the defensive reaction [2, 3, 4, 7, 8, 16, 17 and others], developing in the course of artherosclerosis, on other reactions with a different biological significance.

METHOD

Chronic experiments were performed on five dogs. Atherosclerosis was produced in three of these animals by feeding with cholesterol and methyl thiouracil [15]. The remaining dogs acted as controls, and received methyl thiouracil alone in the same dose as the first animals (1.5g). In some dogs a conditioned postural reaction was first developed, permitting recordings to be made of the ballistocardiogram and other hemodynamic indices in the course of a chronic experiment, both in normal conditions and during the development of atherosclerosis [19]. After its consolidation, this postural reaction was also used for recording [4] the electroencephalogram (EEG). The conditioned postural reaction obeys the general laws of cortical activity [10, 11, 12]. We therefore took it into account when analyzing the influence of atherosclerosis on conditioned reflex activity. In other dogs, conditioned defensive reflexes, produced by the Staritsin-Petropavlovskii technique, were preliminarily reinforced. Control investigations on intact dogs gave rise to an EEG of identical character, in spite of intervals of many days in the experiments in which it was recorded. This can be explained by the fact that, during these intervals, the conditioned postural reaction common to all the experiments was systematically reproduced in other experiments to study the hemodynamics [20]. The same thing was also observed in other dogs which, during the interval in the recording of the EEG, were trained in the technique of the conditioned defensive reflexes.

RESULTS

The conditioned defensive reactions in intact dogs are shown in Figs. 1a and 1b. In the first second of ringing the bell, the dog raised its paw and held it in a state of continuous contraction during the whole time of action of the conditioned stimulus. The respiration showed absence of deep inspirations and expirations, and also of dyspnea. The EEG before administration of cholesterol and methyl thiouracil is shown in Figs. 2a and b. Relatively frequent oscillations of considerable amplitude arose in all leads of the EEG, i.e., the phenomenon of synchronization of the rapid waves was observed. During the application of the signal and the development of the conditioned defensive reaction, synchronization of the rapid waves was also observed in the EEG.

Feeding the dogs with 6-methyl thiouracil and cholesterol was then begun, and continued for $4\frac{1}{2}$ months. The development of atherosclerosis of increasing severity in the dogs was shown by biochemical and morphological investigations and also by hemodynamic changes. No similar changes were found in control dogs which received 6-methyl thiouracil alone. The developing artherosclerosis caused persistent changes in the EEG after $2\text{-}2\frac{1}{2}$ months (Fig. 2b, c, d). The onset of atherosclerosis led to a fall in the voltage of the EEG waves in the experiments on all the dogs (Fig. 2b). In this period of the experiments, the EEG in the premotor and sensomotor area of one hemisphere was appreciably different from that from other areas of the brain. For instance, waves appeared in the premotor area with a frequency of 30-40 cps and a positive phase, with a relatively higher amplitude than the waves in the other leads (Fig. 2c). The waves in the sensomotor area were less frequent and of high amplitude (Fig. 2d). In all the control dogs a fall in the voltage of the EEG appeared on the 11th-13th day of feeding with methyl thiouracil, but on the 16th-17th day this disappeared altogether, and the EEG was not only restored to normal, but even showed an increase in the degree of synchronization (Fig. 2f, g).

The fall in the voltage of the EEG waves reached its maximum degree five months after the beginning of feeding with the atherosclerosis-producing substances. For instance, 28 days after the end of feeding with these substances, when the blood cholesterol concentration was on

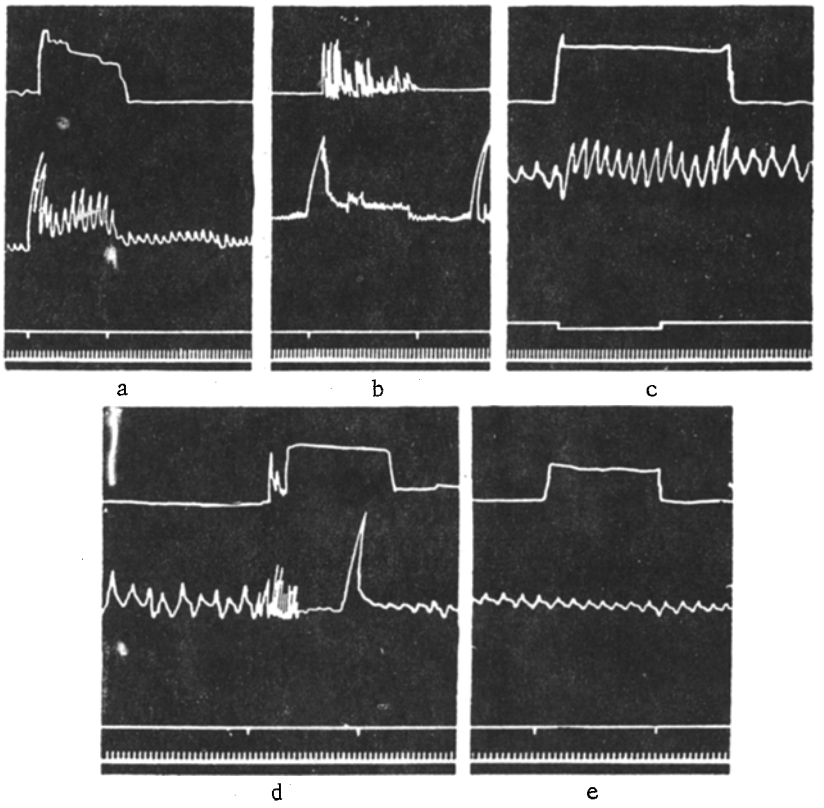

Fig. 1. The effect of methyl thiouracil and cholesterol on the conditioned defensive reflex. a) conditioned defense reflex before feeding with methyl thiouracil and cholesterol; b) disturbance of the conditioned defensive reflex due to feeding on methyl thiouracil and cholesterol (sixth month after production of experimental atherosclerosis); c) conditioned defensive reflex before feeding with methyl thiouracil alone; d) disturbance of the conditioned defensive reflex on the 11th-13th day of feeding with methyl thiouracil; e) recovery of the conditioned defense reflex in spite of feeding with methyl thiouracil (30th day of feeding with methyl thiouracil). Significance of the curves (from above down): contraction of the muscles of the dog's left hind limb; respiration; marker of the conditioned stimulus; time marker (1 second).

the average 2.5 times higher than its initial level, waves of very low amplitude were observed in the EEG (Fig. 3a). It might be thought that the absence of high-amplitude waves was due to the diminished activity of the cortical cells. In order to elucidate the physiological mechanism of the persistent fall in the voltage of the EEG waves, we gave chlorpromazine. This drug is known to block the tonic influence of the reticular system on the cortical cells [1, 23]. If the fall in voltage was due to a diminution in the activity of the cortical cells, then after the administration of chlorpromazine, the voltage of the EEG waves would either remain unchanged or would fall still further. The opposite changes were found, however, and the results were the same in all the experimental dogs. Administration of chlorpromazine (2.5 mg/kg) led to an increase in the voltage and to the restoration of synchronization in the EEG in all leads (Fig. 3b). In contrast to the original EEG, however, the waves observed were slower and of a relatively high amplitude.

After the administration of chlorpromazine, the dogs lay in another position with considerable relaxation of their skeletal musculature. The experimenter's call, i.e., the signal for adoption of the previous postural reaction as was usual during the experiment, again caused a fall in the voltage of the EEG waves (Fig. 3c). In other words, during excitation, which was the cause of the new pose adopted by the dog after the administration of chlorpromazine, with a corresponding unconditioned stimulus, another stimulus was applied which was of special significance for the animal. The latter stimulus evoked excitation, but in another reflex arc, corresponding to the specially developed postural reaction.

The suggestion that 6-methyl thiouracil, by blocking the activity of the thyroid gland, depresses the activating

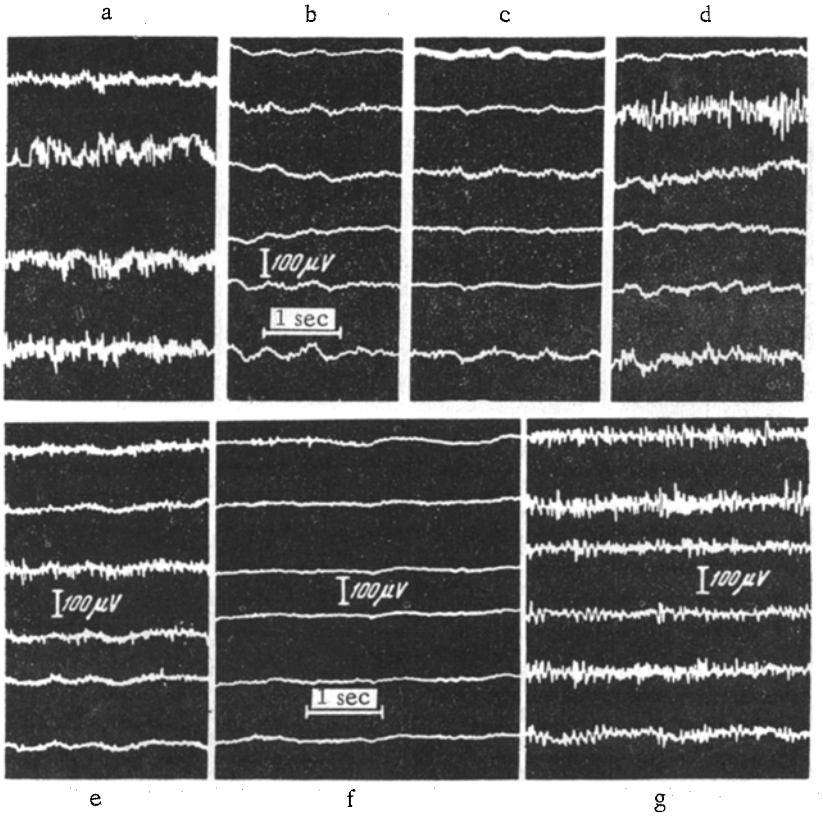

Fig. 2. Changes in the EEG in dogs after feeding with methyl thiouracil and cholesterol. a) before feeding with methyl thiouracil and cholesterol; b, c, d) fall in the EEG voltage after feeding with methyl thiouracil and cholesterol (2-2½ months from the beginning of production of experimental atherosclerosis); e) before feeding with methyl thiouracil; f) fall in the EEG voltage on the 11th-13th day of feeding with methyl thiouracil alone; g) recovery and increase in the EEG voltage in spite of continuing feeding with methyl thiouracil (30th day of feeding with methyl thiouracil). Significance of the curves (from above down): EEG from the premotor, sensomotor, parietal and occipital areas of the right cerebral hemisphere (Fig. 2a); EEG from the premotor, sensomotor, parietal and occipital areas of the right hemisphere; EEG from the premotor and sensomotor areas of the left hemisphere (Fig. 2b, c, d, e, f, g).

influence of the reticular system and thereby brings about a fall in the voltage of the EEG, was also wide of the mark. Evidence against it was provided by the results of the administration of 6-methyl thiouracil alone to control dogs and of the experiment in which chlorpromazine was given to dogs with experimental atherosclerosis.

The facts described thus show that the fall in the voltage of the EEG in atherosclerosis was not due to a diminution of the activity of the cortical cells. On the contrary, the fall in the voltage of the EEG waves was caused by their desynchronization, reflecting the presence in the cerebral cortex of foci of excitation, evidently differing in their rhythm and stimulating reactions of differing significance to the animal.

At that period of the experiments when persistent desynchronization was seen in the EEG, the reactions to stimulation of different biological significance (food stimuli, showing a dog of the opposite sex, or a cat) showed predominance of a general state of inhibition. During the experiment to record the EEG the dogs tried to replace the postural reaction that had been developed with a pose involving less strain on the somatic musculature. The conditioned defensive reactions were also considerably modified. It is clear from Fig. 1b that, at the signal, the dog had lost its ability to produce a tonic form of contraction of the limb. Throughout the whole time of action of the conditioned stimulus, the motor reaction bore the character of a rhythmic withdrawal of the paw. When the paw was raised, the dog did not lower it, although the signal continued to act. In dogs receiving 6-methyl thiouracil, the disturbances were ill-defined and brief in duration. They were observed for 3-5 days (on the 11th-13th days of feeding with 6-methyl thiouracil), and did not subsequently arise (Fig. 1d and e).

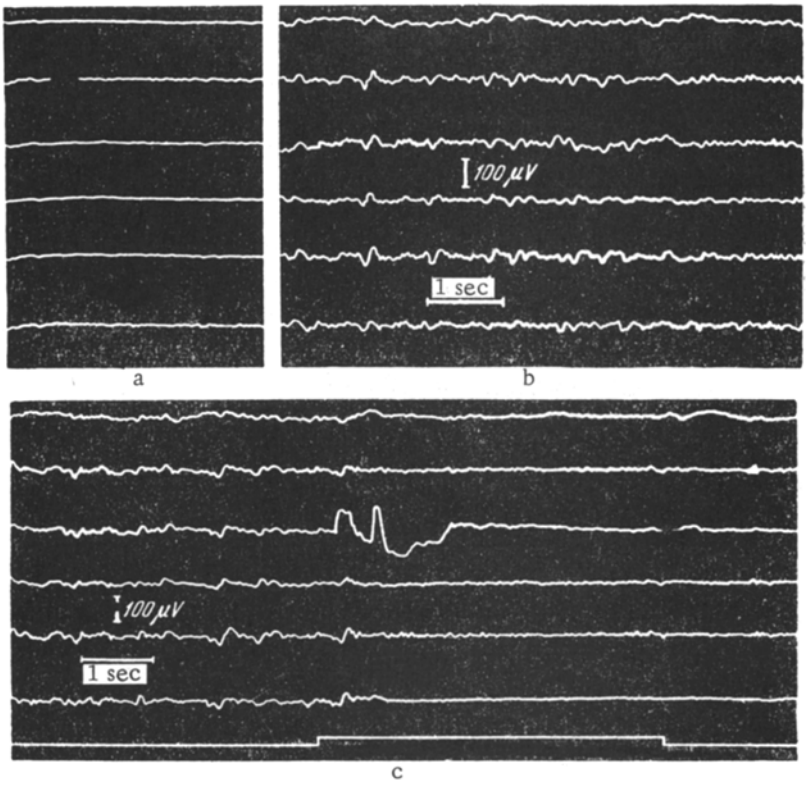

Fig. 3. The EEG in a dog with atherosclerosis after administration of chlorpromazine. a) EEG before administration of chlorpromazine; b) EEG after administration of chlorpromazine; c) EEG during the action of the sound stimulus in association with chlorpromazine. Legend as in Fig. 2. Last line at the bottom of Fig. 3) stimulus marker.

In these experiments the character of the respiratory component began to change: the respiration was superficial, dyspnea developed and isolated deep inspirations and expirations were frequently observed.

After necropsy, performed six months after the beginning of feeding with 6-methyl thiouracil and cholesterol, atheromatous lesions of the vessels, especially the vessels of the base of the brain and of the heart, were found in all the dogs. No signs of atherosclerosis were found in the dogs receiving 6-methyl thiouracil alone.

The concrete analysis of the effect of experimental atherosclerosis on the cortical activity requires a basic assumption in respect of the general nature of the pathology of the animal as a whole. We have in mind the physiological nature of protective inhibition as a defensive reaction of the body.

Since the work of I. P. Pavlov [8] on this problem, many new findings have accumulated. It has been shown, for instance, that in extraordinary situations, the hypothalamus and vegetative nervous system take part in the response reaction of the animal. The participation of these divisions of the nervous system in the reaction of the animal to excessively strong stimuli, which has been detected qualitatively, has been called "Reilly's stimulation reflex" [22, 24, 26, 28, 29]. Moreover, the hypophysis and adrenal glands are also involved in this reaction [27]. It may be postulated from these facts that protective inhibition, as a defensive reaction arising in response to a stimulus causing disturbance or pathological change in the animal body, is a special unconditioned reflex, i.e. this is a reaction based on the process of excitation. It may be thought that the defensive reflex bears special relationships toward its stimuli, the central organization and the effector component. Pavlov [8] mentioned the possibility of such a reflex in 1909, calling it the "self-righting reflex."*

The interconnections between the cerebral cortex and the hypothalamus, and also data on the conditioned reflex reproduction of the defensive reflex [5, 6, 7, 8, 9] testify to the participation of the cortical level and to the possibility of the formation of this reflex as a signal reaction. Like other unconditioned reactions, however, the defensive reflex has it cortical representation, with the participation of which the cerebral cortex forms the outward behavior in accordance with its biological significance.

* Pavlov considered that the phenomena of protective inhibition and the phenomena of recovery were interconnected but not identical. He declared, for instance: "We have said that they are somehow connected, that inhibition is caused by disturbance, but we have never said that inhibition and recovery are identical". ["Pavlov's Wednesday", Izd. AN SSSR 3, 311 (1949).]

We thus hold the view that when the defensive reflex is dominant, the animal's outward behavior is concerned with an active reaction. The latter usually takes the form of that postural reaction in which the minimum number of muscle components is implicated in an active state. When the defensive reflex, like any other reflex, becomes dominant [18], of necessity it is accompanied by the coordinated inhibition of other reactions, for example those based on alimentary and sexual excitation, so that the vegetative control of all the formations associated with somatic activity is reduced to the minimum. This leads, from our point of view, to a state of "general inhibition" of the animal, which is especially pronounced in the period of maximum intensity of the pathological process and of mobilization of the defensive reflex. This state is not the result of inhibition of the entire cerebral cortex, but is the external expression of the presence of a dominant excitation, associated with the defensive reaction, and of an associated inhibition of all other reactions functionally incompatible with the first.

In our experiments the development of atherosclerosis was accompanied by the appearance of desynchronization in the EEG. Other authors, engaged on the study of this disease, have also noted a fall in the voltage of the EEG [13, 21]. It must be emphasized that the phenomenon of desynchronization arises in nonspecific form in various species and in different pathological conditions, and also during conditioned reflex activity in the healthy animal. We consider that the views regarding the phenomenon of protective inhibition that were expressed above enable the general electroencephalographic phenomena (desynchronization and synchronization) to be related to the pattern of formation of cortical coordination, and help to elucidate the nature of the disturbance of this coordination during the development of a pathological process.

Investigations of different cases of cortical activity of the healthy animal have shown that the formation of cortical coordination passes through two stages—a stage of conflict and a stage of increasingly complex coordination [10, 12]. Signs of the stage of conflict are ambiguity in behavior, desynchronization in the EEG and the tense character of the vegetative components, and signs of the stage of increasingly complex coordination are a uniform pattern of behavior, synchronization in the EEG and normalization of the vegetative components [12].

From our point of view, the attempt to extend coordination patterns studied in the healthy animal to the cortical activity in atherosclerosis is perfectly justified. In fact, when the sick dog is placed on the apparatus, antagonistic interaction must inevitably arise in the animal between qualitatively incompatible reactions, based on different forms of unconditioned excitation. On the one hand, excitation associated with the dominant defensive reaction is responsible for the outward behavior of the animal in accordance with the demands of this reaction,— the dog actively attempts to adopt a pose with the minimum number and effort of the muscular components, during which the vegetative control of the somatic activity is considerably diminished, and is mobilized mainly for the needs of the defensive reaction. On the other hand, however, a qualitatively different form of excitation arises in response to the environmental stimulus or the defensive signal. As a result of the previous training, the environmental stimuli stimulate the postural reaction which was developed before the onset of the pathological process, quite different in the composition and intensity of its muscular components. The same thing takes place also during the action of the conditioned stimulus causing the reaction of withdrawing the limb.

As a result of the simultaneous action of stimuli associated with qualitatively different reactions, an antagonistic interrelationship develops between the latter, i.e. conditions are created for the formation of cortical coordination. The unstable character of the hitherto stable conditioned reaction, the desychronization in the EEG and the tense character of the vegetative components, as in the healthy animal, are the expressions of the stage of conflict in coordination, i.e. of the super-threshold excitation of the dominant reaction and of the high level of super-threshold excitation of the competing potential reaction. In the formation of external behavior during atherosclerosis, the defensive reaction may occupy the role of either a dominant or a competing potential reaction with a high level of super-threshold excitation. In both cases, however, the immediate mechanism of coordination is the same.

The distinguishing feature of the cortical coordination in atherosclerosis, by comparison with that in the healthy animal, is the drawn-out character of the stage of conflict.

Our experiments show that dogs with atherosclerosis lose the ability to maintain a high level of excitation throughout the whole time of action of a conditioned stimulus. Coordination is formed as a result of mobilization of the excitation in the reflex arc of the dominant reflex [18]. It may therefore be considered that in the case of atherosclerosis the cause of the drawn-out character of the stage of conflict is a disturbance of brain-stem mechanism [25] ensuring optimal tone of the central excitation necessary for normal coordination. This is possible, for in atherosclerosis, especially in the cerebral form, which is well marked in dogs, the blood supply of the brain is disturbed.

SUMMARY

The phenomenon of the EEG voltage is caused not by the reduced activity of the cortical cells, but by the presence of excitations which are uniform in rhythm, as well as of stimulating reactions possessing different significance for the animal. One of these excitations is connected with the protective reaction arising from atherosclerosis, while another is associated with the reaction mobilizing the organism in another direction, which does not conform to the requirements of the protective reaction. The formation of cortical coordination takes place during the simultaneous action of the stimuli provoking both of these reactions. In

these conditions of desynchronization, the EEG components reflect the conflict stage in the formation of cortical coordination. The effect of experimental atherosclerosis on the cortical activity includes reduction of the cortical excitation as a result of which the conflict stage becomes protracted and is not transformed into the final stage—that of formed coordination—for a long period of time.

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†See C.B. translation.