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NEUROHUMORAL FACTORS CONTROLLING THE BEHAVIOR OF ANIMALS

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- USSR -

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NEUROHUMORAL FACTORS CONTROLLING THE BEHAVIOR OF ANIMALS

/Following is the translation of an article by K. Lissak and E. Endroczi entitled "Neyro-Gumoral'nyye Faktory Kontroliruyushchiye Povedeniye Zhivotnykh" (English version above) in Zhurnal Vysshey Nervnoy Deyatel'nosti (Journal of Higher Nervous Activity), Vol. 10, No. 3, Moscow, 1960, pages 330-336./

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Hemaostasis of the organism is controlled by a mechanism which includes two factors; neural and endocrine, which in their interaction during the process of evolution constantly complicate one another.

Without minimizing the role of neurocortical structures in the development of processes of higher nervous activity, we consider it necessary to analyze the role of subcortical systems and emotional reactions of the organism in the formation of temporary associations.

Since the discovery of the role of the diffuse activating system in maintaining the working state of the cerebral cortex, there have appeared in recent years many reports on this problem. They state that the neural network described 60 years ago in Kakhal's works and now called the reticular formation is subject not only to neutral action but to humoral action as well. Therefore, in analyzing the activity of brain it is necessary to consider the neural organization of the mesencephalon and diencephalon as an integrating system on a complex neurohumoral level.

During the past decade our Institute has been occupied with the study of interrelations between the complex neuroendocrine processes and the behavior of the organism. The problem of neuroendocrine control of conditioned reflexes and the emotional behavior of higher animals is complicated by the fact that, parallel with the intervention of neurostructures, there also takes place endocrine regulation, the changes in which influence the nervous system and animal behavior.

In our earlier studies (Endroczi, Lissak, Telegdy /2/) we demonstrated that a domestic female rat during lactation attacked and killed a frog placed in its cell. Administration of estrone for several days (300 to 400 U per 100 gm weight) completely eliminated this aggressive attitude, though the mother rat continued to worry about its offspring. Hydrocortisone was more effective than progesterone in preventing this follicular action. At the same time it was observed that hydrocortisone not only removes the inhibiting effect of estrone, but it also produces aggressive tendencies in animals that have not exhibited such tendencies previously. This phenomenon is based on the effect of the antagonistic action of two endocrine factors on the central nervous system. The point of application of these hormones has not been cleared up as yet, though we succeeded in obtaining certain data which indicate that some subcortical systems play an important part in this mechanism. For instance, electrolytic injuries to the amigdole Uarea pyriformis and destruction of the septal area also eliminated maternal aggressiveness in a lactating rat. Following the removal of the amigdole and Ammon horn, a cat would lose the reflex of catching mice for an extended period of time, though the animal ate well and its somato-motor activity proceeded satisfactorily (Endroczi, Martin).

These studies demonstrate that the archicortex structures not only play a part in emotional behavior, but are themselves subject to the influence of endocrine factors.

It is commonly known that the hypophysical-adreno-cortical system plays an important role in maintaining the endocrine system in a state of equilibrium; when the latter is disturbed (as shown in previous studies), the suprarenal cortex produces a specific reaction in the form of a change in secretion. The variations in the composition of the secretion of the suprarenal cortex are taken into account by only a few researchers. Nevertheless, according to our data, these variations are important in the regulation of the complex vegetative and metabolic processes as well as in the regulation of complex behavior processes. Analysis of the adrenocortical function is complicated by the fact that there are considerable individual variations of a qualitative and quantitative character not only between various species, but also between various individuals within the same species. How wide the differences are within one species can be demonstrated in the case of variations of the cortical hormone content in the suprarenal

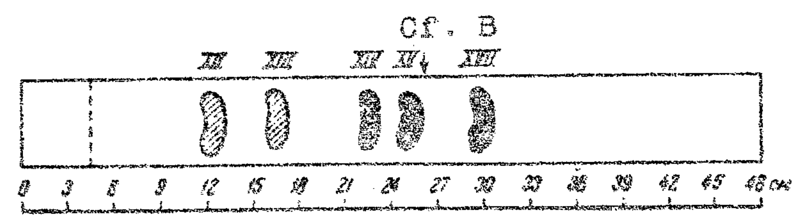

Fig. 1. Chromatogram showing the difference in the corticoid content in the suprarenal venous blood in wild and domestic rats. XII -- Reichstein, C -- basic components in a wild rat, XIII, XIV -- trace components in wild and domestic rats. Cp (corticosterone); XVII -- basic components in domestic rats.

venous blood in domestic and wild rats.

The spectrum of hormones in the suprarenal venous blood is of interest not only from the quantitative point of view, but also because under certain conditions a synthesis of such components may exert a stimulating effect on the central nervous system. Taking all this into consideration, we should like to cite certain data relating to temporary associations of endocrine origin, or neuroses induced by the impairment of these associations.

An alimentary conditioned reflex was developed in a dog as follows: when a positive bell sounded, the dog pushed the door open in order to get food. Another bell served as a negative sound stimulus. After tests for 16 days, consisting of 300 combinations at three-minute intervals, a conditioned reflex was formed free of intersignal reactions. A neurosis was then produced by means of a simultaneous sound of a positive bell and a threefold application of a strong electric current to the posterior extremity of the animal, which caused a painful irritation. Observations were subsequently conducted in order to ascertain the time until complete restoration of the conditioned reflex. After the conditioned reflex had been fully restored, a study of the composition of cortical hormones in the suprarenal venous blood was made.

It is seen in Fig. 2 that despite the fact that all the disturbances of the conditioned reflexes had been carried out under identical conditions, nevertheless in various dogs the inhibition periods were of various lengths and the period was found to be closely related to the suprarenal secretion, or more exactly, to the hydrocortisone/corticosterone coefficient. In the case of a short period of inhibition, the coefficient was low; when the inhibition lasted longer, this coefficient was high.

The question of whether there is a direct connection between adrenocortical secretion and the length of the inhibition period was answered by the following experiment. In the animals who were given hydrocortisone for one week, prior to the impairment of temporary associations, the inhibition period was not only several times longer than in the same animals many months prior to the administration of cortisone, but it was also accompanied by fairly marked neurotic symptoms not observed in control animals. These experiments appear to indicate that the neurotic condition brought on by the impairment of the conditioned reflex was influenced by the interrelation of two basic components secreted by the suprarenal cortex, i.e., hydrocortisone and corticosterone.

The qualitative difference in the action of these

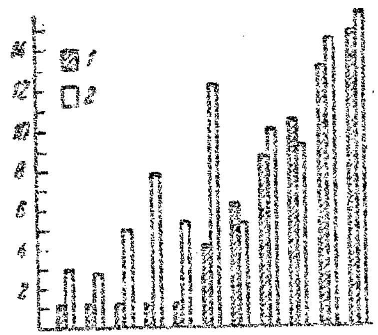

Fig. 2. Connection between the inhibition period of the alimentary conditioned reflex, induced by the irritation of the posterior extremity with the electric current, and the corticoid content in the suprarenal venous blood. 1 -- duration of inhibition period in days, 2 -- correlation between hydrocortisone and corticosterone.

two components on the central nervous system was demonstrated by Woodbury and his associates [6]. According to their observations, hydrocortisone reduces considerably the convulsion thresholds of the central nervous system, whereas corticosterone has no effect on it whatsoever; moreover, corticosterone counteracts the hydrocortisone effect in this respect. The correlation between the two components varies with different individuals -- a fact which is of considerable importance in the development of neurosis, according to some researchers. Our experiments on rats enable us to classify the rats in this respect in four groups with various periods of inhibition. In each group the adrenocortical activity was uniform and fully determined quantitatively (Endroczi, Lissak, Telegdy [1]).

It is our opinion, based on these experiments, that the action of adrenocortical hormones of high polarity leads to an intensification of inhibition processes. Mirsky, Miller and Murphy observed that, following the administration of ACTH (adrenocorticotropic hormone), the protective-defense conditioned reflex in animals is facilitated. On the basis of this one could assume that the hypophiseal-adrenocortical activity supports the neural adaptation of the protective mechanism; however, further experiments showed that ACTH and corticoids not only affect the extraceptive inhibition and neurosis, but also increase the inner inhibition when the positive signal is not reinforced. In these experiments the stable conditioned reflex was extinguished through daily nonreinforcement, until its complete disappearance. In the same animals the period of extinguishing was practically identical, which made it possible to induce changes in the period under the influence of adrenocortical hormones. Fig. 3 shows that in certain cases the ACTH administration considerably accelerated the development of damping (Lissak, Medgyesi, Tenyi, Zorenyi [5]).

A number of instances can be cited as proof that the conditioned-reflex method makes it possible to study the effect of humoral factors on the behavior of animal organisms under objective conditions. Of course, within the range of these limits one cannot directly analyze the immediate effect of endocrine factors on the central nervous system. In our experiments we worked on the assumption that the brain stem and subcortical mechanisms, which play the principal role in the formation of emotional behavior, are related to the integration of conditioned reflex associations as well as to the organization of endocrine mechanisms. Certain data show that humoral factors also exert their influence on these

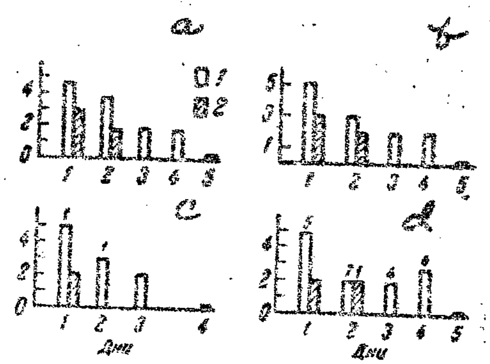

Fig. 3. Development of internal inhibition in dogs. 1 -- without administration of the adrenocortico-tropic hormone, 2 -- following the administration of the adrenocorticotropic hormone for a period of four days (2.0 Iu per kg weight of cincotrophin).

a -- Lady, b -- Hexy, c -- Tigris, d -- Rex structures. Experiments with planted electrodes and electrocoagulation, conducted by means of a stereotaxic device on dogs, cats, rabbits and rats, revealed a complex chain of nervous processes playing an importent part in the regulation of endocrine mechanisms.

Without going into the details of a large number of observations, we should like to dwell on the basic results. The activity of the hypophiseal-adrenocortical and gonad systems represents the function of the state of equilibrium between two complex controlling mechanisms. Only at the level of the central nervous system can we elicit the connection and division of these two controlling systems.

It was elicited in experiments with electrodes planted in the subcortical region that stimulation of the reticular formation of the papillary bodies and intralaminary thalamic nuclei activates the hypophyseal-adrenocortical system. This can be directly determined by the content of corticoids in the suprarenal venous blood by means of measuring the ascorbic acid level and the lymphopenic reaction. In addition to this transitory activating process, there exists a longer neural pathway which, judging by the effect obtained, exerts an inhibiting action.

On the basis of an experiment with the use of stimuli and electrocoagulation, we succeeded in eliciting the following relationship: pathways originating in the reticular formation and passing through the hypothalamus activate the archicortex, including the hippocampus, via septa. Pathways which originate in the hippocampus may inhibit the activation of the function of the hypophiseal-adrenocortical system by acting via the cerebral fornix on the papillary bodies and, partially, on the tegmentum.

Of course, the inhibiting and activating mechanisms are not yet fully understoood. A considerable degree of activation can be induced by stimulating the orbito-frontal area, or the amygdalum and area pyriformis. Of interest in this problem is the division of functions of control of the activity of the hypophiseal-adrenocortical and sexual systems which takes place on the archicortex level. Stimulation of the septum or archicortex, carried out at intervals of six to 10 minutes (90 hz, 0.5 to 2.0 volt, 7.0 m/sec at 0.15 mm bipolar silver electrides), invariably induced the sexual behavior of the animals originating as a trace effect. At the same time, the stimulation inhibited the activation of the hypophiseal-adrenocortical system not only in connection with neurotropic stimuli, but also with humoral factors. This fact explains why the suprarenal cortex reacts not at all or only weakly to the action of adrenalin, histamine, or formalin.

Specific changes in suprarenal cortex secretion are also elicited in an examination of the blood in the suprarenal vein of sexually stimulated animals, which is equivalent to the effect of folliculin on the organism -- i.e., the emergence of progesterone derivatives can be elicited. Thus, a state of prolonged stimulation of the archicortex, produced by repeated stimulations of the hippocampus, leads to the secretion of 17-hydroxyprogesterone (from five to six mg daily). At the same time, priapism and symptoms of copulative activity are observed in the dog (Endroczi, Lissak, etc., [3]).

The question may arise as to how these neuroendocrine controlling mechanisms are related to the behavior process and the development of higher nervous activity. At present there is no doubt that the structures analyzed above in connection with the neuroendocrine control also participate in the formation of a conditioned reflex. The effect of endocrine factors on the central nervous system cannot be regarded as the result of a change in the general metabolic processes of the neural tissue. For instance, according to our observations on dogs, within two to three minutes after an epileptic seizure induced by the irritation of the temporal lobe, the animal reacts normally to a conditioned alimentary stimulus, despite the fact that during the same time a large number of postconvulsion metabolic changes are still taking place in the organism.

On the basis of earlier experiments in which the development of a neurotic state was enhanced by means of adrenocortical hormones, it cannot be denied that the action of endocrine hormones is induced through the inhibition of a special temporary association separated from the entire system of temporary associations which determine the behavior of the animal. The same results can be observed in the action of sexual steroids, but on a different level.

We shall now discuss the problem of the effect of the environment on the development of conditioned reflex associations. During recent years we have been occupied with the study of results of stimulation of the tegment area of the reticular formation on a previously developed alimentary conditioned reflex, in norm and in neurosis. Experiments on dogs have demonstrated that stimulation of the reticular formation or, rather, of the grey matter around the Silvius aqueduct, leads to the formation of a conditioned reflex, even without the use of a positive stimulus. This reminds us of the data obtained by Grastyan et al. [4] from an experiment on cats subjected to stimulation of the diencephalon. It was interesting to follow

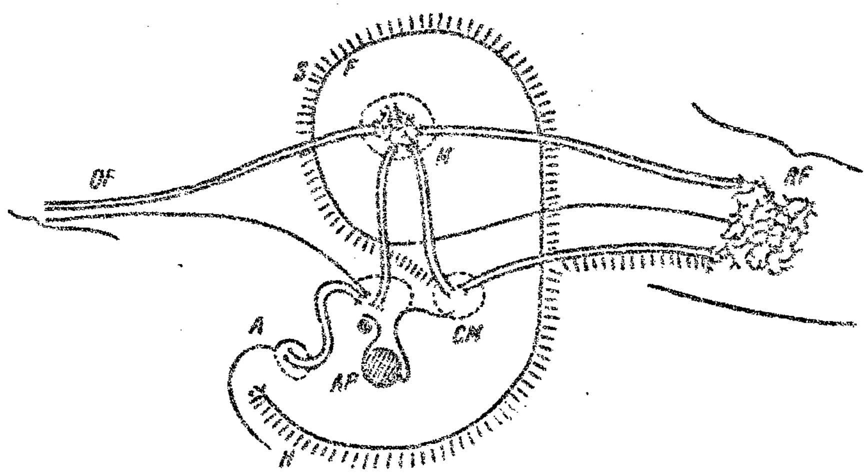

Fig. 4. Basic connections of activation and inhibition of the hypophiseal-adrenocortical system. A -- grey matter of the temporal lobe, AP -- anterior hypophiseal lobe, CM -- papillary bodies, H -- hippocampus, F -- arc, M -- thalamus, OF -- orbito-frontal area, RF -- reticular formation, S -- septum.

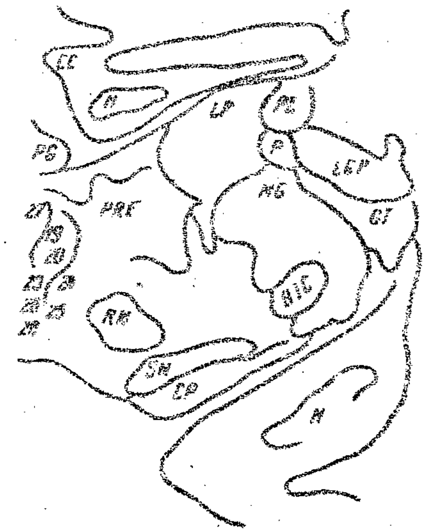

Fig. 5. Schematic drawing of the transverse section of a dog's brain on the mesencephalon level. The numbers indicate points of stimulation which induce a positive conditioned reflex; BIC -- pedicle of the lower corpus Bigeminums, CC -- corpus callosus, H -- hippocampus, LGP -- lateral geniculate body, MG -- median geniculate body, OT -- optical tract, P -- posterior nucleus of the tuber opticus, PG -- posterior commissure, PL -- Pulvinar, RN -- red nucleus, SN -- black substance, PRE -- Pretectum.

up the changes in the behavior of animals which took place during stimulation outside the conditioned-reflex chamber. These experiments brought remarkable results: under the new conditions there emerged either a simple orientation reflex or, more frequently, a conditioned reflex which corresponded to the new environmental medium. Thus, for example, the animal lay down, or sat up, or gave the paw to the researcher, according to the conditioned reflex which had been developed earlier.

Interesting results were obtained by Endroczi and associates (1958) when the stimulation was carried out during neurosis. In animals in whom stimulation of reticular formation induced a conditioned reflex, the state of neurosis was produced by means of a painful stimulation inflicted simultaneously with a positive sound signal. All symptoms of neurosis (barking, defecation, urination, reaction of escape and fear) were produced under these circumstances by the sound stimulus. When, under these circumstances, a stimulation of the reticular formation was started, the animal quieted down and the conditioned reaction appeared as the result of stimulation. However, a few minutes after the cessation of stimulation, the symptoms of neurosis again predominated.

It is necessary to point out that the conditioned reflex induced by the stimulation of the reticular formation appears only in those cases where the parameters of stimulation exceed a definite limit. Upon increase of the intensity of stimulation, there appeared, instead of an orientation or conditioned reflex, emotional reactions (fear, reaction of escape). We can arrive at the conclusion, based on the experiments described above, that a conditioned reflex caused by the stimulation of the diffuse activating system depends on the environment which influences the animal by means of a specific projection system. The state of neurosis is caused by the impairment of temporary conditioned associations between the specific and projection systems.

Consequently, even elementary manifestations of animal behavior are interrelated, with a whole series of neurohumoral processes. The present scientific data do not show precisely which neural structures participate in the changes of animal behavior induced by various endocrine factors. However, these data show that in the development of normal as well as neurotic states the humoral factors play an important role. In the future it will probably be possible to explain, on the basis of individual variations of the endocrine system, why the development of temporary associations and the course of neuroses vary to such an extent in different individuals despite the identical experimental conditions.

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