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PREFACE

Relevance. Hormonal effects on the brain mechanisms of behavior development are of particular interest due to their great importance in the adaptive reactions.

The aim of our studies is to reveal the influence of the pituitary-adrenal axis hormones and ACTH-derived peptides on integrative brain activity when behavior of various biological significance develops.

Material and methods. In numerous experiments on a large number of animals (cats, rats) hormone effects on defensive and alimentary conditioned reflexes, their extinction, on a behavior caused by an electrical stimulation of the brain in cats, and on an affective aggressiveness with unavoidable pain stimulation in rats were studied using the stereotaxic technique: electroencephalography, electromyography, electrocardiography, and neuropharmacological analysis before and after intraperitoneal or intracerebroventricular administration of ACTH, its oliglopeptides and corticosteroids. The peptides were synthesized at the Institute of Molecular Genetics of the Russian Academy of Sciences, the Cardiology Research Center, and also purchased from Serva.

Results. A concept was developed according to which the activation of "endocrinotropic" brain structures and the release of ACTH provoke a dual effect in a given situation: an extraadrenal on brain structures and steroidogenic on the adrenal glands. It was proved that ACTH promotes the choice and maintenance of a biologically adequate behavior due to a selective change in the reticular-hippocampal relations, the mesencephalic and thalamic non-specific influences reaching the neocortex as well as the overall level of activity. The modulatory action of ACTH on the excitation of the hypothalamic - amygdalar motivational complex leads to a change in a motivation level. Hydrocortisone significantly complements the corticotropin central effect: the peculiarity of its effects is the increase in the brain stem activating influences, as well as the excitation in the hypothalamic-amygdalar motivational complex. The neurophysiological basis of the predominant inhibitory effects of DOCA is a decrease in the excitability of nonspecific structures and in weakening the amygdala activating effects on the hypothalamic centers. In a certain way, the balanced hormonal effects modulate the implementation of behavior that is biologically appropriated in a given situation. An idea was formulated, according to which, the likely basis for the differentiated hormonal effects includes the specificity in their action on the brain neurotransmitter systems. The cellular and intercellular mechanisms of the ACTH oligopeptides effects were also revealed due to analyzing the structure-to-function relationships.

Conclusion. The mechanisms of the brain structures and hormones interactions in developing of adequate behavior were clarified. The obtained data provide understanding of the origin of neuropsychiatric disorders which accompany diseases of the hypothalamic-pituitary-adrenal system and others, as well as the adaptation diseases' pathogenesis and the complications of ACTH and corticosteroids therapy. The evidence of the direct neurotropic ACTH action serves as a base for the goal-directed synthesis of oligopeptides as new drugs.

Keywords: ACTH, corticosteroids, melanocortins, integrative brain activity, brain electric stimulation, conditioned reflex behavior, aggression, extinction.

The monograph is useful to physiologists, pathophysiologists, endocrinologists, neuropathologists, psychiatrists, doctors of various clinical specialties, university students, and doctors taking upgrading courses.

INTRODUCTION

Integration of the nervous and hormonal mechanisms of behavior development is one of the fundamental problems of modern physiology. The relevance of studying ACTH and corticosteroids' effects on higher brain functions is determined by the requirements of both theoretical and practical medicine. Research in this field is necessary to elucidate the pathogenesis of neuropsychiatric disorders accompanying diseases of the hypothalamic-pituitary-adrenal system, as well as those arising from the hormones administration for therapeutic purposes. To study the interaction between hormones and brain structures is also necessary to reveal the pathogenesis of adaptation diseases and to prevent them due to activated protection.

Modern scientific and technological progress imposes very stringent requirements on the ability of a human body to adapt: the development of new areas with severe (sometimes extreme) climatic conditions, work on complex technical installations, effects of noise, vibration, and conditions of physical and mental stress. The pituitary-adrenal system activation observed also expresses the state of emotional arousal in these cases. Long and severe emotional overloads can lead to overstrain and exceed the adaptive capabilities of a body. The solution to all these issues, so important for practical health care, is impossible without extensive basic research. Currently, there is significant experimental material indicating the effects of ACTH and corticosteroids on animal behavior, in particular on conditioned avoidance and nutritional reflexes, as well as on exploratory activity. The data obtained made it possible to formulate the main hypotheses explaining the behavioral effects of hormones, in particular, ACTH, their influence on the general level of activity, motivation and memory in animals, as well as in psychophysiological studies in humans. However, the neurophysiological mechanisms of these effects and their relations are still not clear. On the one hand, numerous studies have been performed in which the effect of ACTH and corticosteroids on the excitability of brain structures was shown using electrophysiological techniques. To clarify the points of hormones' effects in the order of feedback, these studies were characterised by using high (pharmacological) doses of hormones and were carried out, as a rule, in conditions of a "behavioral test."

Thus, the central nervous mechanisms that ensure the integration of neuroendocrine and behavioral processes remain not fully understood. Meanwhile, the interest in this problem has particularly increased in recent years after the discovery of neuropeptides, which began “a new endocrinology” (R. Guillemin, 1979). Based on radioimmunoassay and immunocytochemical analysis, it was established that ACTH is a neuropeptide and, together with beta-lipotropin, is formed from a common precursor, proopiomelanocortin (J. Roberts et al., 1977; R. Mains et.al., 1977; M. Hinman et al., 1980). Beta-lipotropin, in turn, produces the beta-melanocytostimulating hormone (β-MSH), endorphins, and ACTH - α-MSH. The existence of a peptidergic neuronal system with ACTH-like in the brain, as well as β-lipotropin and β-endorphin-like activity was found. The area of the highest concentration of immunoreactive ACTH was the mediobasal hypothalamus. Using antisera, the cell bodies and axon extensions were found scattered in the thalamus, amygdala, semicircular gray matter, pons and reticular formation (D. Krieger et al., 1977; S. Watson et al., 1978; K. Kitahama et al., 1984). However, the content of immunoreactive ACTH in the cell pericarion was established only in the arcuate nuclei and adjacent areas of the mediobasal hypothalamus. This fact, as well as the results of this region’s destruction made it possible to consider the arcuate nuclei as a main source of peptidergic axons innervating limbic structures and providing axonal transport of corticotropin (D. Krieger et al., 1979; M.J. Brownstein, 1980; A.S. Liotta et al., 1984). It was shown in experiments on rats with combined removal of the pituitary and adrenal glands, that the regulation of ACTH in the brain structures was carried out independently on the pituitary ACTH control (A. Dijk et al., 1981).

The biological significance of ACTH in the central nervous system was unknown. It is likely that the hormone functions as a neuroregulator, neurotransmitter, neuromodulator or neurohormone (S. Watson et al, 1978). An important basis for this hypothesis was the direct, extraadrenal effect of ACTH on the brain, confirmed in numerous studies (D. Wied, 1977). Structural analysis showed that, in accordance with the universal pattern established for peptide hormones, the ACTH molecule has an address part that includes an active center and a signal peptide. The active part of a hormone molecule, essential for the manifestation of its effects on behavior, is the N-terminal sequence of seven amino acid residues - $ACTH_{4-10}$. This fragment of the molecule is practically devoid of steroidogenic activity and is common for ACTH, α- and β-MSH, and β-lipotropin. The smallest–“key”–peptide that retains the ability to delay the extinction of the conditional avoidance reaction is considered to be $ACTH_{4-7}$.

A set of biologically active peptides formed by secretory cells (anterior and intermediate pituitary, peptidergic neurons) from a common precursor – proopiomelanocortin – depends on its enzymatic activity, which determines the features of post-translational processes. The discovery of the neurotropic fragments of corticotropin poses new questions about the relationship of hormones of the hypothalamic-pituitary-adrenal system with the development of integral, in particular, behavioral reactions of a body. Large experimental and clinical material accumulated to date requires analysis and generalization, without which it is impossible to create a unified theory that can explain various aspects of the hormone's effects on behavior and their mechanisms.

This monograph, in addition to analyzing the relevant literature data, contains materials from our own experimental studies in which the mechanisms of the ACTH and corticosteroids influence were investigated on the complex dynamics of intercentral interactions determining the occurrence and implementation of biologically different behavior. An applied systematic approach combined a behavior analysis with neurophysiological and neuropharmacological methods. A specific role of ACTH and corticosteroids has been established along with a dominant motivation and training in the selective mobilization of brain structures. The facts have been obtained that explained the behavioral, neurophysiological, and neuromodulatory mechanisms of ACTH action and allowed combining various aspects of the hormone effects on the higher brain functions.

Our study results allow us to explain the origin of the neuropsychiatric disorders accompanying diseases of the hypothalamic-pituitary-adrenal system and complicating administration of ACTH and corticosteroids for therapeutic purposes, as well to contribute to the disclosure of the pathogenesis of adaptation diseases.

The material used in the monograph was obtained by the authors through years of research carried out at the Department of Physiology and of Pathophysiology at the Kursk State Medical University. The authors consider the pleasant duty to express heartfelt gratitude to fellow workers for their continued help and assistance.

Regulations

The work with animals was performed in accordance with the Council Directive 2010/63EU of the European Parliament, the Council of 22 September 2010 on the protection of animals used for scientific purposes, World Medical Association (Declaration of Helsinki) (https://www.wma.net/what-we-do/medical-ethics/declaration-of-helsinki/) and the Local University Committee of the Kursk State Medical University (Russia). (Protocol N2, 05.11.2013). Adequate measures were taken to minimise pain or discomfort.

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CHAPTER 1

INFLUENCE OF THE PITUITARY-ADRENAL SYSTEM HORMONES ON HUMAN MENTAL ACTIVITY AND ANIMAL BEHAVIOR

1.1. Mental Functions of a Person

Separate clinical observations indicating mental changes in the hypothalamic-pituitary-adrenal system disorders appeared about 100 years ago, but only by the 30s of the 20th century could it be attributed to the beginning of the data systematization and a focused study of the hormones' influence on the mental human functions. The subject of studies was as follows: the mental disorders in endocrine diseases, neuropsychiatric complications during prolonged therapy with ACTH and corticosteroids, the changes in the pituitary-adrenal system activity in mental diseases, the relationship of these changes with the certain psychotic manifestations and, finally, neuropsychic and psychosomatic disorders that occur during prolonged states of stress, which were known to be accompanied by activation of the hypothalamic-pituitary-adrenal axis.

Based on the experience gained in world clinical medicine by studying mental disorders in the pathology of the endocrine system, a non-specific endocrine psychosyndrome has been described that combined the mental changes in various endocrine diseases (M. Bleuler, 1954). It includes, in particular, a depressive mood with various dysphoric shades and changes in drives, as well as psychotic disorders. At the same time, the certain mental disorders associated with the pathology of a particular gland were described (B. Tselibeev, 1966; E. Barnstein et al., 1971; C. Smith et al., 1972). In particular, the leading psychopathological syndrome is the asthenic one in diseases accompanied by hyper- or hypofunction of the hypothalamic-pituitary-adrenal system. It serves as a "canvas" for the development of other syndromes: depressive, hypochondriac-synestopathic, epileptiform. A special wealth of psychopathological symptoms with personality changes and episodic psychoses were noted in Cushing's disease, and mental disorders were often preceded by somatic ones.

Emotional instability (A. Dobrzhanskaya, 1973; E. Young et al., 2010) or “devitalization” syndrome, characterized by high mental fatigue with loss of energy, apathy and dysphoric or depressive mood (I. Sachar, 1977; D. Zerssen et al., 1980; E. Young et al., 2001) was emphasized. The following disorders were also noted: impulsive flashes of anger and rage, a state of hyperactivity resembling cycloid disorders with depression and euphoria, personality changes, decreased critical abilities (intelligence, memory, attention, drive) (S. Jégou et al., 2013; D. Rosell et al., 2015) and even comorbid epilepsy (T. Druzhkova et al., 2022).

The state of hypocorticism was characterized by attacks of vital melancholy (A. Dobrzhanskaya, 1973; T. Dobzhansky, 1973) and sleep disturbances (J. Gillin et al., 1974; E. Young et al., 2004). In a relatively high percentage of cases (10–20), episodic or, rarely, severe and prolonged mental disorders, states of disorganization of consciousness, psychosis, fear, and sometimes schizophrenic reactions were noted (D. Erlanger et al., 1999; D. Bender et al., 2021; H. Kische et al., 2022).

Electroencephalographic and clinical studies in diseases of the hypothalamic-pituitary-adrenal system made it possible to find damage to deep brain structures and disorders of the cortical-subcortical (in particular, reticulo- and thalamocortical) relationships, accompanied by psychopathological disorders development (T. Dobrzhanskaya, 1973; R. Tucker et al., 1977). Despite the polymorphism of changes, it was possible to distinguish the certain types of electroencephalograms. Numerous observations showed hypercorticism was characterized by a predominant increase in electrical activity and there was a predominance of slow activity for the adrenocortical insufficiency, in contrast. The pronounced neuropsychic changes of increased irritability, euphoria or depression, psychoses (less often) developed in almost half of cases with prolonged administration of ACTH and corticosteroids (especially in high doses) as anti-inflammatory and anti-allergic drugs for collagenoses, infectious, and other diseases (C. Torda et al., 1949; R. Michael et al., 1963; E. Endröczi, 1972).

Administration of large doses of hormones was complicated with the “cortisone” psychoses in some patients. An acute cancellation of hormonal therapy, accompanied by corticosteroid insufficiency, led to severe asthenia. In solving the issue of an interdependence of central nervous and endocrine changes, the study of the endocrinological aspects of a mental illness is of great interest. This led to the formation of a special direction in psychiatry - psychoneuroendocrinology. It has been established that for a number of mental diseases, significant changes in the activity of the hypothalamic-pituitary-adrenal system occur (M. Mogilyantsev, 1967; T. Dobzhansky, 1973; I. Sachar, 1977). As a rule, depression was associated with an increase in ACTH secretion, and mania with an increase in glucocorticoids (A. Prange et al., 1980; E. Young et al., 2004), although an increase in the content of the latter in the cerebrospinal fluid was also observed in depression in some cases (B. Carroll et al., 1976). Activation of the hypothalamic-pituitary-adrenal system is a significant factor in modern theory that explains the so-called endogenous depression origin, since there has been a direct correlation between the severity of depression and the degree of hormonal changes (D. Zerssen et al., 1980; E. Young et al., 2010). This activation, as noted, sometimes reaches the characteristic of the early stages of Cushing's disease, although even a protracted severe depression is not accompanied with such profound metabolic disturbances. Of interest is the development of a new conception of the origin of schizophrenia, according to which a cause of the disease is a violation of the neuropeptides metabolism in the hypothalamic-pituitary system, in particular β-endorphin, β-lipotropin and ACTH (D. Wied, 1980; F. Bramilla et al., 1984).

Finally, clinical observations suggest that the constant activation of the hypothalamic-pituitary-adrenal system, when a human body tries to adapt in prolonged stressful situations, can contribute to the development of mental changes and psychosomatic diseases (D. Zerssen et al., 1980; E. Young et al., 2010).

It is only natural that clinical situations include, as a rule, many variables that complicate a subtle analysis of hormone actions on a person’s mental functions. Therefore, the studies of the psychoactive properties of ACTH and its fragments that have appeared in recent years, performed on volunteers using psychophysiological techniques, are of particular value. Such experiments make it possible to reveal hormonal effects on the individual brain functions: motivation, attention, perception, learning, memory. Thus, the intravenous infusion of $ACTH_{4-10}$ and $AKTH_{4-9}$ in 100 ml of 0.9% solution of sodium chloride in doses of 15 and 40 mg for 4 hours to healthy young men after 30 minutes from the start of administration led to increased selective attention investigated by double discrimination, and shortening the test motor response time with a simple sequence of visual and acoustic signals compared with the placebo control group (C. Sandman et al., 1975; L. Miller et al., 1976; B. Beckwith et al., 1978). Since studied hormone fragments are practically devoid of steroidogenic activity, the conclusion is valid about their direct effect on the brain.

Similar effects were obtained with the administration of MSH (A. Kastin et al., 1973).

The effect of peptides on selective attention is confirmed by changes in electrographic parameters, in particular, in a decrease in the latent period of the first component of the evoked potential (EP) and an increase in its amplitude (B. Rockstroh et al., 1981), as well in low alpha wave power (R. Branconnier et al., 1979). The absence of a decrease in the early component of slow cortical potentials was also found (G. Fehm-Wolfsdorf et al., 1981). These results are consistent with the "dishabituation" or disinhibition phenomenon (E. Endröczi, 1972) discovered previously by ACTH. Its essence is that the intravenous administration of $ACTH_{1\text{-}24}$ (50 IU) and its fragments ($ACTH_{1\text{-}10}$ and $ACTH_{4\text{-}10}$ at a dose of 1-2 mg) 1-2 hours before the experiment significantly suppresses the increase in alpha activity and in EEG- synchronization, which is usually observed during the repetition of stimuli as an expression of addiction. The latter is regarded as a decrease in general arousal (arousal). Since the effect was preserved upon the injection of hormone fragments that did not have a stereoidogenic effect (including $ACTH_{4\text{-}9}$ Org 2766) (J. Born et al., 1985), but was not caused by the $ACTH_{11\text{-}24}$ residue, it is legitimate to assume that the development of disgabitation is not mediated by corticosteroids.

An increase in the level of activity of the central nervous system (CNS) under the influence of $ACTH_{4\text{-}10}$ is also evidenced by an increase in tendon reflexes and heart rate caused by semantic load - solving a double-choice problem (C. Brunnia et al., 1978). There is also evidence of an increase in the amount of visual information processing under the influence of ACTH and its fragments, a reduction in the time taken to proofread texts, a decrease in the number of omissions and errors, a slight acceleration of recovery after visual fatigue (A. Grechko, 1980), as well as a decrease in inhibition in the central nervous system during fatigue attention tests (J. Born et al., 1985). It was shown that $ACTH_{4\text{-}10}$ and vasopressin accelerate the process of dark adaptation and are the most effective in reducing the level of analyzer functioning and visual disturbances in patients with strokes, cerebral atherosclerosis, and head injuries (V. Kolbanov et al., 1984). The peptide administration was also accompanied by an increase in the thresholds of perception with simple detection of stimuli.

As for the mechanism of ACTH influence on attention, it was suggested that the peptide enhanced the "filtering" mechanism, protecting the body from "perceptual noise" and also facilitating fixation of the "attention setting" (C. Sandman et al., 1977). All this makes it possible to more quickly isolate and respond to a significant stimulus (B. Rockstroh, T. Elbert et al., 1981; G. Fehm-Wolfsdorf et al., 1981). If we agree with this assumption, it becomes possible to understand deterioration of completing a more complex task, requiring the distribution of attention between two different groups of stimuli under the hormone action. The expression of this deterioration was as follows: an increase in the latent period of the motor reaction, a decrease in the amplitude of the EP, and an increase in the negative wave of slow potentials in subjects who received the hormone compared with the control subjects. The data, obtained in the study of human sensory functions, are to some extent consistent with the given assumption of the ACTH effect on the mechanism of significant stimuli allocation (R. Henkin, 1970). A significant decrease in the detection of signals with various modalities (taste, smell, hearing, and proprioception) was found in patients with Cushing’s syndrome. On the contrary, there was a significant increase in sensory detection in patients with adrenocortical insufficiency, but a decrease in the ability to recognize signals and, consequently, a deterioration in sensory integration (an example of the complex form of the latter is word recognition). These disorders were corrected by the administration of ACTH (40 IU) and, in adrenalectomized patients, by the administration of gluco- but not mineralocorticoids. Since the improvement of sensory integration with a reciprocal decrease in signal detection is the result of activity of a special nervous mechanism of control and selection of the incoming information, the conclusion is quite valid about the effect of ACTH and glucocorticoids on the activity of this mechanism.

In a number of studies (H. Rigter et al., 1975; L. Miller et al., 1976; M. Ward et al., 1979), the problem was raised about the ACTH effect on learning and memory. An improvement in memorization (in particular, visual memory) and complex learning, as well as a decrease in anxiety in healthy young subjects were found with special tests, against the background of ACTH infusion (C. Sandman et al., 1975). This was also found to be true in the elderly (S. Ferris et al., 1976). Similar data were obtained with the mild senile organic syndrome (R. Branconnier et al., 1979).

Of particular interest are the studies that allow separate assessment of changes in learning and the level of motivation (A. Gaillard et al., 1975). It was found that $ACTH_{4-10}$ (30 mg with subcutaneous administration) prevents increase in the reaction time, which was usually observed as the task was continuously performed (30 min) at an arbitrary pace and was regarded as the result of a decrease in the level of motivation. The usual distribution of time and frequency of reactions were observed in the control subjects who received placebo. These results allowed us to draw a conclusion about the increase in motivation under the hormone influence.

However, ACTH administration does not always lead to sufficiently clear and pronounced effects. So, the only difference related to the drug was to reduce the number of errors in a spatial-digital test when performing tasks on memory testing, tracking, and other behavioral tests against the background of EEG, recording before and 2 hours after the intravenous administration of $ACTH_{4-10}$ or the placebo (W. Sannita et al., 1976).

No significant changes were detected against the background of the peptide action (30 mg with subcutaneous injection) in the following processes: in acquiring and fading the conditional avoidance of a painful electric shock to a finger of the hand (L.Miller et al., 1977), in attention and memory in various psychological texts in patients with depressive psychoses (H.D'Elia et al., 1984), in memory dysfunctions in electroconvulsive shock therapy (J.Small et al., 1977), as well as in spontaneous EEG (M.Fink, 1978). Similar use of the same hormone fragment in women led, on the contrary, to a deterioration in visual attention and the ability to relearn, but to a significant improvement in verbal memory (J. Veith et al., 1978). The group of women who received the peptide in the middle of the cycle also showed the highest level of anxiety.

It is possible that the inconsistency of the results found is due in part to the complexity of psychophysiological studies, during which it is necessary to keep in mind a number of unaccounted variables, such as difficulty of assignment, the existence of different types of training in a person (functional, conceptual, etc.), the sensitivity of measurements, etc. It is necessary to take into account the fact that young healthy subjects performed the tasks optimally and the results obtained from them can significantly differ from the effects of hormones in patients. The variability of the hormone administration route and the time that has passed from the moment of administration to the beginning of the experiments are also equally important.

Summarizing the above data, it should be concluded that ACTH and corticosteroids have a significant impact on human mental activity, changing “the key” processes that underlie adaptive behavior such as perception, attention, motivation, learning, memory, and level of arousal. However, the neurophysiological mechanisms of influence remain inexplicable, and in this regard, clinical observations and experiments on humans have limited possibilities. Therefore, reports of experimental studies on animals began to appear following the first clinical observations. The history of these studies date back at least 80 years.

1.2. Higher Functions of an Animal Brain

The effects of hormones of the hypothalamic-pituitary-adrenal system on behavior were studied on various animal species when analyzing diverse forms of behavior and using various learning methods. At the same time, the classic endocrinological techniques were used: the removal of a studied gland with a demonstration of the failure consequences and replacement therapy, as well as the administration of hormones to intact animals (systemic, intravenous, intramuscular, intraperitoneal, subcutaneous, and local – to the brain or cerebral ventricles). In addition, a correlation was determined between the level of hormones in the blood (or in other body fluids) and behavioral patterns. Numerous studies have shown that the psychoactive properties of ACTH, its fragments and corticosteroids are manifested in various behavioral situations.

1.3. Training

The first studies of hormonal effects on the higher nervous activity of animals were carried out in the 40-60s using the conditioned reflex method in its classical (Pavlov's) version. It was found that the removal of one and denervation of another adrenal gland (M. Yurman, 1929; Z. Bakhchieva, 1966), the predominant removal of the cortical layer (D. Gzgzyan, 1949), as well as the complete removal of both glands (A. Fillipova et al., 1967) were accompanied by significant disorders of the higher nervous activity: weakening of conditioned excitation and inhibition was observed, and the typological features of animals were expressed in the character of changes. The violation of the conditioned reflex activity was especially significant in the late stages after adrenalectomy in dogs. After 1.5-2 years, during the periods of discontinuation of substitution therapy (cortisone, DOCA and saline), conditioned reflexes were excessivly weakened, quickly faded and slowly recovered, and new ones were hardly developed.

The opposite method – the creation of an excess of ACTH and corticosteroids by exogenous administration in the body – showed higher nervous activity changes depending on the dose of hormones, the duration of their administration, as well as the typological characteristics of the animals. It was found that ACTH enhanced and concentrated the excitation process during food consumption (S. Pyshina, 1956; V. Zapadnyuk, 1958; N. Nikolov, 1960; A. Gribanov, 1967) and defensive behavior (B. Voznesensky, 1960), and also enhanced differentiating and extinction inhibition (V. Zapadnyuk, 1958) with subcutaneous and intramuscular administration in small and medium doses (0.25; 0.36; 0.50 and 0.84 – 1 Unit per kg of body mass, respectively) for 30 and 60 min prior to the study in dogs using a salivary secretion technique. There is evidence of a biphasic effect of small and medium hormone doses with the development of arousal and later inhibition (V. Vasilieva et al., 1964). The small doses of hydrocortisone (0.25 and 0.50 mg/kg of body mass) administered intramuscularly 30 min before the experiment increased the excitability of brain structures, which manifested in a shortening of the reflex latent periods as well an increase in the conditioned and unconditioned salivation reflex (V. Zapadnyuk, 1958; N. Nikolov, 1960; A. Gribanov, 1967). A slowdown in the extinction of conditioned reflexes was also observed, which could be caused by weakening internal inhibition (E. Sokolova, 1976). In large doses (3 Units, 2-10 mg), ACTH, cortisol, and DOCA caused, as a rule, inhibition of the conditioned reflex activity, which manifested itself much earlier in animals of a weak CNS type.

Numerous evidences of the ACTH and corticosteroid effects on the brain functioning were obtained in the 60–70s when studying an avoidance behavior in rats. Both passive and active avoidance options were used. Passive avoidance is carried out without moving an animal: having received an electric shock in a dark compartment (attractive for rodents), the animal begins to prefer light compartments. In the case of active avoidance, a rat moves from the chamber compartment, where it received electric shocks, to a pole or to another safe compartment. Thus, in both cases, the behavior of an animal is motivated by fear. In these studies, hypotheses were formulated about the effect of hormones on the main brain functions that are closely related to learning: motivation, memory, and the general level of activation.

1.4. Motivations

It was found that removal of the anterior lobe or complete removal of the pituitary (J. Weiss et al., 1970) worsened acquisition of the active avoidance behavior in rats: a decrease (up to 35%) in the number of animals' responses to a conditioned stimulus, as well as the number of animals reaching a conditioning criteria for a certain period of time in comparison with the control values, was observed. To achieve the criterion, a greater number of reinforcements were needed. The hypophysectomized rats showed a shortened latent period and an increase in the number of entries in the chamber for the passive avoidance model. It should be emphasized that violations of conditional avoidance observed in the operated animals could be prevented by the administration of not only adrenal-supporting doses of ACTH (1.5 IU), but also of its fragments $ACTH_{1-10}$ and $ACTH_{4-10}$ (40 μg/1 ml), and alpha-MSH which were deprived of effect on the adrenocortical function (D. Wied,1966, 1977; B. Bohus et al., 1973). The latter suggests that the behavioral effect of ACTH is not mediated by the adrenal cortex. This assumption was further supported by the evidence that avoidance behavior was not reduced but even intensified in adrenalectomized rats (B. Bohus et al., 1968; J. Weiss et al., 1970; P. Beaty et al., 1970), especially in the rats receiving ACTH (R. Miller et al., 1962; B. Bohus et al. 1969). The administration of corticosterone and hydrocortisone had a depressing effect (D. Wied, 1966). However, a similar result was obtained after adrenalectomy in a number of studies: there was a significant deterioration in reproduction and maintenance of avoidance (E.V. Sokolova, 1976), as well as an extension of the latent period and a shorter running time (B. Bohus et al., 1963). It was considered as a consequence of a decrease in the excitability of brain structures, which was stopped by the administraion of corticosteroids on the background of salt replacement therapy.

The reasons for the inconsistent results obtained in adrenalectomized rats become partially understandable if we take into account the data on the dependence of the hydrocortisone effect on the degree of reflex stabilizing (E. Endröczi, 1972). Namely, corticosteroids influenced the labile phase of training, when the processes of excitation and inhibition were not yet stabilized. Moreover, the conditioned reflex activity was inhibited when the 30-40% criterion was reached and the effect of hormones was absent with the 90% criterion.

The effect of ACTH on avoidance has also been extensively studied in intact rats. In this case, subcutaneous administration of the hormone (at a dose of 3 Units per 1 kg) and its fragments, $ACTH_{4-10}$ and $ACTH_{5-10}$ (0.15 mg per 1 kg), 30-60 min before the experiment accelerated 2-3 times the reproduction of defensive conditional reflex in the U- and T-shaped labyrinths (C. Sandman et al., 1973; A. Grechko, 1980; V. Vinogradov et al., 1980; S. Tikhomirov et al., 1986). The hormone administration enhanced the passive avoidance (L. Koranyi et al., 1967; M. Almedia et al., 1983) and significantly delayed the extinction of the active one (J. Murphy et al., 1955). A decrease in the extinction rate under the hormone influence was also found in the study of unilateral and bilateral avoidance (S. Levine et al., 1965; D. Wied, 1966; C. Nyakas et al., 1981). It was found that the molecule part belonging to the N-terminal end and containing the first 10 amino acids (H. Greven et al., 1973; M. Fekete et al., 1981) was active in behavioral effect, while the effect of the hormone and its fragments seemed to be relatively short-term (several hours).

The noted features of the ACTH effect on the avoidance reflexes: facilitating reproduction, enhancing passive avoidance and slowing down the extinction of active ones, served as the basis for the "motivational hypothesis". It explains the hormonal effect by increased motivation. With regard to corticosteroids, it has been suggested that these suppressed fear that was associated not only with the accelerated extinction of escaping conditioned reflexes, but also with a decrease in the number of intersignal reactions after administration of corticosteroids and, on the contrary, an increase in these parameters after adrenalectomy (J. Weiss et al., 1970). At the same time, the smaller doses (0.2 and 0.1 mg) of dexamethasone and corticosterone more effectively facilitated extinction of the "pole vault behavior". However, there is a dependence of the corticosteroids effect on dose and timing of administration. So, the intraperitoneal administration of the hormone at a dose of 10 mg per 1 kg of body weight, 30 minutes and 2 hours before the study slowed down the development of extinction inhibition. A dose of 50 mg/kg of body mass had the same effect when applied 30 min before the experiment, and, on the contrary, it accelerated extinction when administered 2 hours later. The revealed differences were associated with the distinct effective duration of the increased hydrocortisone content in the blood and with significant differences in its level (M. Mityushov et al., 1970; E. Sokolova, 1976).

It should be emphasized that the hormone effect is independent on suppressing the endogenous ACTH secretion (J. Davidson et al., 1972). It should be noted, however, that in a number of works the hypothesis was not confirmed about the hormones' action on a conditioned behavior due to a change in the level of "fear motivation". Thus, the intraperitoneal administration of ACTH at a dose of 10 IU/kg for 4 days and 30 min before training weakened a unilateral avoidance in chickens, while the administration of hydrocortisone (5 mg/kg) had a facilitating effect (L. Koranyi et al., 1969). The data were also obtained on the weakening of avoidance reactions in rabbits (L. Koranyi et al., 1970) and in rats (J.A.

Weijnen et al., 1970; B. E. Beckwith et al., 1978) under the ACTH influence.

It is also noteworthy that behavioral hormonal effects were studied either with the administration of exogenous hormones or after surgical removal of the glands in all the studies analyzed. The changes taking place at the same time, as a rule, go beyond the physiological hormonal fluctuations. Therefore, it seems especially important to study behavior under conditions when "hormones are secreted through physiological normal pathways in physiologically normal amount" (J. Weiss et al., 1973). Observance of these conditions allows us to solve the fundamentally important question of whether hormones are physiologically involved in an avoidance behavior. To this end, the attempts have been made to determine the correlation of behavioral reactions with parallel changes in the hormones blood content. More definitive results were obtained with respect to ACTH. Thus, high hormone levels correlated with an increased retention of a passive avoidance in rats (M. Gibbs et al., 1973), as well an acceleration in their learning of a two-way avoidance reaction (M. Woodruff et al., 1983). The levels of vasopressin and alpha-MSH measured in the blood by the radioimmune method did not correlate with the severity of these behavioral reactions (Tj. Wimersma Greidanus et al., 1978). A significant positive correlation between the severity of the passive avoidance reaction of a drinker and the level of ACTH in plasma was found in adrenalectomized rats under conditions of water deprivation, after a combination of an attempt to drink with painful shock (E. Endröczi et al., 1977). However, there is evidence of a negative correlation between the level of bilateral avoidance and the pituitary-adrenal system activity (A. Dupont et al., 1970).

Recent radioimmune studies using antisera to $ACTH_{1-39}$, to its fragments 1-10, 4-10, 4-14, 1-24, and MSH deserve special attention in terms of assessing the "behavioral" significance of ACTH levels usual for physiological conditions. The infusion of antisera into the brain ventricles 1 hour before the study facilitated the extinction of the "pole vault reaction" (J. Loeber et al., 1979). So, it may be suggested that endogenously released ACTH is involved in an avoidance behavior, and this is the extra-adrenal effect.

As for the ratio of behavioral activity and the level of corticosteroids, the obtained factual material is very contradictory. So, in part of the studies, a direct relationship was found between the level of corticosteroid secretion, on the one hand, and background motor activity (B. Bohus et al., 1963), as well as the number of pedal compressions that stopped the passage of electric current through the metal mesh of the floor or provide access to food (J. Wertheim et al., 1969), on the other. The operational avoidance behavior was also enhanced against the background of endogenous release of corticosteroids caused by stress 30 min before behavioral tests (J. Weiss et al., 1973). The effect was lost after adrenalectomy and was restored by the administration of corticosterone (3.0 mg per day), DOCA (0.3 mg) or aldosterone (0.03 mg).

At the same time, according to other studies, the plasma corticosterone levels inversely correlated with the learning rate, determined by the total number of positive responses and reactions in an intersignal period (A. Delft et al., 1970; E. Endröczi, 1972), or did not show stable changes (N. Kulikova et al., 1982).

Thus, the facilitating effect of ACTH on avoidance has been found in the vast majority of studies using various experimental techniques. It is due to the direct hormone action on the brain structures, confirmed by the following findings: the preservation of its effects in adrenalectomized animals, the similarity of the ACTH and MSH effects (having a common $ACTH_{4-10}$ heptapeptide, although MSH does not have a stimulating effect on the adrenal cortex), maintaining efficiency by ACTH fragments lacking corticotropic activity, opposite behavioral effects of corticosteroids and, finally, maintaining the ACTH effects on the reproduction and extinction of avoidance when the hormone and its fragments were injected into rat brain ventricles, but weakening when antisera to hormonal drugs were administered in rewarded behavior.

If we consider that ACTH enhances the avoidance behavior due to increasing the level of motivation, then the question naturally arises: is this hormone action specific or can it occur in motivational states of any modality, particularly in rewarded behavior.

Decreases in the latent period of reactions and in the number of errors were found when learning in a T-shaped labyrinth, i.e., it accelerated learning process with a food reinforcement due to daily intraperitoneal administration of $ACTH_{4-10}$ at a dose of 15 μg/ kg no earlier than 30 min before and no later than 1 min after training sessions (I. Ashmarin et al., 1978; I. Ashmarin et al., 1980). The doses up to 50 μg were not accompanied with further acceleration of skill development. Similar results were obtained with drinking reinforcement both when studying the effect of $ACTH_{5-10}$ on learning in a maze (V. Bely et al., 1979), and when it affected the operant learning. The administration of 10-12 units of ACTH 30 min before the experiment led to a very significant increase in the number of clicks on the lever in the last training series and increased reaction during extinction (S. Guth et al., 1971). It should be noted that the hormonal effect was more significant with less thirst.

However, the administration of ACTH did not cause changes in a number of studies when learning in a maze and instrumental eating behavior (B. Leonard, et al., 1975; R. Miller et al., 1973). Ambiguous results were also obtained when studying the effect of ACTH and its fragments 1-24 and 4-10 on the extinction of food and drinking conditioned reflexes: they were noted as decrease in extinction in rats (S. Guth et al., 1971; J. Garrud et al., 1974), acceleration in cats (E Endröczi, 1972), and the lack of change (J. Weijne et al., 1970).

Adrenalectomy greatly facilitated extinction of the food conditioned reflex behavior in rats (D. Micco et al., 1979). This effect was eliminated by the administration of corticosterone, which did not affect the extinction rate, or facilitated in intact animals (R.E. Miller et al., 1973; P. Garrud et al., 1974). Administration of dexamethasone (1 mg/kg of body mass) slowed extinction of a food conditioned reflex in rats (J. Sulc et al., 1983).

The effect of ACTH on conditioned food aversion was investigated in a number of studies. This is a peculiar form of avoidance that was developed in rats by combining drinking a sweet solution (a new taste for them), followed by intraperitoneal administration of toxic lithium chloride. It turned out that the dexamethasone phosphate blockade of ACTH secretion impaired the behavior development (J. Hennessy et al., 1976), and administration of the hormone or its fragments $ACTH_{4-10}$ and $ACTH_{4-10}$-7D-Phe (100 μg per rat) as well as alpha-MSH 30 minutes before an experiment delayed the extinction of conditional food aversion (K. Kendler et al., 1976; J. Hennessy et al., 1980). It should be noted that the peptides were more effective in a situation of choice, when animals could choose sweet or tap water for drinking.

To reveal the possibility of ACTH controlling the level of motivation, it is of particular importance to study a behavior type that does not include the learning process. An aggressive-defensive behavior caused by unavoidable painful electrical stimulation is such a behaviour type. Analysis of its development allows us to consider it as a manifestation of increasing fear (P. Randall et al., 1969). With intensified electric current, an affective overstrain, as a rule, manifested itself first in the appearance of anxiety and squeaks, then in attempts to escape irritation (running and standing up) and, finally, to find a way out in attacks of aggression directed at another animal. A detailed study of this reaction using a video type and mapping bite areas showed that it has many elements of conflict (R. Blanchard et al., 1977), which made it possible to attribute such aggressive behavior to irritability (P. Brain, 1981). To study a provoked aggressiveness, we used a well-known method modified by us (R. Rodgers et al., 1978).

Each animal was used in the experiment only once, and the time of irritation was strictly limited – it stopped when aggression appeared or when the set limit was reached. Close-weighted rats marked with colored spots were placed in pairs in a chamber with an electrified grid floor and irritated with a gradually increasing (1 V/s) alternating current from a programmable stimulator. The thresholds for successive reactions were determined: startle flinching (manifestations of pain), vocalization, standing up and running (avoidance) and fightings (aggression), as well as the number of attacks (in % of the number of trials). The irritation was stopped when aggression occurred or the limit was reached (70 V). The duration of stimulation was about 70 s. Two tests were performed with an interval of 1 min. Thus, two stimulation tests were carried out on each of ten male rats in pairs, so that the total number of measurements for each behavioral reaction was up to 20. In each series of studies, the rats, obtained simultaneously from the nursery of the Russian Academy of Sciences, were divided into control and experimental groups.

We used a chamber measuring 32x27x30 cm with an electrified grating floor. Pairs of equal mass rats were placed in it and subjected to a current, the voltage of which was gradually increased by 1V per second until all components of the affective-defensive behavior were successively obtained. The thresholds for the appearance of the sequentially developing response components and a fighting rate (in % of the number of exposures in two tests) were measured. Thus, the primary painful response was associated with an increasing affective stress motivated by fear, and, finally, outbreaks of aggression were manifested in the characteristic "pose of boxers" and fight reactions.

We also studied the behavioral reactions (flinching, vocalization, running, rising up, squeaking, aggression, etc.) of an isolated rat group in response to the unexpected appearance of an object (stick), touching its nose or back, and grabbing it with a hand. The percentage of various types of reactions was determined for the studied group of rats. Additionally, the vertical component of the exploratory activity was evaluated by the number of risings per 1 min in a glass jar with a diameter of 35 cm and emotionality was evaluated by the number of defecation boluses under these conditions.

The work was performed on outbred and Wistar male rats weighing 180-250 g. It should be noted that each series of experiments, including control and experimental animals, was performed on a group of rats that came from the same nursery and were kept under the same conditions, since within this group the initial indicators of behavioral activity were very similar in magnitude.

Under control conditions (after intraperitoneal injection of physiological saline at a dose of 0.1 ml per 100 g of body weight), the threshold values of individual components of aggressive defensive behavior varied within the following limits: for flinching - from 17.8 ± 1.3 to 26.1 ± 0.9 V; vocalization - 20.9 ± 1.6 and 27.9 ± 1.2 V; standing up - 19.8 ± 2.7 and 30.8 ± 2.4 V; running - 25.7 ± 1.4 and 42.3 ± 1.9 V, finally, for the fighting reaction - from 35.0 ± 1.9 to 45.9 ± 3.1 V. Fluctuations in the frequency of fighting had values of 70 and 100%, and the duration of standing in the "pose of boxers" is 20.0 ± 3.2 and 77.0 ± 17.9 s.

20-30 min after the intraperitoneal administration of ACTH (corticotropin of the All-Union Scientific Research Institute of Blood Substitute and Hormone Technology) at the doses of 0.6 and 1.0 IU per 1 kg of body mass, the thresholds of all components of an aggressive-defensive behavior were decreased in comparison with the results of the control experiments (Figure 1-1, Table 1-1).

In 78% of trials of rats grouped in pairs, this change was statistically highly significant at $p < 0.05-0.001$. In most of the samples (89%), there was also an increase in the frequency of fights (up to 100% in individual groups of animals) and the duration of the "pose of boxers" (by 44-112%). Only 11% of the samples showed a decrease in these indicators (LSeveryanova, 1978, 1981a). The activating effect of the hormone was also noted with the administration of a larger dose of 6.3 IU (R. Rodgers et al., 1978).

Table 1-1. Indicators of behavioral activity of rats under control conditions and with changes in hormonal level

Series of experiments	Hormone dose/kg	N of rats	Fight ing rate	Boxer's pose s	N of risings	N of boluses
Control		50	80	20±30	4,3±0,4	1,6±0,4
ACTH	0,6 IU	30	100	62±3 *	4,9±0,3	1,8±0,4
Hydrocortisone	1,5 mg	30	50	27±7	2,8±0,2*	1,5±0,3
ДОСА	0,3 mg	30	60	30±7	1,0 ±0,2*	1,2±0,4
Control		28	80	76±16	3,1±0,4	1,3±0,2
Adrenalectomy (7 days)		20	75	120±42	2,0±0,3*	0,7±0,2*
ACTH	1,0 U	18	100	252±55	2,1±0,5	0,8±0,1
Adrenalectomy (27 days)		16	100	67±18	1,4±0,4	1,2±0,7
Hydrocortisone	1,5 mg	16	100	53±5	0,8±0,1	0,9±0,2
Control			100	77±18	5,4±0,8	2,0±0,5
$ACTH_{5-10}$	16,7 mcg	20	100	46±25	6,4±0,9	0,6±0,3*
	50,0 -	20	100	60±13	6,2±0,8	0,6±0,2*
	150,0 -	20	100	46±15	6,9±0,5	0,7±0,3*
	450,0 -	20	100	78±26	6,1±0,9	0,7±0,3*
Control		20	100	135±66	5,6±1,2	1,3±0,4
$ACTH_{4-7}$ -PGP	16,7 mcg	20	30	0	3,4±0,5*	0,5±0,3
	50,0 -	20	50	0	4,9±0,7	0,4±0,2
	150,0 -	20	80	0	3,3±0,7*	0,8±0,4*
	450,0 -	20	50	0	5,6±0,5	0,4±0,1*
Control		20	100	0	4,3±0,9	0,4±0,2
PGP-$АКТГ_{4-7}$-PGP	16,7 mcg	20	100	0	5,2±0,7	0,6±0,3
	50,0 -	20	100	0	6,0±1,1	0,5±0,2
	150,0 -	20	100	0	6,5±1,0	0,4±0,2
	450,0 -	20	60	0	7,2±0,8*	0

Note: Here and further in the tables, numbers with an asterisk indicate a significant difference in indicators at p <0.05 - 0.001.

For additional control, the experiments in the chamber were performed twice on 60 rats with an interval of 20-30 days. In this case, the first test was carried out against the background of the ACTH action, the second one was carried out after administration of saline. The same correlation of results is obtained.

It should also be noted that there was an increase in vertical activity (at $p < 0.02$-0.001) and the number of boluses after the administration of ACTH. The predominant change in the test with an approaching subject and touch was an increase in the frequency of the squeak reaction (up to 31%), whereas in the control conditions, indicative reactions prevailed (41% of the samples).

Thus, ACTH enhanced the protective behavior and aggressiveness in rats. The leveling of this effect and the occurrence of opposite changes when testing animals 1 hour 20 min after the hormone administration are quite understandable, given that at this time the content of corticosteroids in the blood of rats increased by 70-80%. Therefore, the weakened aggressive-defensive behavior in this case is the result of the prevalent corticosteroid effect. This conclusion is confirmed by the results of experiments with the administration of hormones in intact animals.

Hydrocortisone ("Gedeon Richter" Company) and DOCA (The Rostov-on-Don Chemical Plant) was administered intraperitoneally 30-40 minutes before the study in doses of 1.0-1.5 mg and 0.3-0.6 mg per 1 kg of body mass. As can be seen from Figure 1-1, corticosteroids caused weakening fear and aggression with electrical painful irritation. In the study of reactions to a provocative object and handling, a decrease in the frequency of the squeak response (up to 11-15%) and vertical activity ($p < 0.05$-0.001) was noted.

7 days after bilateral adrenalectomy (using paraspinal access), the rats showed a decrease in the vertical activity and the number of bowel movements as well as the number of sniffing and vocalization reactions when a subject suddenly appeared and touched, but the frequency of "fading" increased (Table 1-1). In the study of an aggressive-defensive behavior, there was a decrease in the thresholds of vocalization, rising up, and fighting reactions ($p > 0.05$), although the average frequency of fights was lower than in intact animals. The duration of the threat posture in many rats turned out to be significant: they seemed to "freeze" in the stance, however, without showing signs of aggression (blows, bites, etc.).

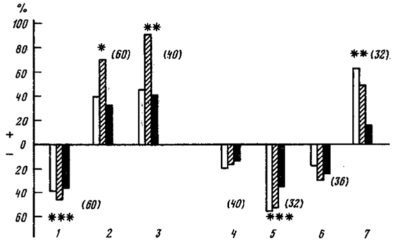

Figure 1-1. The effects of hormones on the aggressive-defensive behavior of rats. Columns: the changes in the thresholds of vocalization reactions (white), rising up and running (shaded) and fighting (black) expressed as % in relation to the control values; 1 - after administration of ACTH to intact rats (at a dose of 0.6 IU/kg); 2 - hydrocortisone (1.5 mg/kg); 3 - desoxycorticosterone (0.3 mg/kg); 4 - 7 days after bilateral adrenalectomy; 5 - 27 days after surgery; 6 - after administration of ACTH to adrenalectomized rats; 7 - after administration of hydrocortisone to the operated rats. A dose of hormones is calculated per 1 kg of body mass. In parentheses is the number of trials. Hereinafter, asterisks indicate the results which are significantly different from the control values ($p<0.05$-0.001).

The ACTH administration after the surgery period was accompanied by activation of affective aggressiveness: a decrease in the thresholds of all the components (at $p <0.05$), an increase in the fighting rate and the threat posture duration.

In adrenalectomized rats, studied 27 days after surgery, the vertical activity was slightly lower than under control conditions. There was an increase (by 34%) in the number of sniffs when studying reactions to the unexpected appearance of an object. The aggressive-defensive behavior was characterized by a decrease in thresholds in comparison with control values and an increase in the frequency of fightings. An increase in pain sensitivity in adrenalectomized rats was also noted on the 9-18th day after surgery (E. Markel et al., 1984). Hydrocortisone administration induced the same behavioral changes in the animals after intervention like in intact animals (Figure 1-1). An inhibitory effect was also found when 100 μg of the hormone was injected into the cerebral ventricles (R.G. Rodgers, 1979).

Activation of an aggressive-defensive behavior after adrenalectomy can be explained by a change in the content and ratio of the pituitary-adrenal hormones that occurs in rats. There is evidence that 5-7 days after bilateral adrenalectomy, the level of corticosteroids in the peripheral blood of animals decreases by 2-3 times (I. Drozdovich et al, 1979), while the