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METHODICAL APPROACHES TO SIMULATION OF NEUROSIS ON ANIMALS

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Abstract

Objective. Analysis and synthesis of literature data on methodological approaches to modeling animal neurosis.

Methods. The basis of this study was a review of the literature on this topic.

Results. Neurosis is a typical form of pathology of the nervous system. Modeling of this pathology in the experiment is achieved by overstrain and disruption of the processes of excitation, inhibition and lability of nervous processes.

Conclusion. Modeling animal neurosis, taking into account the type of higher nervous activity, helps to deepen knowledge about the functioning of the nervous system and adapt it to negative influences, thereby creating the basis for further clinical research on the prevention and treatment of neurosis.

Keywords: neurosis, animal modeling, higher nervous activity

МЕТОДИЧЕСКИЕ ПОДХОДЫ К МОДЕЛИРОВАНИЮ НЕВРОЗОВ НА ЖИВОТНЫХ

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Резюме

Цель. Анализ и обобщение данных литературы о методических подходах к моделированию неврозов на животных.

Методика. Основой данного исследования стал обзор литературы по данной теме.

Результаты. Невроз – типовая форма патологии нервной системы. Моделирование данной патологии в эксперименте достигается путем перенапряжения и срыва процессов возбуждения, торможения и лабильности нервных процессов.

Заключение. Моделирование неврозов на животных с учетом типа высшей нервной деятельности способствует углублению знаний о функционировании нервной системы и адаптации ее к негативным воздействиям, создавая тем самым базу для дальнейших клинических исследований по профилактике и лечению неврозов.

Ключевые слова: неврозы, моделирование на животных, высшая нервная деятельность

Introduction

Neurosis is a typical form of pathology of the nervous system, resulting from overstrain and disturbance of strength, balance and mobility of nervous processes. Strength is the ability to withstand prolonged exposure to a stimulus. Balance is a balance between arousal and inhibition processes. Mobility is the speed of switching the processes of excitation and inhibition.

In connection with the prevalence of neuroses in modern society, it becomes necessary to create adequate models of this pathology in animals, followed by extrapolation of the obtained experimental data to humans and implementation into clinical practice. For the emergence of neurosis, an animal must be affected by a stimulus that exceeds the adaptive capacity of the organism. The nature of the stimulus largely depends on the type of higher nervous activity [16, 23].

Higher nervous activity, its types

The concept of "higher nervous activity" was introduced by the physiologist professor I. P. Pavlov. Higher nervous activity is a set of reflexes – conditioned and complex unconditioned (for example, instincts) and includes such cognitive processes as consciousness, thinking, memory and emotions. Its morphological substrate is the cerebral cortex, mainly the neocortex. Consequently, higher nervous activity is inherent in those animals that have a cerebral cortex, primarily mammals.

According to I.P. Pavlov, there are several types of higher nervous activity: (1) Strong balanced agile. The most resistant to adverse influences due to the adaptive combination of characteristics of nervous processes; (2) Strong unbalanced agile. Vulnerable to neuroses due to the weakness of inhibition processes; (3) Strong balanced inert. Vulnerable due to low mobility of nervous processes. (4) Weak. Most susceptible to negative incentives. It is characterized by rapid exhaustion of the excitatory process, weakness of internal cortical inhibition, passive reaction to stimulation. This predetermines the onset of neurosis as a result of the breakdown of the main cortical nervous processes with the development of inhibition and the formation of passive-defensive reactions.

According to the above specifications, it is easier to induce neurosis in the animal with a weak type of higher nervous activity, more difficult – in a strong balanced mobile because of its high resistance to pathogenic agents. However, an increase in the strength of the stimulus, «collision» of instincts, an increase in activity and repetition of influences can still lead to neurosis [23, 25]. All the reasons that can cause pathology of higher nervous activity are divided into three large groups: (1) arising in the process of interaction of the organism with the environment, including the prenatal period of life; (2) genetically determined; (3) due to a combination of the first two.

The first group of causes is currently the most studied, it is extremely diverse, and therefore their systematization and the selection of the main pathogenic factors among them are extremely important. An external pathogenic agent reaches the brain in different ways, which essentially determine both the pathogenesis of the disease and its clinical manifestations. Given these circumstances, scientists distinguish between functional, post-traumatic and combined pathology of higher nervous activity.

Functional pathology of higher nervous activity is understood as such behavior disorders that are caused by the influence of pathogenic stimuli on external and internal receptors. Post-traumatic pathology of higher nervous activity means behavioral disturbances arising from the direct effect of a pathogenic agent on the brain, for example, when it is injured, hemorrhage into the brain tissue, brain tumors.

Combined (functional-traumatic) pathology of higher nervous activity means disorders arising from the impact both on the receptor system of the body and directly on the brain, which occurs, for example, in radiation and heat injuries of the head, with its mechanical damage. In all three cases, exposure to a pathogenic agent causes primary brain damage.

Violations of higher nervous activity caused by other factors or developing as a result of another pathology of the body, for example, an infectious disease, tumor, cardiovascular disease, are secondary. Most often, the secondary pathology of higher nervous activity is the result of asthenization of the nervous system, a decrease in its stability in relation to psychogenic or other influences [10, 11]. Violations of higher nervous activity caused by other factors or developing as a result of another pathology of the body, for example, an infectious disease, tumor, cardiovascular disease, are secondary. Most often, the secondary pathology of higher nervous activity is the result of asthenization of the nervous system, a decrease in its stability in relation to psychogenic or other influences [10, 11].

Functional pathology of higher nervous activity

This pathology arises for two main reasons: (1) the pathogenic agent directly affects the receptors by the unconditioned reflex mechanism; (2) the pathogenic agent has a signaling value and acts through receptors on the brain according to the conditioned reflex mechanism.

According to I.P. Pavlov, the mechanism of such pathology consists in overstrain of excitation, inhibition, or their mobility. Whatever external reasons the experimental neuroses depend on, they were explained by the weakening of the process of internal inhibition, leading to the predominance of the irritating process or to disturbances in the normal mobility of excitation and inhibition and, as a consequence, to their pathological lability or inertness.

The imbalance between inhibition and excitation contributes to the irradiation of inhibition along the cortex, and then along the subcortical structures, the appearance of phase states. In the early stages of the development of these processes, inhibition has a protective function, arises after the nerve cells reach the limit of the possibilities of normal operation and therefore received the name of transcendent inhibition. But after the exhaustion of the protective function of inhibition, the pathology of higher nervous activity

begins to form. The concepts of the mechanisms of pathology of higher nervous activity are based on taking into account the role of emotions and memory, as well as humoral factors in the onset of pathology.

The role of negative emotions

They arise under the influence of pathogenic irritants and can take on a prologue character. This is facilitated by a long delay in the external identification of negative emotions, accompanied by hormonal and other chemical changes in the blood. These circumstances reduce the resistance of the nervous system to the pathogenic agent and, thus, a self-reinforcing pathological system ("vicious circle"), disorganizing activity of other systems, is formed. However, such a pathogenic influence of negative emotions arises during their long-term stable course: at the early stages of their occurrence, negative emotions often play a biologically positive role, acting as a factor of emergency mobilization of the entire organism in order to counteract the pathogenic agent.

The role of memory

The mechanism of prolonged course of pathological higher nervous activity is complex and is determined by several factors. So, it is believed that pathological conditioned reflexes can be formed as a result of fixation in long-term memory of those states that arise in the brain under the influence of a pathogenic agent. These states can be reproduced on a corresponding conditioned stimulus or in an appropriate situation (situational pathological reactions) or be ubiquitous in the form of a stable pathological state. The latter is also formed with the participation of long-term memory. Another mechanism for the emergence and retention of pathological higher nervous activity may consist in the formation of a pathological temporary connection. Such temporary connections are especially easy to form when the general functional state of the brain is low; they can arise according to the conditioned reflex principle or another principle of learning, be situational or generalized. The general functional state of the brain changes under the influence of many factors. For example, it decreases as a result of prolonged limitation of the influx of visual, auditory, tactile, proprioceptive and other stimuli into the brain, with prolonged hypodynamia. As a result, the resistance of higher nervous activity to pathogenic factors decreases, and the arising pathological reactions are distinguished by a special severity of the course [10, 11, 23, 24, 25].

Informational pathology of higher nervous activity

It means disturbances in the course of the higher functions of the nervous system, as well as mediated disturbances in the vital functions of other body systems that arise during a long stay of the brain in conditions of an unfavorable combination of the following factors: (1) a certain amount of information subject to processing to make an important decision; (2) the factor of time allotted for such brain work; (3) the level of motivation, which determines the importance of information and the need for its processing.

The combination of these three factors (information triad) may not be favorable if, firstly, it is necessary to process a large amount of information (including decision-making) with a long deficit of time allotted for such brain work and a high level of behavior motivation and if, secondly, there is a shortage of information for a long time, the motivation of behavior (for example, the need to make a decision) is very high. So, in both cases, the triad of factors influences and unfavorably combines: (1) the amount of information (in the first case, excessive, in the second it is less than necessary); (2) time (in the first case it is not enough, in the second case it is excessively large); (3) motivation, which in both cases is very high.

If the clinical picture of the disease corresponds to neurosis, then they talk about informational neuroses, if it corresponds to other diseases, then it is advisable to talk about the informational pathology of the corresponding nosology. Studies have shown that with this form of pathology, there are violations of short-term and long-term memory, emotions, signal analysis functions, sexual, food behavior and other instincts, there is a violation of the regulation of cardiovascular function, respiration, digestion and a number of others. A characteristic of this form of pathology is (in the early stages) certain dynamics, that is, a sequence of involvement in the pathology of different systems of the body, and at deep stages – a wide coverage of different systems, a stable violation of the functions of many body systems.

There are two types of global factors influencing the development and formation of information pathology: (1) factors that reduce the stability of the nervous system to the information triad (risk factors); (2) protective factors preventing the development of pathology, raising the stability of the nervous system. The most frequent and significant risk factors include prolonged physical inactivity, violation of intraspecific relationships between individuals, for example, deficiency or perversion of mutual influence

between individuals, especially in the early stages of ontogenesis, some genetically predetermined properties of the nervous system that form the type of higher nervous activity, brain injury, disorders of the nervous system caused by factors that do not correspond to the definition of the information triad. All of them reduce the resistance of the nervous system to the pathogenic influence of the information triad.

The biological significance of the second group of factors that significantly affect the development of information pathology is to protect the body from the onset of pathology or (if it occurs) to activate compensatory mechanisms aimed at limiting and suppressing developing pathological processes [7, 8, 13, 14, 19, 20, 25, 27].

Modeling neuroses

Preliminary asthenization of the body sometimes is carried out before the direct modeling of the neurosis itself. This includes temperature, sound or vibration effects, restriction of food intake and sleep and increased physical activity, which reduce the adaptive capacity of the body. In pups, this is achieved through early separation from the mother or exposure to adverse factors during antenatal ontogenesis. The spring-summer period is considered optimal for modeling neuroses in mammals.

Quite common methods of modeling neuroses in animals include: (1) Restriction of the instinct of freedom – this model is quite simple to implement, but animals quickly adapt. (2) Violation of the natural daily diet or light rhythm associated with the changes of day and night. (3) Hierarchical changes in the group. This method allows you to study complex forms of social behavior, but neurosis isn't formed in everyone and is manifested rather weakly.

In addition, a method of «conflict of afferent excitations» is proposed. For its implementation the following items are used: the light of a 300 W electric bulb, the sound of an electric bell with an intensity of 60 dB and an electric current of a threshold value. Moreover, the impact of each of the stimuli or their combination should be different [1, 3, 11, 12].

However, due to the fact that the results obtained are usually intended for extrapolation to humans and for the study of higher nervous activity. The most specific for this purpose should be recognized as those experimental models that take into account the proposed typology by I. P. Pavlov.

Methods for modeling neuroses depending on the type of higher nervous activity

It is necessary to set an unsolvable problem for the animal to simulate neuroses in an experiment. The type of task depends on the type of higher nervous activity. For this, effects are used that cause overstrain and disturbance of the excitatory and / or inhibitory process, disturbance of their mobility and balance, collision of instincts of alternative biological significance.

1. Overstrain and loss of strength occurs under the influence of a super powerful stimulus (light, sound). The weak type of higher nervous activity is the most sensitive to this type of influence.
2. Overvoltage and violation of braking. This type is modeled mainly in animals with a strong unbalanced mobile type of higher nervous activity. This is accomplished in two ways: a) Delayed reinforcement. The animal develops a conditioned reflex - feeding at a certain time, then the moment of feeding moves further and further in time. The animal waits, but no reinforcements come. b) Development of subtle and complex differentiations. A conditioned reflex has been developed: if the animal is shown a circle, it is fed, an ellipse – not fed. When simulating neuroses in this way, the animal is shown a geometric figure resembling a circle and an ellipse.
3. For example, an animal becomes accustomed to the fact that light indicates feeding time and sound is an electric shock. The meaning of the stimuli changes with the development of corresponding conditioned reflexes.

As a result, the following types of experimental neuroses are formed: (1) In case of overstrain and loss of strength – neurosis with a predominance of inhibition. Its outward manifestations are drowsiness and apathy. (2) With overstrain and breakdown of inhibition – neurosis with a predominance of excitement. It is characterized by constant and inadequate excitement in the aggressiveness and malice of the animal. This type often turns into an inhibitory type neurosis in connection with the development of transcendental inhibition. (3) In case of overstrain and impaired mobility – neurosis with a pathological predisposition (fussiness, aimless movements) or with pathological inertia associated with the development of phobias. (4) Cyclic. It is characterized by the alternation of all the above signs. [23, 25, 26].

Somatic manifestations of neuroses

Manifestations of neuroses include: tachycardia, drop or increase in blood pressure, the development of gastric ulcer and duodenal ulcer, endocrinopathy (often hypo- or hyperthyroidism, diabetes mellitus), obesity or cachexia. Neurotropic disorders occur, which lead to degeneration of internal organs. Hypokinesis, hyperkinesis and sensitivity disorders develop on the part of the nervous system.

Violations of higher nervous activity are manifested in the form of a loss of conditioned, sometimes unconditioned reflexes, the extinction of cognitive processes. Cognitive are the most complex functions of the brain. With their help, the process of rational cognition of the surrounding world and purposeful interaction is carried out. This process includes the following components: perception of information (gnosis), information processing and analysis (voluntary attention, generalization, identification of similarities and differences, establishment of associative links), memorization and storage of information (memory), information exchange, construction and implementation of an action program (skills) [7, 8, 13, 14, 19, 20, 27].

Pathogenetic foundations of neurosis

The formation of neuroses is based on the generator of pathologically enhanced excitation as hyperactive neurons, which are a source of intense uncontrolled impulses. The emergence of the generator occurs under the influence of prolonged and intense stimulation that occurs during the formation of neuroses. A group of overactive neurons can arise in any part of the nervous system. They have autonomy, do not obey the influence of other systems and can exist indefinitely.

New physiological systems, which are necessary for adequate vital activity, cannot be formed in connection with the activity of the generator of pathologically enhanced excitation in the nervous system.

Under the influence of the primary generator, secondary ones can be formed, involving more and more groups of neurons in the focus of pathological excitation, which contributes to disorganization of the activity of the nervous system, both somatic and vegetative, with subsequent loss of functions and the development of pathological processes in internal organs [4-6, 15].

Changes in neurons with neuroses

It has been established by electron microscopy that experimental neuroses are accompanied by destructive changes in the neuronal and glial elements of the neocortex, as well as in its conducting apparatus, and reparative processes proceed in parallel with destructive processes, providing one or another degree of compensation for disturbed functions. Biochemical studies of the neocortex of animals in a state of experimental neurosis revealed both reversible and irreversible disorders of the neurotransmitter system, which is of particular interest from the point of view of the possibility of creating new approaches to treatment. The detection of ultrastructural and neurochemical changes in the brain of animals in a state of experimental neurosis suggests that neuroses also have a structural basis, which confirms the only correct conclusion that any pathology is characterized by structural changes that can be detected by additional research methods [5, 6].

Methods for assessing the severity of disorders of the nervous system of experimental animals with neuroses

The open field test has been proposed to record the behavior and motor activity of animals (Fig.).

Fig. Open field test

It is carried out on a flat surface, lined with lines forming 36 squares of the same size and enclosed around the perimeter. Activity in the horizontal and vertical planes of space, grooming (washing), the study of holes and defecation are examined usually in the «open field» (the time of leaving the center of the site, where the rat is placed at the beginning). Also spheres, for example, to register discoordination, trembling, paresis, paralysis, which can be associated with experimental neurosis, are studied. Horizontal motor activity of animals includes running in different directions, walking in a circle. In this case, the participation in the movements of all limbs of the rat is assessed. One crossed sector is taken as a unit of movement for visual registration of activity.

The motor activity of rats in the vertical plane is represented by two types of stands. In climbing racks, the hind legs of the animal remain on the floor of the surface, and the front paws rest against the wall of the «open field». In racks of the «rearing» type (from «rear» – «stand on their hind legs») the front legs remain suspended. Grooming (washing) is used to study the emotional state of animals. It is divided into short and long-term. Short grooming is a quick circular motion of the front paws around the nose and vibrissae, and a long one is washing eyes, the area behind the ears, washing the entire head, paws, sides, back, an anogenital area and the tail. Exploring holes in the floor consists of sniffing at their edges or sticking animal faces inside the holes. The number of acts of defecation is considered a marker of the «emotionality» of the animal [17, 21, 22].

Methods based on the development of conditioned reflexes are used to study impairments of the cognitive sphere in experimental neuroses.

Passive assumption with a negative (painful) assumption for assessing the memory of animals. The method is based on the natural tendency of rats to avoid illuminated space. The animals are placed in a lighted cage. On the first day of training, rats are shocked in a dark chamber. After that, the time spent by the animal in the illuminated place is examined, which is about two minutes. People have studied the number of rats, not avoiding the light chamber, entering time to the dark chamber at the first painful stimulation and the data after the start of the experiment after 24 hours.

Active avoidance with a negative (painful) attachment. It is investigated in a cage divided by a vertical partition into two compartments. There are grids in the floor through which an electric current is supplied. The strength of which is selected individually for each rat. Skill formation begins with a sound or visual signal. If, after the signal, the rat does not leave the dangerous place within ten seconds, it receives an electric shock. The experiment ends after 80% of the intact animals have developed the skill. Training is considered successful if the rat avoided pain stimulation 18 times in 20 cases. In the study of long-term memory, the rats did not receive an increase in pain, but the disappearance of the skill was investigated over 10 days. The average number of correct answers is fixed depending on the number of presentations, the learning curve (the relative number of animals that achieved stable formation of the skill with a given number of tests) and the average value of the pain threshold, the percentage of erroneous answers, and the rate of expiration of the skill. Learning in the positive (food) reinforcement maze – T, V, or cruciform mazes are used for this test.

The weight of rats is measured before limiting their diet, after the first day of the experiment and after the completion of the learning process. The average number of correct answers is recorded depending on the number of manifestations, emotional reaction to the labyrinth, body mass friction during the learning process, the rotation of the given viewer during the visitor's immobility over time, the length of the path traversed in the maze, the average, maximum and minimum speed at which the rat moved through the compartments, the number of turns and circles in place, activity in the vertical and horizontal planes. The experiments continue until the learning criterion is reached by at least 80% of the animals in the control group. In the absence of differences in the learning rate, the memory of trained rats is examined. In this case, it is necessary that the rats receive the same number of reinforcements in the learning process [2, 9, 10, 18, 22, 24].

Conclusion

Thus, an important role in the emergence of neuroses is played by the type of higher nervous activity, as well as its components – memory, thinking, attention, and the emotional sphere.

Neuroses are not only a functional pathology of the nervous system, but they also have manifestations at the morphofunctional level in the form of ultrastructural and biochemical changes in neurons. There are numerous manifestations of somatization of neuroses. It manifests in the form of pathology of the cardiovascular, endocrine, digestive and other body systems.

Taking into account the type of higher nervous activity, modeling of neuroses in animals deepens the functions of the negative system and its adaptation to negative influences thus creating the basis for further clinical research on the prevention and treatment of neuroses.

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