REVIEWS

Pathologic Integrative Complexes in the Nervous System

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All pathological processes in the nervous systems begin with its damage ("breakdown", according to I. P. Pavlov), which disturbs the integrity of CNS, interrupts neural connections, produces structural defects, inhibition and disintegration of physiological systems and other structural and functional formations. All these changes do not constitute the pathological process by themselves, but initiate it and provide conditions for its implementation. The development is realized via endogenous mechanisms in the damaged nervous system, in particular through the formation of new pathologic integrative complex consisting of primarily damaged and secondarily altered neural structures. By conditions of their appearance and the results of their activity, such integrative complexes are pathologic. They play a role of a pathogenetic mechanism responsible for the development of a pathological process.

In terms of neuronal relationships, this pathological integrative complex is an aggregate of hyperactive neurons, which generates uncontrollable impulse discharges and therefore can be considered as a generator of pathologically enhanced excitation. At the systemic level, such integration is a new pathodynamic organization produced by primarily and secondarily changed subdivisions of CNS. Such organization is a pathological system (PS) with pathogenetic activity.

Generators of pathologically enhanced excitation

Formation of generators in CNS can be modeled by agents disturbing neuron inhibition or by hyperactivity of neurons. Inhibitory deficiency is a necessary condition for the formation and function of the generators. In the former case this deficiency is primary, and in the latter case it is secondary.

Figure 1 demonstrates the formation of a hyperactive generator in the giant nucleus of the medulla oblongata under the effect of tetanus toxin, which disturbs various types of inhibition. Normally, near-threshold stimulation of cutaneous nerve induces only a minor response in this nucleus. After microinjection of tetanus toxin, the amplitude and frequency of discharges of particular neuron groups gradually increases in parallel with the progress of disturbances in inhibitory mechanisms (Fig. 1, *2, 3*). Four hours postinjection, single stimulus of the same strength applied to cutaneous nerve produced intense discharges, which persisted for an indefinitely long period. It attests to appearance of self-sustained excitation in the nucleus or the formation of a network generator.

The generator can appear as a result of intense and long-term synaptic excitation or direct electrical stimulation of cerebral structures. For example, single series (5 electrical pulses) applied to the somatosensory cortex in rats induces no poststimulation discharges, but such discharges appear after the third and, especially, after the fourth series. These long-term charges grow in frequency and strength and include epileptic peak-wave complexes. Such self-maintaining poststimulation discharges with increasing intensity, frequency, and duration attest to spontaneous activity of a network generator, which needs no additional stimulation for persistent long-term excitation. The epileptic foci arising under natural conditions in the cortex and other cerebral subdivisions and characterized by self-maintaining electrical activity are also network of hyperactive generators.

Disturbances of inhibitory mechanisms in neurons composing the generator lead not only to their activation, but also to structural and functional rearrange-

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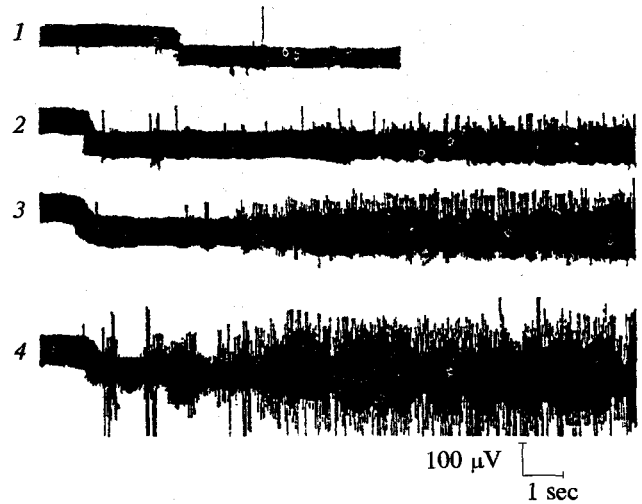

Fig. 1. Formation of a generator in giant nucleus in feline brain after injection of tetanus toxin. Activity in the nucleus (focal leading) was provoked by weak electrical stimulation (single stimulus 0.1 msec) of sciatic nerve: *1*) under normal conditions; *2*, *3*, *4*) 2, 3, and 4 h after injection of tetanus toxin into the nucleus.

ments. Indeed, injection of tetanus toxin into the lateral geniculate body (a subdivision of the visual analyzer) disturbs its inhibitory connections. As a result, neurons of various groups with initially different activity produce a new group, where neurons react to stimulation similarly. These neurons form the structural and functional basis of a generator. A single flash excites the generator, which evokes generalized epileptiform activity recorded in various cerebral structures and in muscles.

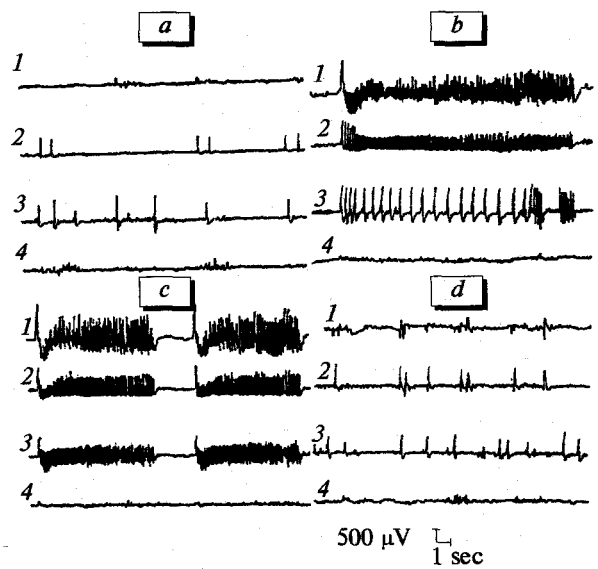

Fig. 2. Formation of a complex of epileptic foci in feline brain with similar activity under the effect of the dominant focus. *1*) orbital cortex; *2*) coronary gyrus, *3*) posterior sigmoid gyrus, *4*) anterior sigmoid gyrus. *a*) after application of penicillin and strychnine; *b* and *c*) 1 and 3 min after application of acetylcholine and neostigmine methylsulfate; *d*) 2 min after application of nembutal.

The generator formed in Deiters' nucleus makes this nucleus hyperactive, and its discharge drastically increases and prolongs spinal monosynaptic reflexes. The latency of this discharge is shortened, and the sensitivity of monosynaptic reflexes is drastically increased. All these phenomena attest to hypersynchronization of neurons in the generator producing this discharge. This is a universal phenomenon, which also takes place, when the centrifugal discharge from generator formed in the medulla oblongata (giant nucleus) produces descending inhibition of spinal reflexes. In this case, the inhibitory discharge is formed with shortened latency, and its effect (inhibition of reflexes) is drastically increased and persisted for a long time.

A pathodynamic organization producing PS also represent a pathologic integration formed at the system level from primarily or secondarily modified subdivisions of CNS. It is formed due to plasticity of CNS, which consolidates not only biologically useful connections that provide the development and activity of CNS, but also the biologically negative effects related to activity of PS.

Pathological determinant

In many cases the important role in the formation of PS is played by a structure of CNS, which becomes hyperactive under the effect of hyperactive generator and acquires capacity to affect related structures and integrate them into PS. This system-forming department, which determines activity of the entire system and its constituents plays a role of a determinant.

Figure 2 illustrates the formation of epileptic system from cortical foci under the effect of pathological determinant. In this experiment, two independent epileptic foci were formed in areas *2* and *3* by application of penicillin (0.5%) and strychnine (0.1%) (Fig. 2, *a*) that were discontinued after appearance of activity. Then a new and more powerful focus was formed in area *1* by application of acetylcholine (10%) and neostigmine (0.5%). This new focus modulated epileptic activity in areas *2* and *3*: in area *2* its character became very similar to that of area *1*; in area *3*, pronounced activation was observed together with the appearance of new components typical of area *1*. Three minutes after application of acetylcholine and neostigmine to area *1*, all three foci (areas *1*, *2*, and *3*) produced a complex with uniform "acetylcholine" activity. In intact area 4, not treated with convulsants, electrical activity remained unchanged (Fig. 2, *c*). Therefore, all three foci formed an epileptic system with uniform epileptic activity generated in area *1*. This dominant focus integrated all foci into a system and determined its activity. It is also confirmed by the fact that inhibition of the determinant focus with by

nembutal (6%) led to disintegration of this system and epileptic foci in areas *2* and *3* became independent (Fig. 2, *d*).

By a number of features, the determinant of a PS is similar to so-called "diseased area" in the brain described by I. P. Pavlov. Activation of this area evokes a systemic behavioral reaction formed under the effect of this generator.

Pathological system

Pathological system is a new pathologic integration consisting of primarily and secondarily modified CNS structures, whose activity is disadaptive and pathogenic. Pathogenic nature is the most important feature of PS, which distinguishes it from other physiologic systems, whose activity is adaptive and provides useful effect. A vivid example of PS is pathological scratching reflex. Its determinant is formed by spinal apparatus of the scratching reflex, which becomes hyperactive. Pathological scratching is manifested in intensive scratching of the projection area of this reflex, which sometimes leads to tissue rupture. In spite of its obvious noxious effect, the animal cannot stop this forced behavior.

The concept of "pathological system" was initially met with skepticism resulting from incorrect interpretation of the nature of PS. According to P. K. Anokhin, every physiological system, which performs a certain function aimed at a biologically useful result is a functional system. Some researchers drew incorrect inference from this thesis: if activity of a set of interacting biological structures does not lead to useful result, it cannot be a system. However, the cornerstone of any system is interaction of its elements that produces a new property. Interacting CNS subdivisions can form physiological or pathological system depending on the character and result of its activity: adaptive and useful effects are typical of physiological systems, while pathogenetic effects correspond to a pathological system.

Figure 3 shows principal scheme of structural and functional organization of PS induced by a pathological determinant. Determinant with its activation mechanism (generator, G-D unit) is the key system-forming element. Pathological system also includes intermediate (I) unit and the central efferent (CE) units. In addition, if the system has an output to the periphery, it includes a peripheral organ, which becomes the target organ (TO unit). In this case, the result of PS activity is functional modification of the organ manifested by corresponding pathological effect (PE unit). This fragment illustrates a mechanisms of disturbances in the nervous regulation. If the terminal element of PS is not a peripheral organ but a CNS structure, the pathological effect is manifested in disorder of the corresponding CNS function.

Activity of PS entirely depends on its determinant, therefore its lifetime is determined by the duration of PS activity. The work of the complex of epileptic foci with uniform activity described above can illustrate this property.

Consolidation of internal systemic positive feedback and the corresponding stabilization of PS underlies chronization of PS and the corresponding pathological process. These relationships enhance PS resistance to both endogenous control and therapeutic interventions.

The basic pathogenetic importance of PS is its role as structural and functional basis of neuropathological syndromes. The latter is a clinical manifestation of PS activity. Each syndrome has its own PS. Relatively simple PS are manifested by symptoms and monomorphous syndromes, while complex and diversified PS consisting of different CNS subdivisions are responsible for polymorphous syndromes, for example parkinsonism with its characteristic triad: akinesia, rigidity, and tremor. These simple syndromes result from activity of secondary determinants formed under the effect of a primary determinant in the caudate nuclei. It is also important that hyperactive PS concomitantly inhibits normal physiological systems. This property aggravates CNS disorganization.

Elimination of PS during recovery and under the effect of inhibitory drugs is characterized by certain regularities. Reduction of PS starts from constituent parts least affected by the determinant followed by suppression of dependent elements. Activity in the determinant structure persisted for a longer period in comparison with other elements. Residual activity of some elements of PS (in particularly, the determinant) after its disintegration and elimination of the corresponding syndrome is the endogenous risk factor of relapse. Breakdown of inhibitory control and compen-

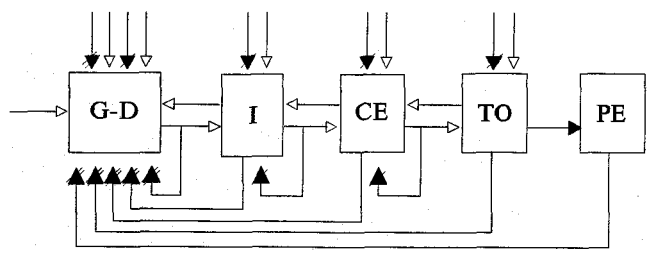

Fig. 3. Principal scheme of structural and functional organization of a pathological system induced by pathological determinant. *G-D*: pathological determinant with generator; *I*: intermediate elements of pathological system; *CE*: central efferent elements; *TO*: target organ; *PE*: pathological effect. Positive and negative feedback connections are shown by the light and dark triangles, respectively. Ineffective and disturbed inhibitory mechanisms are shown by crossed and double-crossed solid triangles, respectively.

sation, stimulation of the former dominant structure and entire PS restore PS. In this process, the determinant is restored earlier than other elements of PS. Even the latent traces of structural and functional alterations of the former determinant and PS can be reactivated by new pathogenetic factors. This is the mechanism of restoration of PS and the entire syndrome.

Modeling of neuropathologic syndromes

Previously, the possibility of experimental modeling of neuropathologic syndromes in animals was vigorously denied and considered methodologically incorrect. However, this viewpoint did not take into consideration the generality of biological mechanisms in higher animals. In addition, this approach models only individual neuropathologic syndromes, but not the nosologic forms of CNS diseases. Recent studies showed that some symptoms of CNS pathology can be experimentally reproduced in higher animals.

The theoretical basis for the development of experimental models of neuropathologic syndromes is our theory of generator, determinant, and systemic mechanisms of these syndromes.

The methodical principle of the development of experimental models of neuropathologic syndromes is the follow: a generator is induced by application of convulsant agents (tetanus toxin or penicillin) to a pathogenetically important structure of CNS, which makes this structure hyperactive, and this structure acts as a determinant, which induces formation of PS. Clinical manifestation of such PS is a modeled neuropathologic syndrome.

Using this method, we developed experimental models of various neuropathologic syndromes: central pain syndrome of spinal origin (generator in the dorsal nuclei of lumbar spinal segments), trigeminal neuralgia (generator in the caudate nucleus of the trigeminal nerve), central pain syndrome of thalamic origin (generator in intralaminar nucleus of thalamus), vestibulopathy (persistent rotation of an animal about its the longitudinal axis, generator in the lateral vestibular Deiters' nucleus), visual syndrome similar to visual hallucinations in cats (generator in the lateral geniculate body of the visual analyzer), photogenic epilepsy in rats (seizures provoked by light flashes, generator in the lateral geniculate body), parkinsonian syndrome with akinesia, rigidity, and tremor (generator in the proximal area of the caudate nuclei), pathological sleep in cats (an animal sleeps persistently and awakes only for physiological reasons, generator in the somnogenic system), catalepsia-catatonia syndrome (an animal maintains imparted uncomfortable posture, generator in the basal nuclei). This method allows to model various disturbances of higher nervous activity and behavior. For example, a generator formed in the lateral hypothalamus, which is responsible for food-procuring motivation, produces an experimental model of pathological food-procuring behavior: a rabbit trained for instrumental procuring of food persistently performs conditioned reaction, although it may not be able to eat all procured food. Such a reaction is an example of forced behavior, which accompanies many forms of CNS diseases and psychic disorders. The forced behavior, rituals, and obsession that cannot be stopped voluntarily by a patient, are demonstrative examples of PS activity affecting the higher nervous activity.

Single injection of a low dose of convulsant (penicillin) into emotiogenic structure (the nucleus in the terminal plate bed in feline limbic system) provokes a complex emotion-behavioral syndrome (abnormal zoosocial behavior, sham aggression, reactive analgesia, eating of inedible objects, refusal of normal food, *etc.*), which gradually progresses and culminates by catatony with fatal outcome.

The possibility of producing the experimental models of various neuropathological syndromes on the basis of the general theory of generator, determinant, and systemic mechanisms attests to productivity of this theory. Our data suggest that anticonvulsants can be benefitially used in the complex antipathogenic therapy with due account for the mechanisms of their inhibitory action and the nature of neuropathological syndromes.