REVIEWS

Pathological Integrations in the Central Nervous System

G. N. Kryzhanovskii

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Damage to the nervous system is a causal and conditioning event leading to the development of pathological processes mediated via such endogenous mechanisms as the formation of integrative complexes from damaged and secondary changed nervous structures that are pathological by their nature, mechanisms, and effects. At the level of neural relationships such pathological integrative complex (PIC) is formed by an aggregate of hyperactive neurons (generator of pathologically enhanced excitation, GPEE) producing uncontrollable ongoing flow of nerve impulses. At the systemic level, PIC is a new pathodynamic system composed of various subdivisions of the CNS, which acts as a pathological system. The subdivision of the CNS containing GPEE assumes the role of a pathological determinant due to its enhanced activity. This pathological determinant induces the formation of a pathological system and controls its activity at the early period of its genesis. Every neuropathological syndrome is a clinical or behavioral manifestation of pathological system activity. Pathological determinant and pathological system are general biological categories that fall outside the scope of nervous disorders. They can arise in various systems at the micro- and macroscopic levels and induce systemic pathology.

Key Words: *pathological integrative complex; pathological system; central nervous system*

The formation of integrative complexes from various nervous structures (neurons, synapses, *etc.*) is a result of inherent plasticity of the nervous system. This process goes on persistently under alternating internal and environmental influences and underlies conditioning of an adequate physiological reaction to specific stimuli. Manifestation and result of these integrative processes in the nervous system are formation of new nervous associations.

Damages to the nervous system lead to structural and functional defects, disturb nervous associations and synaptic processes. Such processes were figuratively termed by I. P. Pavlov as "breakdown". However, such a breakdown is only a part of the events induced by a damage to the nervous system. The damage *per se* is not a part of pathological process, but it acts as a trigger cause and condition for its development, which is effected via endogenous mechanisms of the damaged nervous system, in particular, the formation of integrative complexes combining primarily and secondarily modified nervous structures. Such the formations are pathological by their nature, mechanism, and effects and referred here as pathological integrative complexes (PIC). At the level of neuronal relationships, PIC is an aggregate of hyperactive neurons producing hyperintensive uncontrollable flow of nerve impulses: a generator of pathologically enhanced excitation (GPEE). At the systemic level, PIC is a new pathodynamic system composed of various subdivisions of the CNS, which acts as a pathological system (PS).

Generator of pathologically enhanced excitation can be formed in various subdivisions of the CNS. A prerequisite condition of GPEE formation and activity is deficiency of inhibitory mechanisms in neuron po-

Institute of General Pathology and Pathological Physiology, Russian Academy of Medical Sciences, Moscow

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pulation. Disturbance of the inhibitory mechanisms leads to structural and functional rearrangements and the formation of a new group of specific neurons with similar characteristics from neurons of various groups that initially had different functional properties. This new group of neurons is the basis of GPEE.

It was showed that the degree of disturbance of inhibitory mechanisms in the GPEE determines its activation by provoking stimulation, the number of neurons involved in GREE, the degree of its excitation, and the effects on the CNS. These features were observed in GPEE formed in various subdivisions of the CNS. Progressive impairment of the inhibitory mechanisms and the increase in GREE neuronal excitability due to synchronization of neuronal activity facilitate activation of GREE in response to provoking stimulation and reduce the latency of its effect on the CNS, which become paroxysmal. The same is true for inhibitory effects of the generators in various CNS structures, which attests to the existence of universal mechanisms underlying their activity.

Neurons of GPEE are not only a cell population. They form PIC characterized by neuronal interactions that are realized via both synaptic and nonsynaptic pathways. The nonsynaptic mechanisms involve bioactive substances released by excited neurons (K^+, NO, glutamate, *etc.*) and direct neuronal excitatory effect (cross-excitation). Presumably, the following structures participate in the synaptic transmission: activated synapses that were latent under normal conditions, new synaptic formations (reactive synaptogenesis), intercalary neurons, extensive collaterals, and other neurons. New synaptic interaction is underlain by augmented plastic rearrangements in neuronal clusters under conditions of hyperactivation and disturbed inhibitory mechanisms.

An illustration of neural interaction in PIC is interneural relationships in cortical epileptic foci. In these foci the most active neurons play a trigger role and stimulate other neurons recruiting them in electrogenesis and inducing focal epileptiform activity.

It should be emphasized that the complex of nonsynaptic and synaptic mechanisms determines functioning of a neuronal cluster as a network generator.

The neuronal interaction under conditions of disturbed inhibitory mechanisms and enhanced excitability enables long-term, self-maintaining and even increasing activity of the generator, which requires no additional stimulation. This property is most important for the development of GREE as a PIC of neurons with disturbed inhibitory mechanisms and enhanced excitability.

When the inhibitory mechanisms are preserved, the generator is activated by strong stimuli via a definite input. In contrast, when the inhibitory mechanisms are severely damaged and excitability is considerably enhanced, the generator can be activated by weak stimuli, as well as by stimuli of different origin incoming via different inputs. Further imbalance between inhibitory and excitatory mechanisms culminates in spontaneous excitation of the generator.

The discussed features of activation and performance of generators are manifested in various degree in the character of paroxysms in neuropathological syndromes.

Being a PIC, generator *per se* does not induce pronounced clinical pathology of the nervous system. Neuropathological syndrome can be caused by a more complex PIC composed of modified subdivisions of the CNS. It is formed at the systemic level as a new pathodynamic association (pathodynamic system, PS). The role of a generator in this process is modification of the CNS subdivision containing this generator, which becomes hyperactive and therefore can essentially affect other subdivision of the CNS connected with it. Functional integration of modified and affected CNS subdivisions forms PS and determines its activity. These properties of the hyperactive subdivision of CNS specify its determinant role in PS induced by it.

The role of this determinant in the formation of PS as a complex PIC is seen in the example of the development of PS in the cerebral cortex as a cluster of epileptic foci under the effect of a more powerful focus, which assumes the role of a determinant. Application of a weak convulsant solution (strychnine) to the coronary and sigmoid gyri produces weak solitary epileptic foci in these regions. Application of a high concentration of acetylcholine with neostigmine to the orbital cortex produces a powerful epileptic focus with acetylcholine-specific activity. This focus modifies activity of the preexistent foci and they acquire the properties of acetylcholine-induced focus. At the final stage, activity of the three foci is characterized by a common synchronized epileptiform pattern originated from the determinant focus. This complex of epileptic foci with common characteristics of epileptiform activity represents a PS, i.e. an epileptic system formed by modified cortical structures under the effect of a determinant focus. When determinant focus is suppressed by nembutal, the system disintegrates into isolated foci. Thus, the pathological determinant acts not only as a system-forming, but also as a system-stabilizing factor maintaining the integrity of PS as a PIC.

The described properties of a determinant are clearly manifested in PS of acute origin, for instance in the above described complex of epileptic foci. At the later stages of the pathological process, i.e., in chronic PS, the role of primary determinant fades away, and PS

exists even after elimination of PS due to consolidation of integrative connections as a result of neuronal plasticity.

Plasticity of the nervous system is a blind undirected force. Plastic processes consolidate not only biologically favorable, but also pathological connections. This is the reason why PIC (specifically, aggregates of hyperactive neurons, GPEE and PS) becomes resistant to endogenous regulatory influences and therapeutic interventions.

It has been shown that the larger PIC, the higher its resistance to regulatory influences. For example, a single cortical epileptic focus is less resistant to inhibitory influences of the antiepileptic system (electric stimulation of the caudal pontine reticular nucleus) than a complex consisting of 2 foci, while the latter is less resistant than a complex consisting of 3 foci, *etc.*

Deficiency of endogenous inhibitory mechanisms in the system enables its escape from general integrative control of the CNS that is mediated via inhibitory mechanisms. Unlike physiological system, in which the negative feedback relationships regulate activity of its components, in PS such control is absent or ineffective. At the same time, plastic processes consolidate positive connections due to their persistent activity.

The PS is a pathophysiological mechanism and pathogenetical basis of neuropathological syndromes. All neuropathological syndromes are clinical and behavioral manifestations of activity of the corresponding PS. A salient feature of PS is its enhanced activity, which inhibits function of physiological systems. These properties of PS underlie disorganization of CNS function.

The basic principles of the theory of generator and systemic mechanisms of neural disorders provide the basis for modeling of various neuropathological syndromes in animals. These models are based on induction of GPEE by microinjection of convulsants or electric stimulation of the CNS structure specific for a certain neuropathological syndrome. GPEE hyperactivates this subdivision and transforms it into a determinant inducing the formation of PS. The clinical manifestation of activity of this newly formed system is the corresponding neuropathological syndrome.

This principle is reproduced in the models of some neuropathology syndromes related to various types of CNS activity. Generators in the central structures of the nociceptive system in rats and cats causes the corresponding pain syndromes. GPEE in the lumbar dorsal horns of the spinal cord provokes spinal pain syndrome; GPEE in the trigeminal nucleus caudalis induces trigeminal neuralgia; GPEE in the nucleus gelatinous of the thalamus provokes thalamic pain syndrome. When GPEE is formed in Deiters' (lateral vestibular) nucleus, it produces vestibulopathy manifested in persistent rotation of a rat about the longitudinal axis. GPEE in the lateral geniculate body (a part of the visual analyzer) results in photoreactive epilepsy in rats manifested in seizures provoked by illumination and in spontaneous seizures at the later stages. Such GPEE in cats can produce a syndrome similar to visual hallucinations: a cat persistently watches an object (for example, tail tip). GPEE formed in the somnogenic system (orbital cortex) causes pathologically prolonged sleep in cats. Formation of GPEE in both caudate nuclei due to dopamine deficiency produces typical parkinsonian syndrome characterized by muscle rigidity, akinesia, and tremor. These manifestations partially and even completely disappear after inhibition of this generator by dopamine injection into the caudate nuclei via implanted cannulae.

Similar manifestations of PS formation accompany disorders of the higher nervous activity. In rabbit with GPEE the lateral hypothalamus responsible for food-procuring motivation, this part of hypothalamus acts as a pathological determinant inducing the formation of a food-procuring PS (excessive eating). If the rabbit was trained to gain food by, for example, pulling a ring, it pulls it virtually persistently, although it may not be able to eat all procured food. Thus, the functional system of conditioned food-procuring behavior was transformed due to the action of a pathological determinant into disadaptive PS. Function of this PS is a model of compulsive behavior characteristic of neurological and psychiatric disease, which cannot be controlled by patient.

When GPEE is formed in the nucleus of terminal plate bed in the limbic system, it produces the complex polymorphous syndrome characterized by catatonia-catalepsy, disturbances in zoosocial behavior, sham aggression, reactive analgesia, *etc.* It is noteworthy that this state, which is provoked by a single microinjection of a subconvulsive dose of penicillin into the nucleus, can progress without additional pathogenetical influences and culminate in general catatony with fatal outcome.

The discussed phenomena indicate that PS as clusters of hyperactive neurons (GPEE) and pathodynamic structures (PS) are the endogenous mechanisms of pathological processes in the CNS. Understanding of these pathogenetical mechanisms opens new approaches for modeling and treating of nervous disorders.

When PS formed in the CNS is connected with a visceral organ, it disturbs the function of this organ. If these regulatory disturbances are great enough to constitute a nosologic form, this is the case of neural disorders.

The conceptions of PS and pathological determinant as the pathological mechanisms can be applied not only to nervous disorders. The pathological determinant and pathological system are general biologic categories that may involve various organs, systems, and basic mechanisms. An enzyme escaping from the control or a modified gene play the role of a pathological determinant provoking corresponding systemic pathology.

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