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Pathogenesis of epilepsy and mental diseases, the role of the blood-brain barrier in the context of neurochemical theories

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Abstract
In the article, in light of the hypothesis about the pathogenesis of epilepsy the author considers certain clinical manifestations of epilepsy, touches upon the neurochemistry of behavior, as well as neurotransmitter hypothesis of schizophrenia. According to the hypothesis, in epileptic patients, epileptogenic substances are permanently accumulating in the brain, which in the course of epileptic activity in the brain undergo metabolic changes requiring their removal from the organism. When the concentration of epileptogenic substances in the brain reaches a threshold value, they cause a seizure, and in lower concentrations, they cause epileptic activity typical for the interictal period. In the context of this hypothesis, there are discussed the clinical signs of epilepsy such as forced normalization, reinforcement epilepsy activity during the sleep deprivation and one of the paradoxical effect of antiepileptic drugs such as phenomenon when antiepileptic drugs prescribed cause an improvement of the electroencephalographic image but the clinical deterioration and increasing frequency of seizures, and the change of antiepileptic drugs give us the opposite results: improvement of the clinical picture and the deterioration of the electroencephalographic image. The author suggests names for this type of dissociation (discrepancy) between the clinical and electroencephalographic picture and for the electroclinical dissociation discovered earlier by Weiner, and also for clinical-electroencephalographic dissociation of forced normalization with the ability to easily give names to other types of clinical and electroencephalographic dissociation discovered in the future in patients with epilepsy. According to the supplemented hypothesis, epileptogenic substances, except that, during epileptic activity in the brain undergo metabolic transformations necessary for their removal from the body; there are alsoalternative transformation neurochemical pathways necessary for their further removal (elimination) from the organism. The hypothesis discusses the modern principles of epilepsy and mental diseases treatment. Forced normalization is considered as one of the manifestations of epilepsy aggravation and “clinical-electroencephalographic dissociation”. When reviewing biological antagonism of schizophrenia and epilepsy the author suggests a hypothesis that if an area of the brain producing epileptogenic substances and an area of the brain producing endogenic psychogenic substances causing psychopathology coexist simultaneously, then, in the event of a generalized convulsive seizure involving the brain in full, epileptogenic as well as psychogenic substances are released. At the same time epilepsy is demonstrated, while schizophrenia is not. The same could be the mechanism of therapeutic activity (effect) of electroconvulsive therapy. Psychogenic substances can also be released through interictal epileptic activity. The significance of the blood-brain barrier is considered. In addition to the antiepileptic and antipsychotic system of the brain, the concepts of the borderline and extracerebral antiepileptic and antipsychotic systems are proposed, where the blood-brain barrier is presented as the borderline antiepileptic and antipsychotic system.

Keywords: neuro mediators, forced normalization of electroencephalogram image, aggravation, biological antagonism of schizophrenia and epilepsy, behavior, blood-brain barrier

Introduction

Epilepsy is a chronic disease, the clinical manifestations of which can be both convulsive seizures and various mental disorders and is the object of study of clinical disciplines: neurology, psychiatry, neurosurgery. The history of studies on epilepsy and mental diseases counts many centuries [1,2], vast banks of clinical and physiological data has accumulated, paradigms related to etiology and pathogenesis are changed.However, a general theory combining and explaining these data has not been developed yet. Even in ancient times, mental disorders, including epilepsy, were studied with interest by Empedocles, Aristotle, Theophrastus, Democritus, and others. Hippocrates made a great contribution to the study of mental disorders and epilepsy. The etiology of most mental illnesses remains largely unknown. It is unclear the relationship in the origin of most mental illnesses of heredity, internally determined features of the body and environmental hazards, in other words, endogenous and exogenous factors. The pathogenesis of epilepsy, as well as psychoses, has also been studied only in a general way. ICD-10 (International Classification of Diseases 10th Revision) replaces the concept of "mental illness" with the more general and amorphous concept of "mental disorder". Researchers of various

profiles keep suggesting new theories and hypothesis striving to interpret various demonstrations of epilepsy and mental diseases, to unite them in a single concept [3, 4].

According to the current conception neurochemical mechanisms, disturbances associated with disorders of ionic, mediatorial and energetic processes leading to increased membrane penetration and resulting enhanced depolarization of neurons, their hyperexcitation, neuronal epileptisation, hypersynchronization, formation of epileptic focus and ultimately an epileptic system, play significant role in initiation of epileptic activity [3,4], which in the event of antiepileptic system (consisting of caudate nucleus, cerebellum, lateral hypothalamic nuclei, caudal pontine reticular nucleus) failure leads to development of epilepsy as a disease. An epileptic seizure that develops in epileptic foci localized in certain areas of the brain leads to psychoses and other mental equivalents [5].

Participation of hormonal and immune system in pathogenic process of epilepsy and mental diseases has been established and studies are still ongoing [6-8].

Attention of epilepsy researchers has recently been attracted by channelopathies – pathologic changes in channels of K+ and Na+ - receptors which make it impossible to maintain normal gradient of ion concentration on both sides of the membrane and condition paroxysmal depolarization of membranes. These defective sodium channels remain open too long resulting in neuronal hyperexcitation [9].

Two types of channelopathy are known: genetic, during which ion channel function is abnormal or absent as a result of mutation (genetic channelopathy is the major cause for idiopathic generalized form of epilepsy), and autoimmune channelopathy, when antibodies disrupt channel function. Recent studies have provided growing evidence for the existence of a third type - transcriptional channelopathies - resulting from changes in the expression of non-mutated channel genes [10].

Epilepsy associated with mutations in genes of some non-ionic channels has also been revealed [11].

The role of channelopathies in the development of other mental illnesses is also being closely studied [12].

The opioid neuropeptidergic system and the peptides produced by it - enkephalins, endorphins, and others that play the role of neurotransmitters - have a significant influence on the development of pathology [13, 14].

Glutamatergic system plays important role in induction of epilepsy including in itself NMDA-receptor - ionotropic glutamate receptor, selectively binding N-methyl-D-aspartate (NMDA) and neurotransmitter glutamate. Glutamate is the basic neurotransmitter for excitatory synapses in the brain. Synapses which use glutamate as a transmitter are up to approximately 50% localized in neurons of central nervous system. The largest quantity of them can be found in telencephalon and hippocampus [15].

The neurotoxic effect of elevated levels of glutamate concentration in the development of mental illness and epilepsy is being investigated [16].

In physiological conditions NMDA-receptors are activated at millimolar concentrations of glutamate present in synaptic cleft for several milliseconds [17].

During pathological activation receptors are activated at micromolar concentrations but for a significantly longer period of time [18]. As a result Ca^{2+} concentrations are increased in cells and K+ ions are accumulated in extracellular space. Neuron saturation with calcium ions serves as trigger for mobilization of ions from intracellular depot [19, 20].

Increased concentration of extracellular K+ are viewed as one of the major mechanisms for neurons involvement in epileptic process by many authors.

The participation of disorders of potassium and calcium metabolism in the development of other mental illnesses is being studied [21, 22].

Another possible pathogenetic mechanism of epilepsy includes mutations, resulting in ineffective activities of gamma-aminobutyric acid (GABA) (most widespread inhibitory neurotransmitter of the brain) [23]. As the most common inhibitory neurotransmitter in the brain, GABA and disorders of its metabolism are also the object of increased interest of psychiatrists who study other psychiatric nosologies [16].

Conducted in any direction of research to study the pathogenesis of one mental illness, it is naturally further used to study the pathogenesis of other mental illnesses.

It is clear that the above directions of research for studying the pathogenesis of epilepsy are also conducted to the study of other mental illnesses, which is reflected in the literature we have cited.

Neurochemical Theory of Epilepsy

Hypothesis

A hypothesis is suggested [24] in relation with metabolic mechanisms of pathogenesis of epilepsy in respect of which several clinical manifestations of epilepsy were reviewed, among them the phenomenon of forced normalization of electroencephalogram image (EEG) [25]. According to this hypothesis epileptogenic substances are constantly accumulating in the brain of an epileptic patient and when reaching the threshold value cause a seizure. In addition, epileptogenic substances during epileptic activity in the brain undergo metabolic transformations required for their removal from the body. If the concentration of epileptogenic substances in the brain fails to reach the threshold value, they cause weak epileptic activity mostly reflected in epileptic bioelectric phenomenon, typical for EEG pattern of interictal period. Moreover, certain parts of epileptogenic substances apparently ‘drive out’ interictal epileptic activity of the brain (part of epileptogenic substances is released during interictal epileptic activity).

Certain Clinical Manifestations of Epilepsy

The authors have reviewed the following clinical manifestations of epilepsy from the perspective of the given hypothesis.

Cases when prescription of anti-epileptic drugs is associated with improved electroencephalographic pattern, but with the deterioration of the clinic and frequent seizures, are observed in practice of epileptologists [26, 27]. The drug change leads to the opposite result - improvement of the clinical picture and the EEG deterioration.

According to the hypothesis, the given clinical manifestation of epilepsy may be explained as follows. In the course of interictal epileptic activity of the brain parts of epileptogenic substances are released, as a result of which the threshold concentration of the given biogenic amines is slowly accumulated and reaches the maximal value within a longer period of time. Thus time intervals between seizures grow in proportion with the intensity of epileptic activity of the brain during interictal period. By prescribing certain anti-seizure medications it may be achieved that cell neurons will not be responsible for epileptic activity at sub-threshold concentration of epileptogenic substances, however, the seizure will still develop if the concentration of epileptogenic substances reaches the threshold value. In such case, in terms of absence of epileptogenic substance release through epileptic activity of the brain during interictal period their accumulation up to the threshold value will be faster, seizures will develop more frequently, however interictal EEG pattern will improve.

In case of appropriate ("successful") selection of anti-seizure drugs if improvement of EEG pattern including its normalization (known as forced normalization of EEG) as well as improvement of clinical condition including total elimination seizures is achieved, the patient often experiences psychogenic discomfort to the extent when in order to get rid of it he/she stops administration of medications thus provoking a seizure [25, 28].

When explaining the given fact by forced normalization of EEG it should be noted that anti-seizure drugs are selected so that neurons are exhausted (or blocked) and stop responding by epileptic activity at the threshold as well as sub-threshold value of epileptogenic substance concentrations. The given biogenic amine accumulate in the brain, which is manifested in psychoneurological disorders. However the seizure provoked by the patient himself/herself removes epileptic substances which improves mental health of the patient.

It is also common knowledge that during physiological sleep epileptic bioelectric phenomenon is much more frequently revealed. Sleep deprivation leads to emersion of epileptic bioelectric phenomena while waking, and in case of presence of the latter – to increase of their frequency. Prolonged deprivation may provoke a seizure [4, 29].

As for the above mentioned clinical manifestation of epilepsy, according to the hypothesis, sleep deprivation is more likely to lead to a quicker accumulation of epileptogenic substances as they are not eliminated through increased epileptic activity during sleep. High concentration of epileptogenic substances leads to increased epileptic activity while waking. And prolonged sleep deprivation leads to accumulation of epileptogenic substances up to the threshold value thus provoking a seizure.

Supplement to the Hypothesis

However, the proposed hypothesis does not explain the whole spectrum of contemporary principles for treating epilepsy, according to which by subscribing anti-epileptic drugs cessation of epileptic bioelectric phenomena and normalization of EEG, as well as cessation of seizures are achieved, and anti-epileptic drugs are usually discontinued after two years upon cessation of seizures and normalization of EEG [30]. An supplementation to the given hypothesis was proposed later [31]. According to this supplementation, epileptogenic substances, in addition to undergoing metabolic transformations required for their further removal from the body during epileptic activity in the brain, also have alternative neurochemical metabolic pathways of transformation required for their further elimination from the body.

When epilepsy responds to contemporary treatment principles alternative neurochemical pathways of metabolism of epileptogenic substances required for their further elimination from the body are activated. This additional chain of neurochemical transformation may be activated spontaneously when certain concentrations of epileptogenic substances are reached in the brain, this mechanism may function under normal conditions, simultaneously preventing occurrence of epileptic seizure at increased concentrations of epileptogenic substances in the brain. In epilepsy, this chain may be activated under the influence of anti-epileptic drugs.

In case of presence of a certain biochemical defect causing absence of alternative pathways of metabolism of epileptogenic substances the phenomenon of forced normalization may be observed, as well as the above described phenomenon, observed during epilepsy treatment, when prescription of anti-epileptic drugs is accompanied by improvement of EEG pattern but deterioration of clinical condition and increased frequency of seizures, while changes in the prescribed drugs lead to a reversed effect – improvement of clinical condition and deterioration of EEG pattern, also the phenomenon of activation of epileptic activity by deprivation of sleep up to development of epileptic seizure.

With successful treatment of epilepsy - when the patient is cured, and after the withdrawal of antiepileptic drugs, he does not have a seizure and normalization of the EEG is noted, it is possible that the production of excess epileptogenic substances decreases during treatment or the alternative neurochemical chain of the transformation of the epileptogenic substances continues to function even after withdrawal taking antiepileptic drugs. It is possible that during the treatment, in some cases, both of these sanogenetic mechanisms may be included.

If these sanogenetic mechanisms are not turned on, the patient is not cured, and is forced to take antiepileptic drugs all his life.

Kharibegashvili *et al* [31] previously had proposed to name the phenomenon when the prescription of antiepileptic drugs is accompanied by an improvement in the electroencephalographic picture, but with a deterioration in the clinic and an increase in seizures, and a change in drugs leads to the opposite result - an improvement in the clinical picture and a deterioration in the electroencephalographic picture --,,clinical-electroencephalographic dissociation'', in short,,,clinical-EEG dissociation".

Even earlier, Weiner S. P. and al [32] proposed to name the phenomenon observed in neonatals in which the clinical component of a seizure occurs from time to time with or without an electrical correlate -,,electroclinical dissociation''. One must think that the further development of epileptology will open up new varieties of discrepancy between the expressions of the clinical and electroencephalographic pictures (manifestations) in patients with epilepsy. Therefore, it may be better if all types of discrepancy between the clinical and electroencephalographic picture in epilepsy will be called one of the above terms: electroclinical dissociation or clinical-EEG dissociation and provide them with an abbreviation (such as magnetic resonance imaging has the abbreviation MRI): electroclinical dissociation -ECD or clinical-EEG dissociation - CED, and additionally specify what type of discrepancy between the severity of the clinical and electroencephalographic picture they refer to.

For example, if we accept the term "clinical-EEG dissociation" (CED) to denote all types of inconsistencies in the severity of clinical and electroencephalographic pictures in epilepsy, then the phenomenon described by Weiner S.P. and al, in which the clinical component of a seizure occurs from time to time with or without an electrical correlate in neonatals and called by them,,electroclinical dissociation" can be called,,neonatals clinical-EEG dissociation ", in short,,, neonatals CED". And the phenomenon described above, when the appointment of antiepileptic drugs is accompanied by an improvement in the electroencephalographic picture, but with a worsening of the clinic and an increase in seizures, and the change of drugs leads to the opposite result - an improvement in the clinical and deterioration of the electroencephalographic picture, and called,,clinical-electroencephalographic dissociation", one can call,,drug clinical-EEG dissociation", in short, 'drug CED".

Or, if we accept the term "electroclinical dissociation" (ECD) proposed by Weiner S. P. and al to refer to all types of inconsistencies in the severity of the clinical and electroencephalographic picture in epilepsy, then these phenomena can be called, respectively,,,neonatals electroclinical dissociation", in short,,,neonatals ECD" and,, drug electroclinical dissociation", in short,,, drug ECD".

While reviewing forced normalization and aggravation of epilepsy as a result of anti-epileptic drugs administration in connection with each other, it should be noted that in the overwhelming majority of cases of epilepsy aggravation normalization of EEG is not observed [25], while in case of forced normalization deterioration of the patient's condition is noted, which is evidenced by the fact that patients, unaware of forced normalization of EEG, often discontinue administration of anticonvulsants and provoke seizure in order to "improve" their condition.

From this perspective it is possible to agree with the authors [25] regarding forced normalization being one of the demonstration of epilepsy aggravation. In addition, this phenomenon may be viewed as "clinical-encephalographic dissociation" as improvements in electroencephalography (EEG) and deterioration of clinical picture is observed. And we can specify and name this type of,,clinical-encephalographic dissociation",,forced clinical-encephalographic dissociation", shortly,,forced CED''.

Cases of forced normalization in migraine are described, when, upon achieving remission and stopping episodic migraine attacks, it is accompanied by a psychiatric behavioral disorders. It must be thought that forced normalization occurs in migraine patients whose attacks are accompanied by an aura. During remission, there is an accumulation of psychogenic substances that cause an aura, since due to remission they are not consumed during attacks, which leads to mental disorders of behavior.

Certain mental manifestations of epilepsy was considered [33], among them the theory on biological antagonism of schizophrenia and epilepsy. Author touched upon the neurochemistry of behavior, as well as neurotransmitter hypothesis of schizophrenia, including dopamine theory of schizophrenia, and drew parallels with the given theory and the hypothesis he proposes.

Considering the significance of neurotransmitters, as well as endogenic psychogenic substances enhancing or inhibiting neurotransmitters production or their impact, attempts of applying the given hypothesis are feasible for explain other forms of normal or pathological brain activity.

Certain Mental Manifestations of Epilepsy

Epilepsy is characterized by neurological as well as mental clinical manifestations. Consider certain mental manifestations of epilepsy.

Regarding ambulatory automatism and other psychic epileptiform paroxysms, a multitude of data given in relevant literature links behavior (both, inborn and acquired - learnt) with neurotransmitters. Various neurotransmitter theories have been developed which explain different pathologies of behavior, psychic disorders, including schizophrenia, by excess number of certain transmitters or deficiency of others [34]. Dopamine hypothesis is dominant among these theories [35].

The author supports neurotransmitter hypothesis.

Inborn behavior derived from simple unconditioned reflexes to complex instincts (such as migration of birds in autumn to warm countries, returning of fish from oceans to rivers for spawning, striving of newborn turtles towards the sea); acquired behavior based on a complex of interrelated unconditioned and conditioned reflexes

with temporary connections and neuronal nets, chains and ensembles taking part in these forms of behaviors (both inborn and acquired), are connected to certain neurons [36]. While these neurons in their turn, function through certain excitatory or inhibitory neurotransmitters. Therefore, it is not surprising that rising or falling levels of certain excitatory or inhibitory neurotransmitters, their disbalance, lead to disorders various types of behavior.

It is interesting to review deprived behavior [36]. If any given behavior is deprived, neurotransmitters responsible for the given behavior are accumulated, as they (neurotransmitters) are not consumed in the process of the given behavior. When concentration level for the given neurotransmitter reaches certain threshold, forced manifestation of this behavior occurs, sometimes in distorted manner: being alone a person starts to speak to himself/herself, in case of sleep deprivation, one may see dreams while awake, during sex deprivation sex may be manifested perversely.

Thus according to the hypothesis suggested by us epileptiform psychic paroxysms, such as ambulatory automatism, clouded state, epileptic psychosis, are developed in the event of accumulation of certain neurotransmitters, stimulating certain neurons responsible for certain behavior, to the threshold values, after which epileptiform psychic paroxysm is developed during the course of which epileptogenic and psychogenic substances (epileptogenic substances may simultaneously serve as such (psychogenic)) undergo metabolic changes necessary for their further elimination from the body. These epileptiform psychoses develop as a consequence of an epileptic seizure, are ictal psychoses, and usually develop when the epileptic focus affects the temporal or frontal lobe.

Interictal psychosis can develop according to the mechanism of forced normalization, when the concentration of psychogenic substances, having reached a threshold value in the brain, causes psychosis, causing non-epileptic activity of the cells responsible for behavior, and the attack will not be accompanied by epileptic activity of cells and epileptic patterns on the EEG.

In this regard EEG examination of all psychic pathologies accompanied by paroxysms during the paroxysms as well as the inter-paroxysmal period is actual.

EEG examination results [37] reveal increase in B-activity during multiple (numerous) psychic diseases, while B-activity, as we know, is activated during cogitativity. It is interesting, that brain activity in patients with severe forms of schizophrenia resembles to the clinical pattern characteristic to people taking strong psychostimulants and amphetamine. In such case, if we presume that intensification of certain cogitative and other psychic processes are linked to increased production of certain excitatory neurotransmitters, then increase in production of these neurotransmitters will distort the given cogitative or psychic activity (causing “plus” symptoms such as delirium and hallucination). Lowering the level of excitatory or increasing the level of inhibitory neurotransmitters will initiate the appearance of “minus” symptoms.

Natural science is familiar with drawing analogies between multiple similar events as well as similarity between development mechanisms of these events.

This brings the proposition, that certain endogenic toxic psychogenic substances may also accumulate during non-epileptiform psychic paroxysms, among them autoimmune antibodies (a large majority of mental diseases, including schizophrenia, has endogenic character), which may themselves have neurotransmitter function or induce growth in production of certain neurotransmitters. When reaching specific threshold, they cause psychic paroxysm (non-epileptiform), during which psychogenic substances undergo metabolic transformation, necessary for their further eliminations from the body, but at the same time the EEG image will not reveal patterns characteristic to epilepsy. Therapeutic benefits of plasmapheresis during psychic diseases favors the existence of possible toxic endogenic psychotic substances (including autoimmune antibodies) [38].

Moreover, it is possible, that similar mechanisms of pathogenesis are in action during paroxysms of non-psychotic nature too (other than psychiatric part of medicine, such as general medicine) where other chemical substances, different from neurotransmitters, reach threshold value, for example, during hypertonic crisis – the substances increasing blood pressure, and which undergo metabolic changes required for their further elimination during this paroxysm.

Therapeutic benefits of sleep in treatment of Delirium Tremens are well-known [39]. The facts that during Delirium Tremens epileptic syndrome is often developed, while EEG imaging of epileptic patterns become more frequent during sleep, attracts the attention. Metabolic changes in neurotransmitters or endogenic psychogenic substances required for the elimination in the process of epileptiform, as well as non-epileptiform brain activity may enhance during sleep.

Kindling-effect [40] is noteworthy the essence of which is that frequent subthreshold stimulation increases convulsive readiness and may lead to spontaneous convulsions in previously healthy experimental animal.

Kindling may play important role in secondary epileptic syndromes (more often it may be a pathogenic element specifically in epileptic syndromes – secondary epilepsy) where primary focus of the disease, such as tumor, stroke, may play the role of subthreshold stimulators and provoke convulsive seizures as well as epileptiform mental paroxysms, reducing the activity threshold (concentration threshold) of epileptogenic substances.

Similarly, we may think that pathological focuses in the brain resulting from own irritant activity may decrease the activity threshold of endogenic psychogenic substances in pathogenesis of development of non-epileptiform psychic paroxysms, and promote development of secondary mental pathologies in neuropsychiatry [41].

Epilepsy and Schizophrenia

Biological antagonism of schizophrenia and epilepsy is identified [42]. In the event of presence of generalized epileptic seizures, characterized with seizures with loss of consciousness and tonic-clonic seizures of extremities (limbs) the brain is fully involved in the epileptic activity. In such case, if there is an area of brain producing epileptogenic substances and an area generating an excess of behavioral neurotransmitter, surfeit of which leads to psychopathology, then during convulsive seizures transformation and elimination of both neurotransmitters occurs, whereupon epilepsy is manifested and schizophrenia is not as during the seizures apart of neurotransmitters causing convulsive seizures abundance of neurotransmitters resulting in psychopathology are also released, and their levels (neurotransmitters resulting in psychopathology) fail to reach the level causing pathology of psyche. With convulsive therapy of schizophrenia, a similar process of transformation and elimination of neurotransmitters of behavior may take place.

Psychogenic substances can also be released during interictal epileptic activity of cells, as a result of which the accumulation of psychogenic substances may not occur to a threshold value and psychopathology will not manifest itself. Or the accumulation of psychogenic substances up to the threshold value will slow down, the achievement of the threshold value and the manifestation of psychopathology will occur less frequently.

When reviewing the possible association between epilepsy and schizophrenia G. Huber [43] wrote: "There is not a single symptom or syndrome of schizophrenia which is not met in patients with epilepsy, but this rule does not work counter-wise.'' This may be explained by the fact that pathological process during schizophrenia touches upon only the areas of brain responsible for emotional and cognitive functions, while epileptic process, epileptization of neurons apart from these areas, may affect any functional group of neurons.

Regarding dopamine theory of schizophrenia [34-36], dopamine increases general activity and reactivity of the brain in a majority of brain neurotransmitters. Knowing the association between dopaminergic system with seven other neurotransmitter systems, it cannot be excluded that association to other neurotransmitter systems will be discovered in future. This is why neuroleptic agents decrease general activity of the brain, which is linked to multiple side effects and manifestation of neuroleptic agents, including general retardation of patients. It may be presumed that treatment of mental diseases will further develop towards searching a more selective neurotransmitters and their antagonists. As it is commonly known, polymorphism of schizophrenia forced E. Bleuler to interpret it as a group of related diseases. This is why it cannot be excluded that in the event of various forms of schizophrenia various neurotransmitters play the leading role in the development of pathology.

The importance of the blood-brain barrier (BBB) disorders in the development of epilepsy and mental diseases.

In this article the author considers the importance of the blood-brain barrier (BBB) disorders in the development of epilepsy and mental diseases.

The BBB may play a significant role in the development of epilepsy. The literature contains descriptions of the BBB disorder in these diseases [44-45].

There is a large gradient of glutamate in the blood in relation to the cerebrospinal fluid; there is much more of it in the blood [46]. A violation of the BBB and an increase in the concentration of glutamate in the cerebrospinal fluid can cause an attack [16] and the development of epilepsy. Violation of the BBB can be genetically determined and acquired - caused by trauma, stroke, etc. Depending on the duration, it can be permanent, temporary, and possibly paroxysmal, for example, in response to a paroxysmal change in the concentration of certain substances in the blood or brain. It can be general or selective in relation to certain epileptogenic and psychogenic substances. Why psychogenic? Psychogenic because the toxic, psychopathogenic effect of blood serum of a patient with schizophrenia is known when administered to experimental animals, their behavior after that changes. In favor of finding psychopathogenic substances in the blood is evidenced by the positive therapeutic effect of plasmapheresis in mentally ill patients. So a violation of the BBB in relation to psychogenic substances can also cause mental paroxysms and mental illness. Probably, the psychogenicity and epileptogenicity of not all substances - blood components - have been established, and not all their gradients from blood to cerebrospinal fluid have been established.Therefore, it seems that a search in all these directions can lead to interesting finds.

It is also possible that under certain conditions, an increase in the BBB permeability can play a positive role in the treatment of epilepsy and mental illnesses. For example, in pathology, when there is an increase in the production of epileptogenic or psychopathogenic substances in the brain and cerebrospinal fluid, while their content in the blood is low, an increase in the BBB permeability will make it possible to transfer their excess from the cerebrospinal fluid into the blood, if an increase in their content in the blood is not associated with pronounced side effects, but will help to neutralize them and remove them from the body.

Thus, in addition to the antiepileptic system of the brain, consisting of the caudate nucleus, cerebellum, lateral nuclei of the hypothalamus, and the caudal reticular nucleus of the pons, at this stage one can also note the extracerebral antiepileptic system, consisting of the blood-brain barrier and homeostatic blood mechanisms. Or, perhaps, the BBB can be attributed to the borderline antiepileptic system, and the homeostatic mechanisms of blood - to the extracerebral.

In addition, as can be seen, the BBB and blood homeostatic mechanisms are also an extracerebral antipsychotic system. Since their sanogenetic functioning can reduce the severity of psychopathology or prevent its

manifestation. The search for brain structures that inhibit the action of psychopathogenic substances may lead to the formation of the concept of an antipsychotic system of the brain.
It has been said above that the role of hormonal and immune systems in the development of epilepsy and mental deseases is established and studies in this direction still continues. Recent intensive ongoing studies have shown the presence of the brain's own immune system, the immune functions of microglia is shown. The hormonal structures of the brain have long been established (hypothalamus, pituitary gland).Then the cerebral hormonal and immune structures of the brain, depending on the pathogenetic or sanogenetic role they perform, can be attributed both to the intracerebral epileptic or psychotic system, and to the intracerebral antiepileptic or antipsychotic system.
The possible pathogenetic and sanogenetic mechanisms of epilepsy development described above in the article parts, Hypothesis'' and, Supplement to the hypothesis'' and presented by us, depending on the production of epileptogenic substances, can also be considered as components of the epileptic and antiepileptic systems of the brain. The same mechanisms can be considered in relation to psychogenic substances and related to the psychotic and antipsychotic systems of the brain.
The same can be said about the extracerebral hormonal and immune structures - they can play the role of both an extracerebral epileptic or psychotic system, and an extracerebral antiepileptic or antipsychotic system, depending on the role they play.
New substances are being discovered [47] that are produced outside the brain in the human body and play a role in the development of mental illness. For example the association of amyloid protein produced by the liver with the development of neurodegenerative processes and Alzheimer's disease in mice has been shown.

Discussion

When giving neurochemical explanation to the above mechanism of seizure occurrence, it has to be noted that according to available literature absolute or relative (in comparison with inhibitory neurotransmitter) increase of excitatory transmitters in the neurons of the brain at the pre-convulsive stage of seizure is revealed [48].
We believe, that occurrence of epileptic seizures is conditioned by spontaneous local or generalized instability of membranes of cortical neurons resulting from inherited or acquired particularities of metabolic processes: disbalance of excitatory and inhibitory neurotransmitters. In the process of functioning of neurons, the potential of their membranes simultaneously (synchronously) alters. In the event of channelopathies with lower threshold of neuronal excitability, epileptic seizures may occur at much lower concentrations of epileptogenic substances.
Various researchers have shown frequent extensive dental disorders in the form of tooth lesions (caries, aplasia) in patients with mental illness [49]. It would be expedient to study calcium metabolism and functions of calcium channels in brain neurons in these patients.
It may be assumed that further development of neurochemistry and neuroimmunology of epilepsy will provide opportunities to classify epileptic seizures based on as to increase of which excitatory transmitters or decrease of which inhibitory transmitters cause the disbalance as a result of which neurons in the process of epileptic activity "are forced to get rid of increased level of excitatory transmitters". In this regard all substances need to be considered (and primarily the ones acting as neurotransmitters of the brain: aminoacids, kinurenine, serotonin, dopamine, agonists of gamma-aminobutyric acid receptors [34-36] etc.) increase in absolute or relative levels of which directly or indirectly give rise to sodium-potassium pump activity impairment, increased penetrability of membranes, increased tendency towards depolarization and consequently hyperexcitability of membranes. By analogy, it is necessary to find out which disbalance of which neurotransmitters leads to particular psychopathology, and all the processes leading to this disbalance.

Conclusion

Development of Neurotransmitter theories is a major achievement in contemporary psychiatry. Completely new role of more and more neurotransmitters in mental disorders - schizophrenia and depression - is being identified. On the basis of the above developments new medicinal preparations– neuroleptics and antidepressants are being created. There is a search for more selective neurotransmitters, more selective antipsychotics are being created, such are atypical antipsychotics [50].
It is advisable to accelerate such developments – studying the role of neurotransmitters - in the field of epileptology. There is also an urgent need to intensify the search for more selective neurotransmitters for schizophrenia and other mental illnesses and to develop more selective antipsychotics.
However, it should be noted that neurotransmitter link represents an intermediary link in neurochemical chain, which is preceded by other links (stages), the activities of which result in neurotransmitter link, which in its turn, precedes another links of chain. Apart of neurotransmitter link, from the perspectives of development of psychiatry we may presume that more attention will be given to studying links of neurochemical chain of pathogenesis which precede the neurotransmitter link, so as to eliminate development of pathology at an earlier stage.
It is interesting to study the impact of biological treatment methods on neurotransmitter balance and metabolism in psychiatry.
All methods for studying brain neurochemistry, both non-invasive and invasive, can be mobilized. Microdialysis of the brain can give a lot.

Proposed assumptions and hypothesis require serious experimental studies, good experimental capability and in case of their verification new paradigms, theories, new approaches to treatment of epilepsy and mental diseases with conservative as well as surgical methods may emerge.

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