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Review

Classical neurotransmitters and neuropeptides involved in generalized epilepsy in a multi-neurotransmitter system: How to improve the antiepileptic effect?

Felix-Martin Werner [a,b,*], Rafael Coveñas [b,1]

[a] Höhere Berufsfachschule für Altenpflege und Ergotherapie der Euro Akademie Pößneck, Pößneck, Germany
[b] Institute of Neurosciences of Castilla y León (INCYL), Laboratory of Neuroanatomy of the Peptidergic Systems (Lab. 14), University of Salamanca, Salamanca, Spain

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ABSTRACT

Here, we describe in generalized epilepsies the alterations of classical neurotransmitters and neuropeptides acting at specific subreceptors. In order to consider a network context rather than one based on focal substrates and in order to make the interaction between neurotransmitters and neuropeptides and their specific subreceptors comprehensible, neural networks in the hippocampus, thalamus, and cerebral cortex are described. In this disease, a neurotransmitter imbalance between dopaminergic and serotonergic neurons and between presynaptic GABAergic neurons (hypoactivity) and glutaminergic neurons (hyperactivity) occurs. Consequently, combined $GABA_A$ agonists and NMDA antagonists could furthermore stabilize the neural networks in a multimodal pharmacotherapy. The antiepileptic effect and the mechanisms of action of conventional and recently developed antiepileptic drugs are reviewed. The GASH:Sal animal model can contribute to examine the efficacy of antiepileptic drugs. The issues of whether the interaction of classical neurotransmitters with other subreceptors (5-HT_7, metabotropic 5 glutaminergic, A_{2A} adenosine, and alpha nicotinic 7 cholinergic receptors) or whether the administration of agonists/antagonists of neuropeptides might improve the therapeutic effect of antiepileptic drugs should be addressed.

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1. Introduction

Generalized epilepsy (grand mal epilepsy and petit mal epilepsies) is a frequent neurological disease. Generalized epilepsy can be idiopathic, while the susceptibility genes are being indentified and symptomatic, for example, due to a meningitis, a stroke, or a tumor [1]. A sequence of seizures without recovering consciousness is called status epilepticus, which can be treated, although insufficiently, with $GABA_A$ agonists [2]. In epileptic foci, alterations of ion channels and of neurotransmitter and neuropeptide function can be found [3]. In generalized epilepsy, neurotransmitter and neuropeptide alterations can be detected in the hippocampus. In this sense, altered sodium, chloride, calcium, and potassium currents have been reported, and an enhancement of Ca^{2+} influx can contribute to ictogenesis [4]. A neurotransmitter imbalance with a GABA hypoactivity via $GABA_A$ receptors and a glutamate hyperactivity via NMDA receptors can be found. Besides, other neurotransmitters (dopamine and noradrenaline hyperactivity and serotonin hypoactivity) and neuropeptides show dysfunction [5]. The Genetic Audiogenic Seizure Hamster (GASH:Sal) model represents a reliable animal model of generalized epilepsy because the animals exhibit generalized tonic clonic seizures of genetic origin in response to auditory stimuli [6]. Abnormalities of GABA have been detected by immunohistochemistry in the central nucleus of the inferior colliculus (CNIC) of the epilepsy-prone hamster (GPG/Vall) [6]. Here, we discuss the antiepileptic effect of current and recently developed antiepileptic drugs (AEDs) in these animal models of audiogenic epilepsy [7].

2. Alterations of classical neurotransmitters in generalized epilepsy

In generalized epilepsy, a hypoactivity of GABA, which exerts a presynaptic inhibitory function, and a hyperactivity of glutamate, which acts mainly as an excitotoxic, postsynaptic excitatory neurotransmitter

* Corresponding author at: Instituto de Neurociencias de Castilla y León (INCYL), Laboratorio de Neuroanatomía de los Sistemas Peptidérgicos, Laboratorio 14, c/Pintor Fernando Gallego, 1, 37007 Salamanca, Spain. Tel.: +34 923 29 44 00x1856; fax: +34 923 29 45 49.
E-mail addresses: felixm-werner@versanet.de (F.-M. Werner), covenas@usal.es (R. Coveñas).
[1] Institute of Neurosciences of Castilla y León (INCYL), Laboratory of Neuroanatomy of the Peptidergic Systems (Lab. 14), c/Pintor Fernando Gallego, 1, 37007 Salamanca, Spain. Tel.: +34 923294400x1856.

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and partly as a presynaptically inhibitory neurotransmitter, have been reported [4,8]. Catecholamines (noradrenaline, dopamine) show hyperactivity and serotonin hypoactivity [4,9]. Noradrenaline at low doses in the hippocampus exerts a proconvulsant and at high doses an anticonvulsant effect [4]. Selective dopamine reuptake inhibitors and citalopram, a selective serotonin reuptake inhibitor, at low doses had no protective effect on rats with limbic seizures, but in high doses, they had an anticonvulsant effect [4]. Here, we describe the alterations of these neurotransmitters and the subreceptors on which these neuroactive substances exert their effects [4,10]. This review mainly focuses on these alterations, although disturbances of ion channels associated with neurotransmitter and neuropeptide function are also considered.

2.1. Gamma-aminobutyric acid (GABA)

Gamma-aminobutyric acid, a presynaptic inhibitory neurotransmitter that mainly acts on the $GABA_A$ receptor, is distributed throughout the central nervous system. In animal experiments, $GABA_A$ antagonists and glutamate can prolong electrographic seizure activity, whereas $GABA_A$ agonists and NMDA antagonists have an antiepileptic effect [11]. Status epilepticus, which cannot be blocked by $GABA_A$ agonists, can often be treated by NMDA antagonists because during prolonged seizures, synaptic $GABA_A$ receptors move from synaptic to extrasynaptic sites and NMDA receptors move from extrasynaptic to synaptic sites [12]. Generalized epilepsy can be induced through susceptibility genes, which have been partly identified, or exogenously, through a reduced GABAergic presynaptic inhibition and an excitotoxic glutaminergic action [13]. In ictogenesis, $GABA_B$ receptors play a role. It remains to be elucidated whether $GABA_B$ receptors exert a presynaptic inhibition on other GABAergic neurons and whether $GABA_B$ antagonists have any influence on proneness to seizures [14].

2.2. Glutamate

Glutamate mainly exerts an excitotoxic, postsynaptic excitatory effect, and partly a presynaptic inhibitory effect on ionotropic receptors, for example, NMDA, KA (kainate), and AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid). In the hippocampus, NMDA receptors may be involved in the presynaptic inhibition of serotonergic neurons [10]. Metabotropic glutaminergic receptors (mGluRs) could play a role in ictogenesis by increasing or decreasing the effects exerted by ionotropic receptors [4]. The release of excitotoxic glutamate acting on NMDA, KA, or AMPA receptors can induce seizures. In the hippocampus, brain insults, traumatic brain injuries, or status epilepticus can cause an imbalance between the GABAergic and glutaminergic systems, while GABA has a hypoactivity action and glutamate exerts an excitotoxicity action [10]. The mRNA expression of the mGlu2/mGlu3 receptor is decreased after status epilepticus, and activation of the m5GluRs could exert an epileptogenic effect [15].

2.3. Noradrenaline

In generalized epilepsy and major depression, which often are comorbid, an altered postsynaptic effect of noradrenaline and serotonin and an altered presynaptic effect of GABA and glutamate have been reported [16]. At low doses, noradrenaline has a proconvulsant action and at high doses, an antiepileptic action; the blockade of beta- and alpha2-adrenergic receptors, which enhances the concentration of noradrenaline, reduces epileptic activity [17].

2.4. Dopamine

Dopamine exerts a modulating effect on seizures. In rats with genetic absence epilepsy, the number of D_2-like receptors is higher in the frontal and parietal cortices and lower in the CA_3 region of the hippocampus in comparison with that found in control groups [18]. A selective dopamine reuptake inhibitor, GBR-12,909 has anticonvulsant properties during limbic seizures and exerts an antiepileptic effect through D_2 receptors [19].

2.5. Serotonin

Serotonin, a mainly postsynaptic excitatory neurotransmitter, has a modulating effect in ictogenesis. Selective serotonin reuptake inhibitors (SSRIs) have a slight antiepileptic effect through activation of 5-HT_{1A} receptors [20]. In children suffering generalized epilepsy and major depression, seizure control was maintained with treatment with SSRIs [4]. A susceptible gene, Mpdz, encodes the multi-PDZ domain protein which blocks 5-HT_{2C} and $GABA_B$ receptors, inducing hyperexcitability in the central nervous system [4]. Animals lacking this gene show fewer severe handling-induced convulsions in response to both 5-HT_{2C} receptor antagonists and $GABA_B$ receptor agonists. These antagonists and agonists exert a proconvulsant effect. The question of whether the activation of 5-HT_{2C} receptors exerts an antiepileptic effect or not arises. Since it has been reported that 5-HT_7 receptor agonists increase the seizure threshold in animal experiments [21] and that the proconvulsant drug picrotoxin, a potent selective $GABA_A$ antagonist, had to be increased after the administration of 5-carboxyamidotryptamine, a potent 5-HT_7 agonist, another question as to whether these agonists have antiepileptic properties arises.

2.6. Acetylcholine

Acetylcholine is involved in epileptogenesis and exerts its effect upon muscarinic and nicotinic cholinergic receptors (nAchRs). The activation of the muscarinic-1 (M_1) receptor has a proconvulsant action. Atropine, an M_1 receptor antagonist, and donepezil, a partially reversible inhibitor of cholinesterase, exert an antiepileptic effect [22]. The activation of nAch alpha7Rs, which enhance GABAergic neurotransmission, has an antiepileptic effect [23].

2.7. Other neuroactive substances: Adenosine

Adenosine is involved in ischemic brain damage, neurodegenerative diseases such as Alzheimer's and Parkinson's disease, and epilepsy. Adenosine exerts a neuromodulating effect in epilepsy through the A_{2A} receptors. The question is whether adenosine A_{2A} receptor antagonists could exert an antiepileptic effect [24].

3. Alterations of neuropeptides in generalized epilepsy

Neuropeptides play a role in the pathogenesis of neurological and psychiatric diseases such as Alzheimer's and Parkinson's disease, schizophrenia, major depression, and epilepsy [4,25–27]. They exert an excitatory or an inhibitory action in generalized epilepsy and in status epilepticus: inhibitory anticonvulsant neuropeptides (dynorphin, galanin, and neuropeptide Y) are decreased, whereas proconvulsant neuropeptides (substance P and neurokinin B) are increased [4].

3.1. ACTH (adrenocorticotropic hormone)

Adrenocorticotropic hormone and cortisol levels are reduced shortly before seizures, increased after seizures, and remain increased thereafter. Adrenocorticotropic hormone is used in a well-established therapy for generalized childhood epilepsy. It can be used for the treatment of intractable generalized epilepsy, especially for atypical absence seizures [28].

3.2. Dynorphin

In the hippocampus, predynorphin knockout animals show neuronal loss after injections of kainate acid into the hippocampus. Kappa opioid receptor agonists could exert an antiepileptic effect [29].