

Neuropeptides and Neurotransmitters Involved in Generalized Epilepsy: How Can the Antiepileptic Effect be Improved?

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Abstract

Here, we describe the alterations of neurotransmitters and neuropeptides that act on specific subreceptors in the brain areas involved in generalized epilepsy. A neurotransmitter imbalance between GABAergic and serotonergic neurons with hypoactivity and glutaminergic and dopaminergic neurons with hyperactivity is described. Considering the alterations in neurotransmitters and neuropeptides, neural networks in the hippocampus, hypothalamus, thalamus and cortex are described. The mechanisms of action of some recently developed antiepileptic drugs are addressed. In sum, a multimodal antiepileptic pharmacotherapy acting at several specific subreceptors is suggested. We recommend the development of an antiepileptic drug, that exerts simultaneously a GABAA agonistic and an NMDA antagonistic effect.

Keywords: Generalized epilepsy; Antiepileptic drugs; Dopamine; Serotonin; GABA; Glutamate; Acetylcholine; Levetiracetam; Lamotrigine; Topiramate

Introduction

Generalized epilepsy (grand mal and petit mal epilepsy) has a prevalence of 0.7% in the population. Generalized epilepsy can be idiopathic, while the susceptibility genes have been identified or symptomatic, the primary cause of which may be a tumour, a stroke or an episode of meningitis [1]. Often, status epilepticus, i.e. a sequence of seizures without patient recovering consciousness, cannot be treated with gamma-aminobutyric acid (GABA)A agonists [2]. In the epileptic foci, alterations of ion channels, e.g., altered sodium, chloride, calcium and potassium currents, and alterations of neurotransmitters and neuropeptides have been described [3]. In this sense, a neurotransmitter imbalance with GABA hypoactivity, via GABAA receptors, and glutamate hyperactivity, via ionotropic glutamate receptors, increases ictogenesis [4]. Furthermore, other neurotransmitters (dopamine and noradrenaline hyperactivity and serotonin hypoactivity) and neuropeptides (galanin and neuropeptide Y hypoactivity) play an important role in ictogenesis [4]. A neurotransmitter imbalance between anticonvulsant GABAergic and excitotoxic, proconvulsant glutaminergic neurons is located in the hippocampus and depends on the thalamocortical and neural circuits and on the interactions between the hippocampus and hypothalamus [4]. In light of the foregoing, here we describe the neural networks in the hippocampus, hypothalamus and thalamus involved in generalized epilepsy and the antiepileptic effects of current and recently developed antiepileptic drugs [5].

Generalized epilepsy: alteration of classical neurotransmitters and neuropeptides

In epileptic foci, both GABA hypoactivity, which reduces the activity of dopaminergic neurons through a presynaptic effect via GABAA receptors, and glutamate hyperactivity, which mostly has an excitotoxic, postsynaptic excitatory effect on ionotropic receptors and a partly presynaptic inhibitory effect, have been reported [6]. Catecholamines, i.e. dopamine and noradrenaline, show hyperactivity and serotonin shows hypoactivity. Noradrenaline only has an anticonvulsant effect at high doses, whereas at low doses it exerts a proconvulsant effect [4]. In ictogenesis, neuropeptides act as neuromodulators. The effects of classical neurotransmitters and neuropeptides in ictogenesis will be described below.

Gamma-aminobutyric acid

Gamma-aminobutyric acid (GABA) is a presynaptic inhibitory neurotransmitter which exerts its effect upon GABAA and GABAB receptors. In animal studies, GABA withdrawal or GABAA antagonists can prolong epileptic seizures, whereas GABAA agonists and NMDA antagonists show antiepileptic properties [7]. Status epilepticus, which cannot be treated with GABAA agonists, can often be treated with N-methyl-D-aspartate (NMDA) antagonists [8]. GABAB receptors are also involved in ictogenesis [9]. Thus, there are two issues to be addressed: 1) whether GABAB receptors exert a protective function upon GABAA GABAergic neurons, and 2) whether GABAB antagonists exert an antiepileptic effect [9].

Glutamate

Glutamate mainly exerts an excitotoxic effect on ionotropic receptors, i.e. NMDA, kainate (KA) and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, together with a partly presynaptic effect [10]. In the hippocampus, through ionotropic receptors glutaminergic neurons can activate D2 dopaminergic

neurons, and they can inhibit presynaptically 5-hydroxytryptamine (HT)2C serotonergic neurons. Metabotropic glutaminergic receptors are also involved in ictogenesis, since the activation of subtype 5 of metabotropic glutaminergic receptors (m5Glu receptors) has a proconvulsant effect [11].

Dopamine

In seizures, dopamine has a modulating effect [12]. The proconvulsant or anticonvulsant effect is mediated via D2 receptors. GABAergic neurons showing hypoactivity and located in the hippocampus, weakly inhibit presynaptically D2 dopaminergic neurons. GABA hypoactivity and dopamine hyperactivity can enhance an epileptic seizure [4].

Noradrenaline

In generalized epilepsy and major depression, alterations of noradrenaline and serotonin, both of which exert a postsynaptic excitatory effect, and of GABA and glutamate, which exert a presynaptic inhibitory effect, have been described [13]. At low doses, noradrenaline can enhance an epileptic seizure, whereas at high doses it has a protective effect on seizures [14].

Serotonin

Serotonin, a mainly postsynaptic excitatory neurotransmitter, has pro- and anti-convulsant effects in ictogenesis. In patients with a comorbidity of generalized epilepsy and major depression who were treated with a selective serotonin reuptake inhibitor, the treatment for the generalized epilepsy was maintained. The antiepileptic effect was achieved via activation of 5-HT1A receptors [15]. Clinical trials should be carried out in order to determine whether 5-HT2C or 5-HT7 agonists might exert an antiepileptic effect, as observed in animal experiments [16]. In the hippocampus, glutaminergic neurons via NMDA receptors might strongly inhibit presynaptically 5-HT2C serotonergic neurons [4].

Acetylcholine

Acetylcholine, which exerts its effect on muscarinic and nicotinic cholinergic receptors, has a pro- and an anti-convulsant action. The activation of the muscarinic-1 (M1) receptor has a proconvulsant effect [17]. Alpha4beta2 nicotinic cholinergic (alpha4beta2 nACh) neurons activate D2 dopaminergic neurons and alpha7 nACh neurons activate GABAergic neurons located in the hippocampus [18].

Dynorphin

Dynorphin plays a role in ictogenesis, and kappa opioid receptor agonists may exert an antiepileptic effect [19].

Galanin

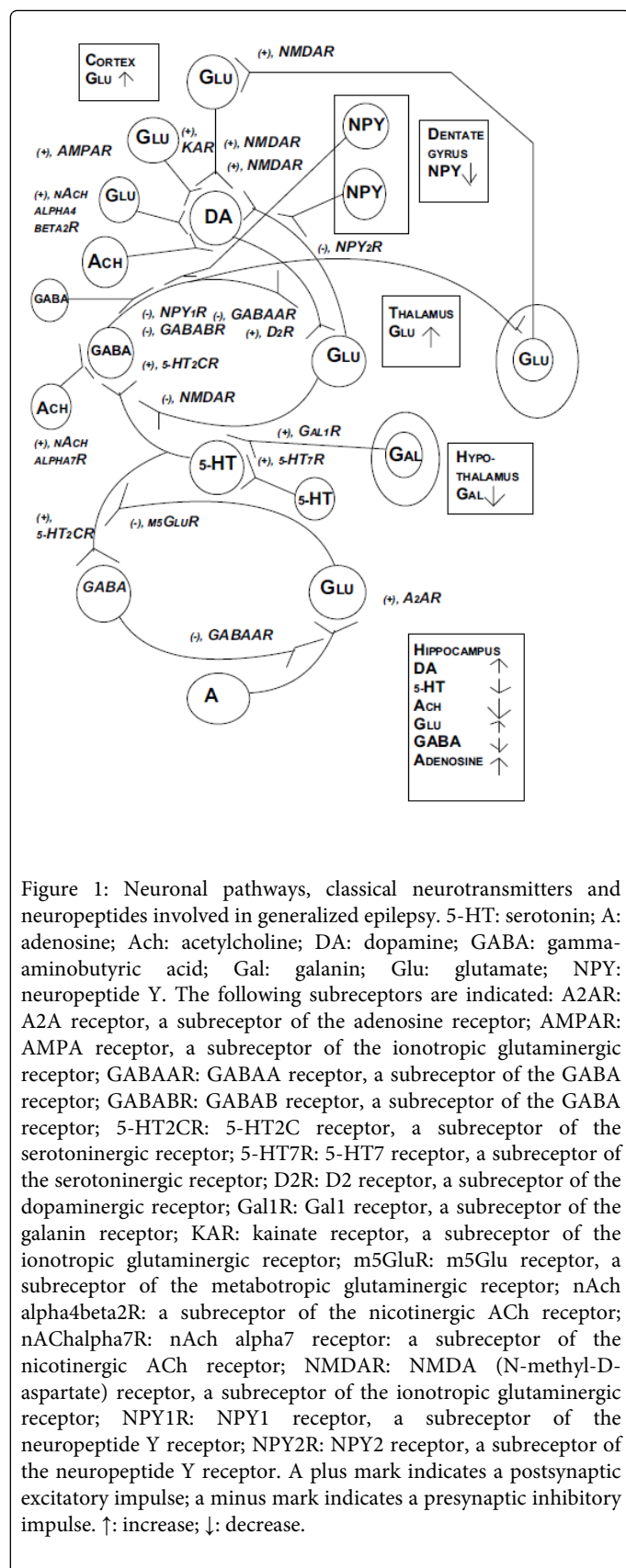
Galanin exerts its effect upon Gal1, Gal2 and Gal3 receptors and its activation or blockade is important in neurological diseases and generalized epilepsy. Gal1 receptor agonists may have antiepileptic properties, because they activate 5-HT2C serotonergic neurons [18,19].

Neuropeptide Y

Neurons containing neuropeptide Y (NPY) and located in the dentate gyrus inhibit GABAergic neurons, via NPY1 receptors, and inhibit glutaminergic neurons via NPY2 receptors. In animal studies, NPY2 receptor agonists, which inhibit the epileptogenic glutamate release, have been found to exert the highest antiepileptic effect [20].

Generalized epilepsy: neural circuits

Neural networks in the hippocampus, hypothalamus and thalamus, shown in figure 1, can be described as follows: D2 dopaminergic neurons with a high activity strongly activate glutaminergic neurons, which strongly inhibit 5-HT2C serotonergic neurons via NMDA receptors. Glutaminergic neurons also exert an excitotoxic effect on D2 dopaminergic neurons via NMDA, AMPA and KA receptors and can enhance ictogenesis. 5-HT2C serotonergic neurons weakly activate GABAergic neurons, which weakly inhibit via GABAA receptors D2 dopaminergic neurons. Withdrawal of the GABAergic presynaptic inhibition of D2 dopaminergic neurons can set off an epileptic seizure. GABAergic neurons weakly inhibit glutaminergic neurons located in the thalamus, which activate other glutaminergic neurons located in the cortex. Cortical glutaminergic neurons, via NMDA receptors, can activate D2 dopaminergic neurons located in the hippocampus. 5-HT2C serotonergic neurons weakly activate GABAergic neurons, which weakly inhibit A2A adenosine neurons via GABAA receptors. A2A adenosine neurons with a high activity strongly activate glutaminergic neurons, which strongly inhibit 5-HT2C serotonergic neurons via m5Glu receptors. Hypothalamic galanin neurons weakly activate 5-HT2C serotonergic neurons via Gal1 receptors, and 5-HT7 serotonergic neurons exert a weak postsynaptic excitatory effect upon 5-HT2C serotonergic neurons. In the dentate gyrus, neuropeptide Y neurons inhibit GABAergic neurons via NPY1 receptors and inhibit glutaminergic neurons via NPY2 receptors. Nicotinic cholinergic neurons activate D2 dopaminergic neurons via alpha4beta2 nACh receptors and activate GABAergic neurons via alpha7 nACh neurons [18].



Recently developed antiepileptic drugs in the treatment of generalized epilepsy

Here, we describe the mechanisms of action of some recently developed antiepileptic drugs for the treatment of generalized epilepsy [4, 18]. The activation or blockade of specific subreceptors of classical neurotransmitters and the blockade of ion channels are discussed.

Lamotrigine

Lamotrigine is approved for the treatment of childhood epilepsy. It blocks voltage-gated sodium channels, nAch alpha4beta2 receptors and NMDA receptor, and to a lesser extent AMPA receptors [21].

Levetiracetam

In children, levetiracetam is used for the treatment of refractory generalized epilepsy. It increases the presynaptic inhibitory effect of GABAergic neurons and blocks NMDA receptors [22].

Rufinamide

In children, rufinamide is an antiepileptic drug used as adjunctive pharmacotherapy for the treatment of Lennox-Gastaut syndrome. Rufinamide exerts an antiepileptic effect by prolonging the inactivity of sodium channels [23].

Topiramate

In children, topiramate is used for the treatment of generalized epilepsy. It blocks not only KA and AMPA receptors, but also NMDA receptors, and it stabilizes dopaminergic neurons [24].

Zonisamide

Zonisamide is accepted as an add-on therapy in generalized epilepsy and as an anti-Parkinsonian drug. It blocks Na⁺ channels and Ca⁺ channels and increases dopamine contents by inhibiting the MAO(B) enzyme [25].

Possible treatments of generalized epilepsy according to the neural networks described

According to the neural networks described, the following antiepileptic drugs or add-on therapies might be possible:

- Combined GABAA agonists and NMDA antagonists, since GABAA agonists and NMDA antagonists may stabilize the neural networks.
- NMDA, AMPA and KA receptor antagonists.
- NPY2 receptor agonists which inhibit glutamate emptying, and NPY1 receptor antagonists, which decrease the presynaptic inhibition mediated by NPY, would enhance the GABAergic presynaptic inhibition.
- Gal1 agonists, which would increase serotonin levels.

Conclusions

In the present work, in generalized epilepsy, we describe the alterations of neurotransmitters and neuropeptides in epileptic foci in the hippocampus. A neurotransmitter imbalance between presynaptic GABAergic neurons, with hypoactivity, and glutaminergic neurons, with excitotoxicity, enhance ictogenesis. Postsynaptic excitatory

neurotransmitters are also involved in the neural networks, since dopamine hyperactivity via D2 receptors and serotonin hypoactivity via 5-HT_{2C} receptors have a proconvulsant effect. Other neurotransmitters and neuropeptides and their specific subreceptors and their activation or blockade with alpha4beta2 nACh antagonists, alpha7 nACh agonists, 5-HT₇ agonists, GABAB antagonists or KA or AMPA antagonists might have an additional antiepileptic effect. A multimodal pharmacotherapy acting at different subreceptors should be developed. Moreover, in this context we emphasize the importance of developing antiepileptic drugs exerting a GABAA agonistic and an NMDA antagonistic effect.

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