Epilepsy

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Introduction to Epilepsy

Epilepsy is a complex syndrome comprised of seizures and associated comorbidities affecting approximately 50 million people worldwide. The disease is characterized by excessive electrical discharges in hyperexcitable neuronal clusters that result in spontaneous and recurrent seizures. The seizures may be subclinical and thus only apparent on an electroencephalogram (EEG), but more often they fit into two clinical classifications: partial and generalized. Partial seizures have a focused origin in the brain, and, therefore, seizure symptoms may present in a localized manner. Generalized seizures lack a focal origin and instead involve the entire brain. Epileptic seizures can range from altered states of consciousness to those involving motor function with clonic and/or tonic components.

Our understanding of the pathophysiological processes that turn a normally functioning brain into a hyperexcitable one remains limited. Many theories exist to explain the apparent disruption of homeostatic functions that alter neuronal excitation and/or inhibition. Research has thus far examined extracellular ion homeostasis, altered energy metabolism, changes in receptor function, and alterations in transmitter uptake.

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Pathophysiology of Epilepsy and Metabolic Alterations

Epileptic seizures result from significant electrical discharges in hyperexcitable groups of neurons in which the normal neurophysiology is pathologically altered to favor excitation over inhibition. This can be caused by decreased inhibitory or increased excitatory signals or altered response to these input signals, all of which probably contribute to the etiology of epilepsy.

Within neurons, altered functions of ion channels, such as those controlling the flux of Ca^{2+}, K^{+}, or Na^{+}, a decrease in inhibitory γ-aminobutyric acid (GABA) signaling, or an excess in glutamatergic excitatory signaling, all contribute to the hyperexcitable state of neuronal networks. Those mechanisms generally decrease the threshold for neuronal activation, and, thus, stimuli that normally are subthreshold are now able to trigger excessive excitation. Another feature of epileptogenic groups of neurons is synchrony, which is favored by altered neuronal connectivity leading to recurrent circuitry.

Recent evidence suggests that neuronal hyperexcitability in epilepsy is not only an intrinsic deficiency of neurons but to a large degree determined by the disruption of homeostatic and metabolic functions, which are controlled by astrocytes (Fig. 1) [1]. Many forms of epilepsy,

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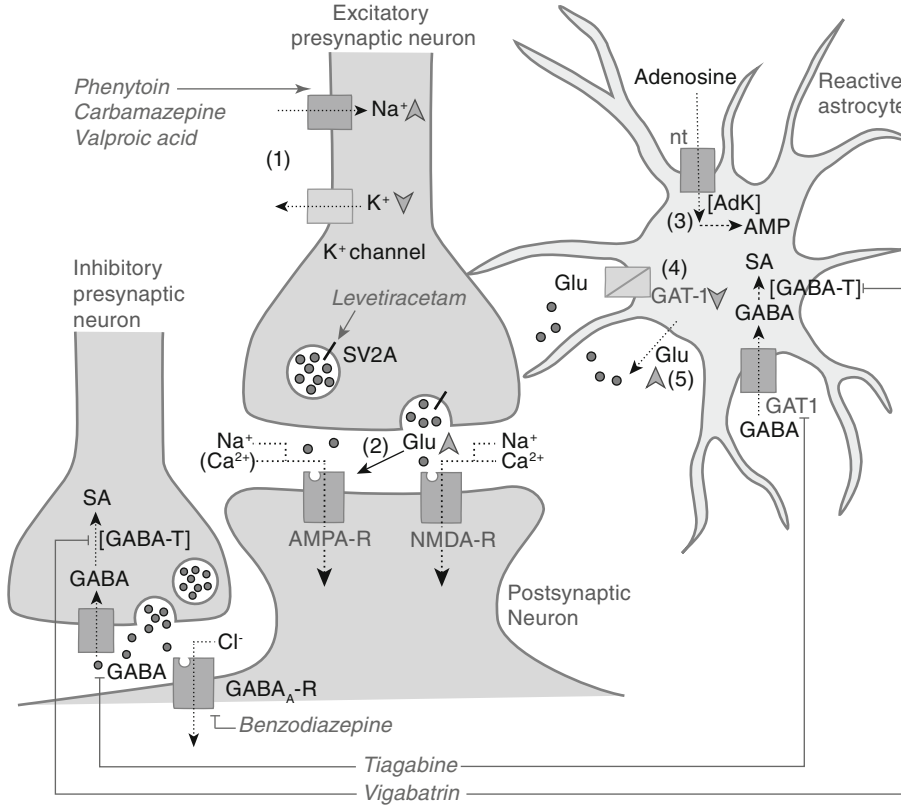

Fig. 1 Disruption of multiple systems in epilepsy involving neurons and astrocytes. (*1*) Hyperexcitable neurons are associated with overactivation of voltage-gated Na^+ channels and reduced activity of K^+ channels, which generate an action potential that leads to (*2*) increased release of glutamate (*Glu*). This activates AMPA and *N*-methyl-D-aspartate (*NMDA*) receptors on the postsynaptic membrane, causing excitatory synaptic potentials. (*3*) Upregulated adenosine kinase (*AdK*) in reactive astrocytes increases the removal of extracellular adenosine, enhancing hyperexcitability. (*4*) Decreased membrane transporters for K^+ (not shown) and Glu (such as *GAT-1*) on reactive astrocytes further enhance hyperexcitability. (*5*) Excessive Ca^{2+} intake in astrocytes even induces Glu release. Points of interference of a few antiepileptic drugs are also shown. These drugs generally aim to decrease hyperexcitability by reducing glutamate release or signaling or by increasing glutamate removal or inhibitory signaling. *SV2A* synaptic vesicle glycoprotein 2A, *nt* nucleoside transporter, *GABA* γ-aminobutyric acid, *GAT-1* GABA transporter-1, *GABA-T* GABA transaminase, *SA* succinic semialdehyde

particularly those involving the temporal lobe, are characterized by astrogliosis, a macroglial response that leads to increased proliferation and hypertrophy of astrocytes. Astrogliosis in turn is associated with changes in the membrane conductance for ions, which limits the buffering capacity of astrocytes for K^+, Ca^{2+}, and H^+, and disrupts the homeostasis of neurotransmitters such as glutamate (Glu) and of neuromodulators such as adenosine. As a consequence of those alterations in astroglial physiology, the extracellular concentrations of K^+ and Glu are increased, whereas those of adenosine are decreased. In particular, overexpression of adenosine kinase, the key enzyme for the metabolic clearance of adenosine through astrocytes, has been identified as a key pathological hallmark of epilepsy as it results in adenosine deficiency [2].

Adenosine is a key link between energy homeostasis and metabolic activity and has been termed a "retaliatory metabolite" due to its capability to adjust energy consumption to energy supplies [3]. In general, under any conditions of stress or distress, the levels of adenosine rise, and it is this rise in adenosine that limits further neuronal energy consumption [4] by binding to

inhibitory adenosine A_1 receptors [5], which couple to inhibitory G_i and G_o proteins and thereby (1) lead to a decrease in the intracellular messenger cAMP, (2) induce neuronal hyperpolarization by augmenting G protein-coupled inwardly rectifying K^+ channels, and (3) induce presynaptic inhibition by limiting Ca^{2+} influx into the presynaptic neuron. More specifically, in epilepsy, seizures consume a large amount of energy, which leads to a rise in adenosine that acts as an endogenous anticonvulsant and seizure terminator [6].

Treatment of Epilepsy

Treatment of epilepsy with antiepileptic drugs (AEDs) generally attempts to correct the disruption in normal electrical functionality via decreases in excitatory processes or increases in inhibitory processes. AEDs aim to reduce seizures by regulating the nervous system's primary excitatory neurotransmitter, Glu, its primary inhibitory neurotransmitter, GABA, or ion channels that control the conduction of electrical impulses in neurons. It should be noted, however, that the treatment of epilepsy, based on the modulation of neuronal downstream targets, fails to control seizures in more than 30 % of patients with epilepsy [7, 8]. The control of neuronal excitability by blockade of ion channels such as those for Na^+, K^+, and Ca^{2+} is a mechanism of commonly used AEDs (e.g., phenytoin, carbamazepine, valproic acid). Newer AEDs act by interfering with the synthesis, function, release, and metabolism of neurotransmitters and their receptors. Levetiracetam binds to the synaptic vesicle glycoprotein SV2A and inhibits presynaptic Ca^{2+} channels. Presynaptic mechanisms are thought to impede impulse conduction across synapses. Vigabatrin blocks GABA transaminase, the major GABA degrading enzyme, and tiagabine blocks reuptake of GABA via GABA transporter 1 (GAT1), thereby increasing the level of extracellular GABA in the brain. Moreover, AEDs can enhance the effect of GABA (e.g., benzodiazepine). However, conventional pharmacological strategies frequently fail due to the development of pharmacoresistance, and the global manipulation of ion channels leads to widespread side effects, particularly in the cognitive domain, at higher and more effective doses. Alternative treatments include surgical resection of a seizure focus. The goal of surgical resection is to remove the seizure origin or disrupt the spread of the seizure throughout the brain. If an epileptogenic focus is found and does not reside in cortical areas responsible for speech, it may be possible to remove without compromising neurological functions. Surgery has been successful in reducing seizures and in some instances may completely alleviate the need for other treatments [9]. While AEDs and surgery have been the classical foundation of epilepsy treatment, they do not provide a satisfactory solution for many patients (see below). In contrast, dietary therapies may provide seizure control in drug-resistant forms of epilepsy [10]. The therapeutic effect of fasting on the control of seizures has been known since Hippocrates. Fasting's suppression of seizures can be mimicked by a high-fat, low-carbohydrate ketogenic diet (Fig. 2). The anticonvulsant effects brought on by metabolic changes during this diet therapy offer great promise for identifying new antiseizure targets as well as providing insight into the pathophysiology of the epileptic brain (see below).

Influence of Treatment on Metabolism

The sharp decrease in carbohydrate intake during ketogenic diet treatment reduces glucose utilization as an energy source. Instead, the liver utilizes fatty acids to produce ketone bodies, mainly β-hydroxybutyrate and acetoacetate. Neurons in turn will use these ketone bodies for cellular metabolism in place of glucose (Fig. 2). Many hypotheses exist to explain the anticonvulsant action of the ketogenic diet, but despite its name, the ketone bodies themselves may not necessarily be the primary effector, and the underlying mechanisms leading to reduced seizure activity are largely unknown. Among beneficial metabolic changes induced by ketogenic diet therapy are (1) increased levels of adenosine [11], (2)

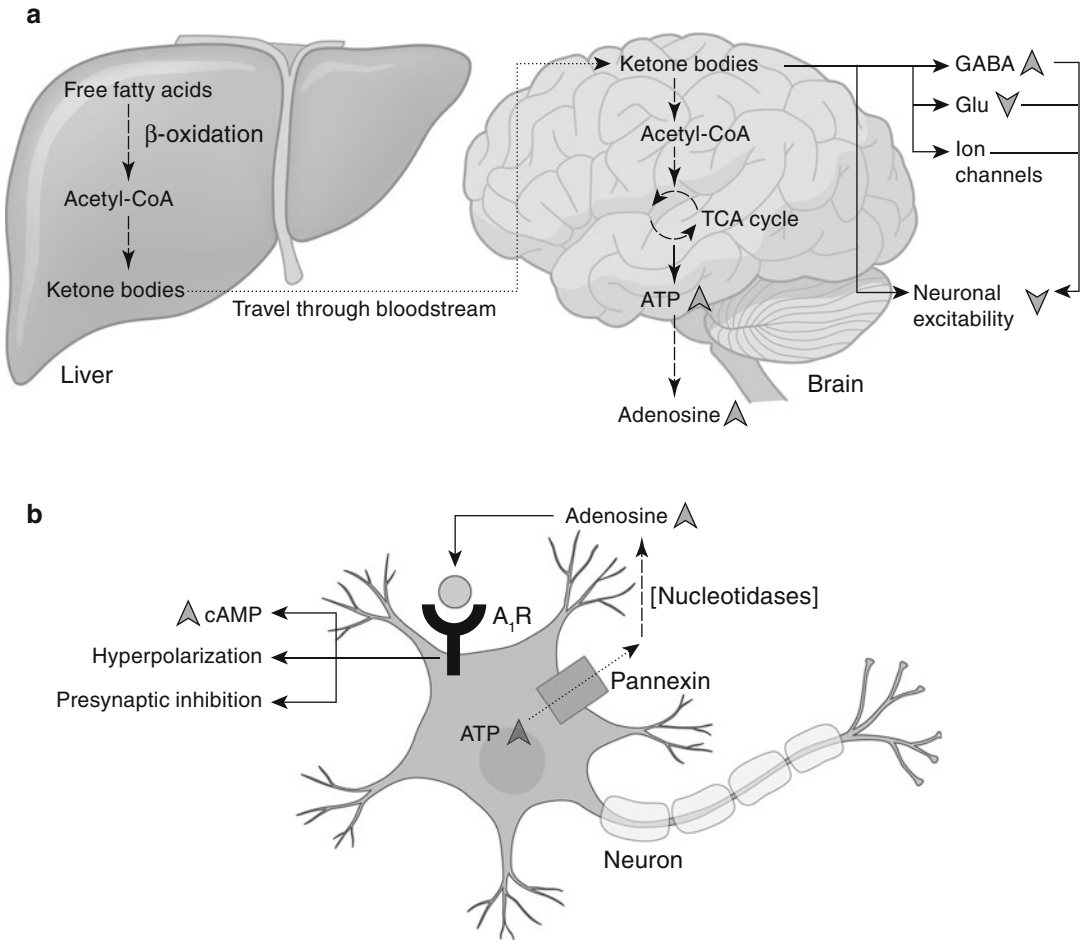

Fig. 2 Mechanism of action for the ketogenic diet. (**a**) Schematic diagram illustrating ketone body formation from fatty acids present in the ketogenic diet and their subsequent use in the brain as fuel for ATP production. Ketogenic diet is reported to increase adenosine and γ-aminobutyric acid (*GABA*), to decrease glutamate (*Glu*), and to directly act on neurotransmitters subsequently reducing neuronal excitability. (**b**) Increased intracellular ATP moves ATP along its concentration gradient through pannexin to the extracellular space. Here, it is degraded by nucleotidases to its core constituent, adenosine, which can act on inhibitory A_1 receptors (A_1R) to cause presynaptic inhibition and hyperpolarization to prevent seizures. *cAMP* cyclic adenosine monophosphate

increased GABA, (3) and decreased Glu, which all combine with a direct action of ketone bodies on ion channels to reduce neuronal excitability [10]. Ketosis increases mitochondrial biogenesis and thereby the production of ATP, which is a direct metabolic precursor of adenosine (as it leaves the neuron via the transmembrane channel pannexin and is converted to adenosine extracellularly (Fig. 2) [12]. It is this unique metabolic modulation that builds excitement not only for a deeper understanding of the ketogenic diet but for metabolic manipulations in general as a novel anticonvulsant strategy with good efficacy and few side effects.

Perspectives

Inefficacy of current AED treatment in 30 % of patients signals the need for a deeper understanding of homeostatic mechanisms that govern the pathophysiology of epilepsy. Future studies should investigate the metabolic changes in epilepsy in order to establish novel treatment

approaches. Current investigations consider a variety of alternative therapeutic interventions such as focal cooling [13], cell therapy [14, 15], gene therapy [16–18], or focal adenosine augmentation [15] to harness endogenous anticonvulsant mechanisms of the brain therapeutically.

Indeed, it is time to redefine epilepsy as a complex syndrome of disrupted network homeostasis, which includes seizures not only as the major pathological trait but also a wide range of so-called comorbidities including cognitive impairment, sleep dysfunction, depression (see chapter "Major depressive disorder"), and psychiatric impairment. Conventional AEDs were solely designed to suppress seizures, which is only a symptom of epilepsy, albeit the most obvious. Based on the neurocentric rationale of drug development, it becomes clear that conventional AEDs are a poor choice to treat epilepsy as a syndrome in a "holistic" sense. Novel therapeutic avenues aimed at reconstructing the homeostasis of network regulation may ultimately provide better treatment options and hopes for finding a cure for epilepsy. In this regard, metabolic interventions and focal adenosine augmentation appear to be promising homeostatic therapies, which might be effective in pharmacoresistant epilepsy and poised to reduce the disease burden of epilepsy.

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