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Recent Biochemical Developments in Epilepsy: Case Study of Glutamate and GABA

Ben Li[1*] & Michael Xie[1]

[*]Authors contributed to equally to this work.
[1]Bachelor of Health Sciences - Biomedical Specialization Student Level II, McMaster University
Direct Correspondence To: xiem5@mcmaster.ca, lib42@mcmaster.ca

Abbreviations
GABA: gamma-aminobutyric acid, $GABA_A$: gamma-aminobutyric acid receptor A, $GABA_B$: gamma-aminobutyric acid receptor B, AMPA: alpha-amino-2,3-dihydro-5-methyl-3-oxo-4-isoxazolepropanoic acid, NMDA: N-methyl-D-asparate, K^+: potassium ion, Na^+: sodium ion, Cl^-: chlorine

Introduction

Epilepsy is a neurological disorder characterized by recurrent seizures that cause changes in attention or behaviour[1]. Epileptic seizures occur due to abnormal, excessive, and hyper-synchronous neuronal activity in the brain[2]. Currently, antiepileptic drugs are ineffective for 30% of all epileptic patients and most only provide short-term relief and have high levels of inter-patient variability in treatment effectiveness[3-5]. These treatments do not directly address the core causes of epilepsy, which include acquired damage to neural circuits, congenital abnormalities, and genetic deficiencies[5]. This is attributed to a lack of understanding of the molecular pathways responsible for epileptogenesis[6]. Because it affects approximately 50 million people worldwide, it is critical to understand the underlying biochemical mechanisms contributing to this condition to develop more effective therapeutics[7].

Current Role of Biochemistry In Epilepsy Research

The majority of our current understanding of epilepsy has come from clinical and epidemiological studies that provide us with minimal information on the etiology of the disease[8]. With developments in technology, biochemical investigations have helped to improved our understanding of the fundamental mechanisms underlying epilepsy, including the key neurotransmitters involved[2]. Below, we will discuss how novel biochemical investigations into the neurotransmitters glutamate and gamma-aminobutyric acid (GABA) have advanced the field of epilepsy research.

The Role of Glutamate and GABA in Epilepsy

The major excitatory neurotransmitter is glutamate and its activity has been linked to epilepsy[9]. The ligand-gated ion channel (ionotropic) class of glutamate receptors include alpha-amino-2,3-dihydro-5-methyl-3-oxo-4-isoxazolepropanoic acid (AMPA), kainate, and N-methyl-D-aspartate (NMDA) receptors. Upon ligand binding, these glutamate receptors cause a net influx of Na^+ ions that depolarizes the neuron. Ionotropic receptors contribute to hyper-excitation of neurons, which plays a key role in epileptic seizures[10].

The major inhibitory neurotransmitter is GABA and its receptors are $GABA_A$ and $GABA_B$. $GABA_A$ are ligand gated Cl^- ion channels that cause Cl^- influx and $GABA_B$ are coupled with secondary messengers that cause K^+ efflux. Both receptors generate inhibitory postsynaptic potentials in neurons[10].

Normally, the Glutamate-GABA axis is held in equilibrium by physiological mechanisms. Glutamate and GABA released into the synapse are recycled by neighbouring astrocytes via active transport into the cell and catabolism into glutamine[11]. Deregulation of this axis results in increased excitability, excitotoxicity, and epileptic activity. A loss of function in glutamine synthetase, which metabolizes glutamate into glutamine, has been linked to neuronal hyper-excitability[11]. Abnormal glutamate release by glial cells can also cause spontaneous excitation of surrounding neurons[12]. Moreover, certain seizure activity has been attributed to insufficient GABA synthesis, such as those seen in glutamic acid decarboxylase cofactor deficiencies[13]. Overall, excessive stimulation of glutamate receptors or under stimulation of GABA receptors results in hyper-excitation of neurons and epileptic activity[14].

The integral role of the Glutamate-GABA axis in regulating neuronal excitability makes it a potent therapeutic target in the treatment of epilepsy. However, there has been a lack of momentum in translating the vast amount of biomedical research into effective therapies, primary due to poor clinical trial results[15]. Many recent findings have provided insight into the mechanism underlying the Glutamate-GABA axis and its relation to neuronal excitability. These findings provide new ways of approaching the treatment of epilepsy.

Successes in Translating Glutamate/GABA Studies into the Clinical Setting

Current biochemical research focuses on targeting glutamate and GABA receptors to maintain a balance in excitatory and inhibitory

neurotransmission[14]. To date, the role of many different classes of ligand-gated glutamate receptors in epilepsy have been studied. AMPA and NMDA glutamate receptors are the primary mediators of excitation in the central nervous system and have been widely targeted for the treatment of epilepsy[16]. AMPA and NMDA antagonists, such as Perampanel and Felbamate, have shown moderate anticonvulsant effects[17].

A newly emerging field of research on a less widely studied class of glutamate receptor, known as kainate receptors, has recently generated significant interest. Topiramate was FDA approved in 2012 as a kainate receptor antagonist for the treatment of epilepsy. In a meta-analysis of seven double-blind, randomized controlled trials of adults with treatment-resistant partial-onset seizures, 41% of topiramate-treated patients exhibited a ≥50% reduction in seizure frequency compared to 15% in the placebo control[18]. Furthermore, benzodiazepines, a class of drugs that act as positive allosteric modulators of the $GABA_A$ receptor, have been approved as efficacious anticonvulsants[19]. By strengthening inhibitory GABA signals, benzodiazepines such as diazepam and clonazepam reduce risk of epileptic seizures[20]. A randomized trial involving 258 adults showed that diazepam reduced duration of seizures by 33%[21].

The extensive understanding of the glutamate and GABA receptors provide a strong biochemical foundation for drug discovery and greatly improve the probability of designing glutamate/GABA-related antiepileptics with high clinical success. One major limitation of biochemical approaches is that they may not accurately predict clinical success. However, these models provide the basic understanding necessary to develop effective therapeutics. The lack of potent drugs may be attributed to incomplete biochemical investigations before moving them to clinical trials[15].

Conclusion and Implications

Current generation antiepileptics have high inter-patient variability in terms of treatment effectiveness, and matching a patient to a successful drug largely depends on trial and error[3,5]. To create broad spectrum, lasting antiepileptics, future ventures should attempt to further grasp the underlying biochemistry before initiating clinical trials. The past decade of research into the protein structure and function of glutamate and GABA receptors has provided scientists with opportunities to target these receptors for therapeutic purposes. The current challenge stems from the ubiquitous presence of glutamate and GABA receptors which are important in maintaining proper neural activity. It is crucial to develop highly specific drugs that target these receptors in areas of the brain most prone to epileptiform activity. Importantly, molecules targeting ligand-receptor interactions are not the only effective therapeutic targets. Biochemistry provides us with the tools to understand the synthesis, synaptic release, and termination of glutamate and GABA, allowing us to develop a wide range of therapeutics targeting different stages of these neurotransmitters' life cycle.

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