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Review

Antiepileptic drug effects on mood and behavior: Molecular targets

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ABSTRACT

With almost 100 years of clinical experience, antiepileptic drugs (AEDs) remain the mainstay of epilepsy treatment. They suppress epileptic seizures by acting on a variety of mechanisms and molecular targets involved in the regulation of neuronal excitability. These include inhibitory-GABAergic and excitatory-glutamatergic neurotransmission, as well as ion (sodium and calcium) conductance through voltage-gated channels. On the other hand, accruing evidence indicates that these mechanisms and targets are also implicated in the regulation of mood and behavior, which may explain why each AED is associated with specific psychotropic effects. These effects, however, cannot be explained solely on the basis of the known mode of action of each AED, and other mechanisms or targets are likely to be implicated. In this article, we review positive and negative effects of AEDs on mood and behavior, discuss putative underlying mechanisms, and highlight knowledge gaps which should be addressed in future studies.

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1. Introduction

The introduction of approximately 15 new antiepileptic drugs (AEDs) in the past 20 years has significantly expanded the pharmacological armamentarium for epilepsy [1]. Although some of these agents offer appreciable advantages in terms of pharmacokinetics, tolerability, and lower drug interaction potential, improvements in clinical outcome have fallen short of expectations, with no more than 15–20% of patients with seizures refractory to older AEDs attaining seizure freedom without unacceptable toxicity [2]. In this regard, treatment-emergent adverse psychiatric effects have a considerable impact on health-related quality of life and may affect patients' compliance [3]. On the other hand, AEDs are widely used in psychiatric practice for a broad spectrum of psychiatric disorders. The primary application is in mood stabilization [4], but interesting data are also emerging for anxiety disorders [5] and withdrawal syndromes [6].

In patients with epilepsy, it is often difficult to determine which psychopathological manifestations are due specifically to AED therapy and which may be related to other factors affecting the patient. In fact, psychiatric complications often have a multifactorial origin with AEDs being only one of many putative causes. Moreover, the mechanisms of action of several AEDs are not always known with certainty. As with several other drug classes, AEDs have a diversity of actions on biological systems; only some of which are related to the desired anti-seizure effect (Table 1). Therefore, the psychotropic effects of AEDs in epilepsy derive from a number of variables related to the single compound (i.e., mechanism of action), to the underlying neurological condition (i.e., neurobiology of seizure control), and to the individual (i.e., family history or personal history of psychiatric disorders) [7].

In this article, we discuss the role of mechanisms and molecular targets of AEDs in mood and behavior, review positive and negative psychotropic effects of each AED (in chronological order of licensing, Table 2), and highlight current knowledge gaps which should be addressed in future studies.

2. Mechanisms and molecular targets of AEDs in mood and behavior

2.1. γ-aminobutyric acid (GABA) transmission

Over the past 30 years, converging evidence from animal and human studies has suggested that GABAergic mechanisms may be implicated in the pathophysiology of mood disorders. Alterations in plasma, cerebrospinal fluid, and brain GABA levels have been found in experimental animal models and individuals with major depressive disorders [8]. Mood stressors and psychotropic drugs can affect GABAergic function, and, conversely, GABAergic agents exert an effect on mood [8]. Gamma-aminobutyric acidergic dysfunction has also been recently reported to be relevant for the development of behavioral problems, such as aggression [9].

Benzodiazepines can be considered the prototype of psychotropic agents potentiating the GABAergic system. Their sedative and anxiolytic

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Table 1
Putative mechanisms of action of antiepileptic drugs (AEDs).

AEDs		Voltage-gated Na^+ channel blockade	Voltage-gated Ca^{2+} channel blockade (channel subtype)	Enhancement of GABA transmission	Inhibition of glutamate transmission (receptor subtype)	Other mechanisms[a]
First generation	Barbiturates	–	?	++	?	+
	Phenytoin	++	?	?	?	+
	Ethosuximide	–	++ (T)	–	–	?
	Benzodiazepines	–	–	++	–	–
	Carbamazepine	++	+ (L)	?	+ (NMDA)	+
	Valproate	?	+ (T)	+	+ (NMDA)	++
Second generation	Vigabatrin	–	–	++	–	–
	Zonisamide	++	++ (N, P, T)	+	?	+
	Lamotrigine	++	++ (N, P/Q, R, T)	+	++ (NMDA, AMPA)	+
	Felbamate	++	+ (L)	+	++ (NMDA)	+
	Gabapentin	–	++ (N, P/Q)	?	–	?
	Topiramate	++	+ (L)	++	++ (AMPA)	+
	Tiagabine	–	–	++	–	–
	Oxcarbazepine	++	+ (N, P/Q)	?	+ (NMDA)	+
	Levetiracetam	–	+ (N)	?	?	++
	Stiripentol	–	–	++	–	–
	Pregabalin	–	++ (N, P/Q)	–	–	–
Third generation	Rufinamide	++	–	–	?	–
	Lacosamide	++	–	–	–	+
	Eslicarbazepine acetate	++	–	–	–	–
	Retigabine	–	–	?	–	++

Na^+ = sodium, Ca^{2+} = calcium.
"+" secondary action; "++" primary action; "–"not described; "?" controversial.
[a] Include synaptic vesicle modulation, carbonic anhydrase inhibition, potassium channel activation, and chloride channel complex interaction.

effects are widely recognized. However, these agents may cause a paradoxical disinhibition syndrome in children, elderly, and individuals with intellectual disabilities, which is characterized by agitation, aggressiveness, irritability, and hyperactivity [10]. In addition, the abrupt discontinuation of benzodiazepines can be accompanied by severe seizure exacerbation and changes in mental status, including anxiety, agitation, confusion, depression, psychosis, and even delirium [11,12].

Several AEDs potentiate GABAergic neurotransmission, either by interacting with $GABA_A$ receptors or by modifying the activity of enzymes and transporters involved in the turnover of GABA (Fig. 1). Enhancement of GABAergic neurotransmission is considered to be a primary mechanism of action for barbiturates, vigabatrin (VGB), stiripentol (STP), and tiagabine (TGB). Robust GABAergic effects, however, are also displayed by other compounds, such as topiramate (TPM) and valproate (VPA) (Table 1).

2.2. Glutamate transmission

The role of glutamatergic dysfunction in the pathophysiology of mood and behavioral disorders has gained attention only in recent years. Glutamatergic neurotransmission is an important component in the stress-responsive cascade of events ultimately leading to hippocampal and cortical alterations associated with mood disorders [13–15]. Stress increases extracellular glutamate concentrations [16] and alters glutamate receptor binding profiles and subunit expression in several brain regions [17,18]. A number of studies found that glutamate levels are increased in the plasma of patients with mood disorders [19,20]. Furthermore, psychotropic drugs can alter the binding profile of glutamate receptors [15], and several agents acting on glutamatergic neurotransmission exert positive effects on mood and behavior [9,15].

Inhibition of glutamatergic neurotransmission is the primary or secondary mechanism of action for a number of AEDs (Table 1), but it is of relevance for felbamate (FLB), lamotrigine (LTG), and TPM (Fig. 1).

2.3. Voltage-gated sodium channels

There has been a tendency to investigate the role of neurotransmitter systems in the pathophysiology of mood and behavioral disorders [21,22], whereas other systems, such as disturbances in sodium and calcium transport, have been examined to a lesser extent [22]. Nevertheless, evidence that sodium homeostasis is altered in mood disorders exists. Early studies found that erythrocyte and whole body intracellular sodium concentrations are increased in patients with depression and bipolar disorder and return to normal levels with recovery [23,24]. Furthermore, several effective mood-stabilizing and antidepressant treatments reduce intracellular sodium concentrations or inhibit, through blockade of voltage-gated sodium channels, sodium influx [25]. Of note, blockade of voltage-gated sodium channels also results in inhibition of glutamate release [26], which is itself associated with positive effects on mood and behavior.

Many AEDs act primarily as sodium channel blockers (Table 1 and Fig. 1), including carbamazepine (CBZ), phenytoin (PHT), oxcarbazepine (OXC), eslicarbazepine acetate (ESL), lacosamide (LCM), and rufinamide (RUF). Of note, blockade of voltage-gated sodium channels is also an important mechanism of action for LTG, FLB, TPM, and zonisamide (ZNS).

2.4. Voltage-gated calcium channels

Voltage-gated calcium channels are multimeric proteins composed of five co-assembled subunits (α_1, α_2, β, γ, and δ), which can be broadly classified into high-voltage-activated channels (further subgrouped as L-, R-, P/Q-, and N-types) and low-voltage-activated channels (T-type). Evidence that these channels, particularly high-voltage-activated channels, may be implicated in the pathophysiology of mood disorders exists. Genetic variation in *CACNA1C*, a gene encoding the alpha 1C subunit of the L-type voltage-gated calcium channel, has been associated with bipolar disorder, depression, and schizophrenia [27]. In some experimental models, voltage-gated calcium channel antagonists display antidepressant properties [28,29], whereas agonists lead to depressant-like effects [30]. Inhibition of voltage-gated calcium channels probably translates into a reduction in excitatory neurotransmission [31,32], which may be ultimately responsible for positive effects on mood and behavior.

Ethosuximide (ETX) is a low-voltage-activated T-type channel-blocker, whereas gabapentin (GBP) and pregabalin (PGB) are high-voltage-activated channel blockers through interaction with the α_2–δ