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Review

Do certain signal transduction mechanisms explain the comorbidity of epilepsy and mood disorders?

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ABSTRACT

It is well known that mood disorders are highly prevalent in patients with epilepsy. Although several studies have aimed to characterize alterations in different types of receptors associated with both disturbances, there is a lack of studies focused on identifying the causes of this comorbidity. Here, we described some changes at the biochemical level involving serotonin, dopamine, and γ-aminobutyric acid (GABA) receptors as well as signal transduction mechanisms that may explain the coexistence of both epilepsy and mood disorders. Finally, the identification of common pathophysiological mechanisms associated with receptor–receptor interaction (heterodimers) could allow designing new strategies for treatment of patients with epilepsy and comorbid mood disorders.

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1. Introduction

It is well known that many individuals with epilepsy suffer comorbid mood disorders [1,2]. The fact that patients with epilepsy suffer depression more frequently compared with the general population leads to the suggestion that seizure activity augments the risk of depression or vice versa. Indeed, patients with longer duration of active epilepsy show higher comorbidity of depressive disorders [3]. An alternative hypothesis may be that epilepsy and mood disorders are different manifestations of the same molecular substrates. These may comprise disturbances in transmission and/or signal transduction mediated by serotonin, norepinephrine, glutamate, and gamma-aminobutyric acid (GABA), hyperactivity of the hypothalamic–pituitary–adrenal axis, and central nervous system inflammation [4]. Both epilepsy and mood disorders are chronic disorders with episodic manifestations that often happen simultaneously. Unfortunately, both epilepsy and mood disorders are complex disorders that implicate changes in multiple neurotransmitters, and a comprehensive understanding of the underlying mechanisms is still in its infancy.

Several studies support the notion that alterations in neurotransmission mediated by serotonin, norepinephrine, and/or dopamine in the central nervous system are the mechanisms underlying mood disorders [5]. Receptor binding evaluated by in vivo procedures such as positron emission tomography (PET) has been considered as a pathophysiological and diagnostic marker to identify a specific disease process and/or understand the biology of the disorder. In this article, we review the changes in neuroreceptor function and downstream signal transduction shared by epilepsy and mood disorders which may be critical in the understanding of their comorbidity. In addition, we present recent findings related to signal-transducing G proteins in patients with epilepsy and mood disorders.

2. Neurotransmitters and receptors

2.1. 5-HT_{1A} receptors

Positron emission tomography studies carried out in patients with depression show reduced 5-HT_{1A} receptor binding in several brain regions, including the raphe, limbic areas, and temporal neocortex [6–9]. It is suggested that the downregulation of hippocampal 5-HT_{1A} receptor gene expression and binding in the hippocampus and amygdala arises in response to cortisol hypersecretion in depressive subjects [10,11].

Autoradiography experimental assays using antagonists have led to the suggestion that the low 5-HT_{1A} receptor binding found in the cortex of patients with depression is the consequence of a decrease in the

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number or affinity of 5-HT_{1A} receptors in the free state, i.e., those 5-HT_{1A} receptors in reserve not coupled to a target functional protein (Gαi or Gαo). This situation may diminish 5-HT_{1A} receptor-induced signaling when additional reserve of these receptors is needed (Fig. 1) [12].

Paralleling findings in depression, we found that PET and autoradiography studies demonstrate that patients with temporal lobe epilepsy (TLE) present lower 5-HT_{1A} receptor binding in both medial and lateral temporal regions, ipsilateral to the epileptic foci [13–15]. Patients with TLE and comorbid major depression show significantly more prominent reduction in 5-HT_{1A} receptor binding, which extends into nonlesional limbic brain areas that do not include the epileptic focus [16]. Indeed, the 5-HT_{1A} receptor distribution volumes in the hippocampus inversely correlate with depression ratings of patients with TLE and comorbid mood disorders [17,18]. Considering that decreased 5-HT_{1A} binding in epilepsy is highly correlated to the degree of epileptogenicity [19], it is possible to suggest that the comorbidity of epilepsy and depression is a situation associated with the degree of epileptogenicity. Future studies should be carried out to evaluate this hypothesis and whether there is a compensatory receptor upregulation early in the pathophysiological process of epilepsy (Fig. 1).

Increased activation of 5-HT_{1A} receptor neurotransmission has been related with antidepressive and anticonvulsant effects. Electroconvulsive shock administration results in antidepressant effects associated with sensitization of postsynaptic 5-HT_{1A} receptors in the neocortex and hippocampus [20,21], an effect that is prevented when the $G_{i/o}$ proteins are inactivated by pertussis toxin [22]. On the other hand, activation of 5-HT_{1A} receptors by in vivo administration of 5-HT_{1A} agonists, such as 8-hydroxy-2-(di-n-propylamino) tetralin (8-OH-DPAT) and indorenate, decreases epileptic activity in different experimental models [23–25]. This effect is more evident in the frontal cortex than in the epileptic focus, suggesting an inhibitory role of 5-HT_{1A} receptors in the propagation of seizure activity [26].

2.2. Dopamine receptors

Several studies support the notion that the dopaminergic system is involved in mood disorders. Data obtained from experimental models indicate that increased anxiety levels are associated with lower dopaminergic functioning [27,28]. Patients with different disorders associated with anxiety present low cerebrospinal fluid (CSF) levels of homovanillic acid (HVA, the metabolite of dopamine) [29] and decreased striatal dopamine reuptake sites [30]. Concerning D2 receptor binding in striatal and extrastriatal brain regions of patients with anxiety, studies show conflicting findings probably because of the different imaging methods used [31,32] (Fig. 2).

Patients with depression exhibit low D1 receptor binding potential in bilateral striata [33]. In contrast, increased D2 receptor binding has been detected in the basal ganglia, mesolimbic structures, and temporal cortex [34–37], a situation that has been explained by depletion of dopamine or dopaminergic hypofunction [38,39] (Fig. 2).

It is suggested that chronic administration of antidepressant drugs enhances the dopaminergic modulation at least in part by increased D1-like receptor binding [40] or the proportion of high-affinity state D1 receptors as a consequence of increased levels of Golf, a stimulatory G protein that is coupled with the dopamine D1 receptor [41]. Antidepressants do not modify the total D2/3 receptor density but augment receptor function in major depressive disorders [42–44]. It is possible that this effect is induced by sensitization of D2/3 receptors as a consequence of increased coupling to G proteins. However, no data exist to support this hypothesis. The antidepressant effect induced by electroconvulsive therapy (ECT) has been associated with transient increases in D1 receptor binding, without significant alterations in binding potential to D2 receptors in the striatum [45], but decreased D2 binding in the rostral anterior cingulate cortex [46]. These results suggest that antidepressant therapeutic strategies induce significant changes in dopaminergic neurotransmission (Fig. 2).

Studies indicate that dopaminergic neurotransmission is altered in the temporal lobe of patients with TLE. Concerning D1 receptors, there is an increase in protein expression and binding. Protein expression of D2 receptors is reduced, but its binding has been reported to be decreased or not modified [47,48]. However, elevated D2-like-induced activation of G proteins was detected in the temporal neocortex of patients who presented a shorter duration of TLE with no comorbid anxiety or depression. These findings suggest that higher activation or sensitization of D2 subfamily receptors in the cerebral neocortex of patients with epilepsy reduces symptoms produced by depression [49,50], with effects more evident during the early years following epilepsy onset. In contrast, lower D2 receptor-induced neurotransmission is detected in patients with drug-refractory epilepsy of longer duration and comorbid psychiatric disorders [2,51,52] (Fig. 2).

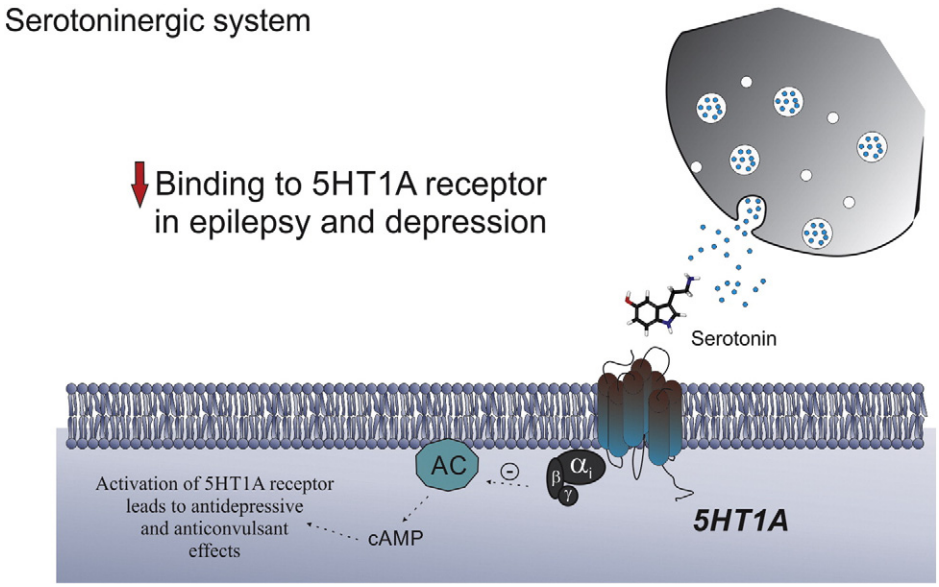

Fig. 1. Schematic illustration of 5-HT_{1A} receptor-induced activation of transductional mechanisms. Several studies suggest that 5-HT_{1A} receptors mediate inhibitory effects, and the binding to those receptors is decreased in both disorders. cAMP, cyclic adenosine monophosphate; AC, adenylate cyclase.

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