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Neurobiology of Depression as a Comorbidity of Epilepsy

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Summary

The study of depression as a comorbidity of epilepsy in humans is limited by the attendant iatrogenic and psychosocial variables. In order to study the neurobiology of this clinically important phenomenon without the above-mentioned confounding factors, we have studied the behavioral and biochemical correlates of epilepsy-associated depression in two rodent models of limbic epileptogenesis. For an expanded treatment of this topic see *Jasper's Basic Mechanisms of the Epilepsies, Fourth Edition* (Noebels JL, Avoli M, Rogawski MA, Olsen RW, Delgado-Escueta AV, eds) published by Oxford University Press. Available on NCBI Bookshelf.

Keywords

animal models; glucocorticoids; hypothalamus-pituitary-adrenal (HPA) axis; interleukin-1 β ; seizures; serotonin

Depression represents one of the most disabling comorbidities of epilepsy and impacts profoundly negatively on the quality of life of patients with epilepsy. In clinical circumstances, the contributions to this problem include psychosocial factors, iatrogenic factors as well as neurobiological links between the two conditions, namely, epilepsy and depression. Our laboratory has undertaken to study the neurobiological connection between depression and epilepsy with the hope that such knowledge may contribute to mechanism-driven therapy development for depression in epilepsy.

We examined the development of behavioral and neurochemical markers of depression in two models of limbic epileptogenesis. We employed the rapid-kindling model of epileptogenesis to describe the association first, since this model is not accompanied by discernible injury to the hippocampus or other structures (Mazarati et al., 2007). Rats subjected to rapid-kindling displayed an increase in immobility time in the forced swim test (behavioral equivalent of despair) and loss of taste preference (representing anhedonia). These animals had decreased serotonin turnover in the raphe and compromised evoked release of serotonin into the hippocampus upon raphe stimulation. These effects were also duplicated in the lithium-pilocarpine model of temporal lobe epilepsy (Mazarati et al., 2008). Pharmacologic studies revealed a cascade of disturbances which include enhanced interleukin-1 β signaling in the hippocampus and enhanced “gain” in the hypothalamus-pituitary-adrenal (HPA) axis (Mazarati et al., 2009, 2010). Higher circulating glucocorticoid concentrations were connected to changes in serotonergic 5-HT_{1A} receptor activity. These phenomena were observed in post-status epilepticus animals with or without spontaneous seizures, reminiscent of observations in humans that showed a lack of relationship between seizure frequency and depression scores. Chronic infusion of recombinant interleukin

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receptor antagonist into the hippocampus, as well as infusion of a selective glucocorticoid receptor antagonist mifepristone or selective 5-HT_{1A} blocker WAY-100635 restored behavior as well as evoked serotonin release. Our studies suggest that the pilocarpine model may serve as a model of comorbidity between epilepsy and depression and furnish a screening platform for mechanism-driven therapeutic approaches.

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