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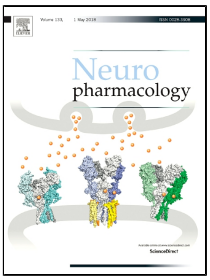

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Mechanisms underlying anticonvulsant and proconvulsant actions of norepinephrine

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Abstract

Norepinephrine (NE) has been shown to exert a potent suppressant effect on seizure development. On the other hand, several lines of evidence have shown that increased NE level is proconvulsant under certain conditions. These data suggest that variations in NE levels could affect modulatory action of noradrenergic system on seizures. Less, however, is known about the mechanisms by which adrenergic pathways protect against seizures or promote seizures. Knowing the mechanisms involved in anti- or proconvulsive effects of NE may help to the development of new therapeutic candidates for patients with refractory epilepsy. Here, we present some possible mechanisms involved in actions of NE on seizures.

Keywords: Adrenergic receptors, Anticonvulsant, Mechanism of action, Norepinephrine, Proconvulsant

Introduction

Epilepsy is a disorder of the central nervous system (CNS) characterized by spontaneous recurrent seizures (Fisher et al. 2014). Norepinephrine (NE) has been shown to act as a potent anticonvulsant (Weinshenker and Szot 2002; Giorgi et al. 2004) affecting the initiation (Bregman et al. 1985; el-Etri et al. 1993), spread (Bregman et al. 1985; Giorgi et al. 2003) and termination of the seizures (Tsuda et al., 1993). It is released from noradrenergic terminals originating primarily in locus coeruleus (LC), which in turn sends projections of NE-containing axons to many different brain regions, including areas involved in epilepsy (Loughlin et al. 1986; Berridge and Waterhouse 2003; Iversen et al. 2009). Noradrenergic abnormalities are involved in increased seizure susceptibility and severity detected in genetically epilepsy-prone rats (GEPRs), a model of generalized tonic/clonic epilepsy (Jobe et al. 1984; Dailey and Jobe 1986; Browning et al. 1989; Lauterborn and Ribak 1989; Dailey et al. 1991). Moreover, NE levels (Tsuda et al. 1993) as well as the density of adrenergic receptors (Brière et al. 1986; Nicoletti et al. 1986) are reduced following seizures, depending on seizure type or brain area affected. Generally, pharmacological agents or therapies that elevate extracellular NE levels have anticonvulsant actions (Szot et al. 2001; Weinshenker and Szot 2002; Kaminski et al. 2005; Schank et al. 2005; Martillotti et al. 2006; Weinshenker 2008). Conversely, NE depletion or administration of adrenergic receptor antagonists accelerate the rate of seizures (Corcoran and Mason 1980; McIntyre and Edson 1982; Kokaia et al. 1989).

While anticonvulsant effects of NE and noradrenergic drugs have been detected in various forms of epilepsy, both human and animal studies demonstrate that increased levels of NE may be proconvulsant under certain conditions (Dailey and Naritoku 1996; Lancaster and Davies 1991; Fitzgerald 2010). Furthermore, antiepileptic effects of some antiepileptic drugs including valproic acid and phenytoin (Baf et