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Epilepsy Research 66 (2005) 117–128

Epilepsy Research

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Adrenergic receptor modulation of hippocampal CA3 network activity

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Received 28 April 2005; received in revised form 14 July 2005; accepted 27 July 2005
Available online 2 September 2005

Abstract

Norepinephrine (NE) has demonstrated proconvulsant and antiepileptic properties; however, the specific pharmacology of these actions has not been clearly established. To address this, we studied the effect of NE on hippocampal CA3 epileptiform activity. Frequency changes of burst discharges in response to NE were biphasic; low concentrations increased the number of bursts, while higher concentrations reduced their frequency, suggesting the involvement of multiple adrenergic receptor (AR) types. This hypothesis was confirmed when, in the presence of βAR blockade, increasing concentrations of NE caused a monophasic decrease in epileptiform activity. Antagonists selective for α_1 or α_2ARs were then used to determine which αAR type was involved. While discriminating concentrations of the α_1AR antagonists prazosin and terazosin had no effect, selective amounts of the α_2AR antagonists RS79948 and RX821002 significantly reduced the potency of NE in decreasing epileptiform activity. Furthermore, this antiepileptic action of NE persisted when all GABA-mediated inhibition was blocked. This data suggests that, under conditions of impaired GABAergic inhibition, the excitatory and inhibitory effects of NE on hippocampal CA3 epileptiform activity are mediated primarily via β and α_2ARs, respectively. Moreover, our results imply that the antiepileptic effect of α_2AR activation in CA3 is not dependent on the GABAergic system.

Keywords: Norepinephrine; Hippocampal CA3 region; α_2 Adrenergic receptor; Field potentials; Bicuculline; Epileptiform burst activity

1. Introduction

Norepinephrine (NE), an endogenous neurotransmitter, has profound effects on seizure activity (Giorgi et al., 2004). While these actions may have poten-

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doi:10.1016/j.eplepsyres.2005.07.007

tial therapeutic relevance, the specific pharmacology of these effects has not been unequivocally established (Weinshenker and Szot, 2002). This lack of knowledge has hindered the determination of these underlying mechanisms and limited their possible clinical application. Delineating which adrenergic receptors (ARs) mediate the various actions of NE would not only be extremely useful for examining the role of NE in epilepsy, but could be exploited pharmacologically for future antiepileptic drug development.

Among the major targets of the NE system in the brain is the hippocampus (Loy et al., 1980), which contains one of the highest densities of NE-containing terminals (Schroeter et al., 2000). As part of the limbic system, the hippocampus is an essential component of the neural circuitry which governs emotions, attention, and certain memory processes (Milner et al., 1998; Aston-Jones et al., 1999; Eichenbaum, 2000). The hippocampus also plays a major role in epilepsy. It has an extremely low seizure threshold and thus is frequently involved in hyperexcitable episodes (Johnston and Amaral, 2004). Furthermore, the disinhibited hippocampus is often used as a model of acute focal epilepsy (Schwartzkroin, 1986), since the excitatory pyramidal neurons in the hippocampus, particularly those in the CA3 region, can develop synchronous depolarizations under conditions of impaired synaptic inhibition.

The NE system has been demonstrated to play a critical role in modifying epileptic activity (Chauvel and Trottier, 1986; Weinshenker and Szot, 2002). Stimulation of ARs has profound anticonvulsant properties in many seizure models (Weiss et al., 1990; Ferraro et al., 1994). Conversely, destruction of the NE system using pharmacological or transgenic techniques impairs the ability to prevent seizures (Arnold et al., 1973; Weinshenker and Szot, 2002). Furthermore, an intact NE system appears to be requisite for the antiepileptic effects of the ketogenic diet and vagal nerve stimulation (Krahl et al., 1998; Szot et al., 2001). It should be noted, however, that depending on the epilepsy model and brain region studied, NE exhibits both proconvulsant and antiepileptic actions (Weinshenker and Szot, 2002). Uncovering the multiple functions of NE has been complicated by the diversity of ARs that it binds and activates.

Based on both pharmacological and molecular biological evidence, ARs are classified into three major types (α_1, α_2, and β), each of which consists of three subtypes (Bylund et al., 1994). Although all ARs are coupled to G proteins, each receptor type appears to have its own distinct pharmacological characteristics (Pupo and Minneman, 2001). Activation of these different AR types is often seen to produce different, if not opposing, effects within the same cell or system.

The effect of AR activation in the rat hippocampus is still under debate, as most of the past investigations used either non-selective pharmacological agents or concentrations of agents which were not discriminatory. While several studies have suggested that NE's antiepileptic actions are mediated through α_1AR activation (Stanton et al., 1992; Rutecki, 1995), some have indicated a role for βARs (Ferraro et al., 1994), and others, α_2AR involvement (Stoop et al., 2000). Conversely, other studies found NE to be proepileptic, further confounding the role of AR stimulation in the hippocampus (Mueller and Dunwiddie, 1983; Leung and Miller, 1988).

The specific mechanisms underlying the antiepileptic actions of NE in the hippocampus are also not known. A potential mechanism could be a NE-mediated increase in synaptic inhibition. In the hippocampus, the synaptic inhibition is generated by the inhibitory neurotransmitter, γ-amino-butyric acid (GABA) acting through $GABA_A$ and $GABA_B$ receptors. Since NE increases the release of GABA from hippocampal interneurons (Doze et al., 1991; Bergles et al., 1996), the NE-enhanced GABA release would be expected to increase GABA receptor-mediated inhibition, and thus could reduce hyperexcitability.

The aim of this study was to determine the AR types mediating the various actions of NE on hippocampal CA3 burst activity using selective concentrations of AR antagonists. Another goal was to clarify the role of the GABAergic system in the anticonvulsant effects of NE. Our results indicate that, under conditions where the GABAergic inhibition is impaired, the excitatory and inhibitory effects of NE on hippocampal CA3 epileptiform activity are primarily due to activation of β and α_2ARs, respectively. Furthermore, these results imply that enhanced synaptic inhibition is not the underlying mechanism for the antiepileptic effects of NE-mediated through α_2AR activation.