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Invited review

Adenosinergic signaling in epilepsy

Detlev Boison

Robert Stone Dow Neurobiology Laboratories, Legacy Research Institute, Portland, OR 97232, USA

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ABSTRACT

Despite the introduction of at least 20 new antiepileptic drugs (AEDs) into clinical practice over the past decades, about one third of all epilepsies remain refractory to conventional forms of treatment. In addition, currently used AEDs have been developed to suppress neuronal hyperexcitability, but not necessarily to address pathogenic mechanisms involved in epilepsy development or progression (epileptogenesis). For those reasons endogenous seizure control mechanisms of the brain may provide alternative therapeutic opportunities. Adenosine is a well characterized endogenous anticonvulsant and seizure terminator of the brain. Several lines of evidence suggest that endogenous adenosine-mediated seizure control mechanisms fail in chronic epilepsy, whereas therapeutic adenosine augmentation effectively prevents epileptic seizures, even those that are refractory to conventional AEDs. New findings demonstrate that dysregulation of adenosinergic mechanisms are intricately involved in the development of epilepsy and its comorbidities, whereas adenosine-associated epigenetic mechanisms may play a role in epileptogenesis. The first goal of this review is to discuss how maladaptive changes of adenosinergic mechanisms contribute to the expression of seizures (ictogenesis) and the development of epilepsy (epileptogenesis) by focusing on pharmacological (adenosine receptor dependent) and biochemical (adenosine receptor independent) mechanisms as well as on enzymatic and transport based mechanisms that control the availability (homeostasis) of adenosine. The second goal of this review is to highlight innovative adenosine-based opportunities for therapeutic intervention aimed at reconstructing normal adenosine function and signaling for improved seizure control in chronic epilepsy. New findings suggest that transient adenosine augmentation can have lasting epigenetic effects with disease modifying and antiepileptogenic outcome.

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E-mail address: dboison@downeurobiology.org.

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1. Introduction

Thirty-five years ago it was first demonstrated that endogenous adenosine may act as an endogenous anticonvulsant of the brain (Dunwiddie, 1980). Since then a large number of studies have validated the concept that adenosine acts as endogenous anticonvulsant and seizure terminator of the brain (Ault and Wang, 1986; Dragunow, 1991; Dragunow et al., 1985; Dunwiddie and Fredholm, 1984; Lee et al., 1984), not at least supported by studies showing a rise of seizure-induced endogenous adenosine coinciding with seizure termination (During and Spencer, 1992; Van Gompel et al., 2014). Neuronal excitability in the brain is modulated by activation of G protein coupled adenosine receptors (A_1, A_{2A}, A_{2B}, A_3) (Fredholm et al., 2001, 2005, 2011). Therefore, excitability depends on the equilibrium of different receptor-mediated effects, receptor expression levels, and availability of endogenous adenosine to activate the receptors. In addition, adenosine has receptor independent effects that regulate biochemical enzyme reactions and that affect epigenetic functions (Williams-Karnesky et al., 2013). Whereas different sources of adenosine from neurons and astrocytes affect synaptic versus homeostatic adenosine signaling (Cunha, 2001, 2008), overall levels of adenosine are largely under the control of metabolic clearance through the astrocyte-based enzyme adenosine kinase (ADK) (Boison, 2013; Fedele et al., 2004; Lloyd and Fredholm, 1995; Pak et al., 1994). Maladaptive processes that determine adenosine availability and signaling have been associated with the development of epilepsy and – consequently – therapeutic approaches aimed at restoring normal adenosinergic function hold promise for the therapy of epilepsy (Boison, 2008, 2012a). The following sections will review maladaptive changes of the adenosine system in epilepsy and discuss the therapeutic potential of adenosine augmentation therapies.

2. Imbalance of adenosine receptor activation

Several lines of evidence suggest that maladaptive changes in adenosine receptor signaling contribute to the pathophysiology of epilepsy. It is conceivable that any shift in the ratio of inhibitory A_1R vs. stimulatory $A_{2A}Rs$ directly affects neuronal excitability. Material covered in subsequent sections summarizes findings that show that the epileptic state is indeed characterized by decreased A_1R signaling and increased $A_{2A}R$ signaling. However, it is currently unknown whether changes in adenosine receptor expression are cause for or consequence of epilepsy.

2.1. Adenosine A_1R

Experimentally, a decrease in A_1R density and the failure of endogenous adenosine-based seizure control mechanisms have been described in the rat kindling model of epilepsy suggesting the failure of endogenous seizure control mechanisms in epilepsy (Rebola et al., 2003). Receptor knockout studies have shown that mice lacking the A_1R have spontaneous electrographic seizures (Li et al., 2007a) and develop lethal status epilepticus following the intrahippocampal injection of kainic acid, or a traumatic brain injury (Fedele et al., 2006; Kochanek et al., 2006). These studies directly show that A_1R activation is needed to prevent seizure spread. Histopathological and biochemical analyses from specimen surgically resected from patients with intractable epilepsy show decreased expression levels of A_1 receptors, suggesting that decreased A_1R expression may contribute to seizure generation in human chronic epilepsy (Glass et al., 1996). Experimentally, dynamic changes in A_1R signaling or expression have been described as a direct consequence of acute seizures. Desensitization of A_1R responses but normal receptor levels have been described in the hippocampus of rats after status epilepticus elicited by performant path stimulation (Hamil et al., 2012), whereas upregulation of the A_1R in the entorhinal cortex has been described as a response to spontaneous seizures induced by electrical stimulation (Hargus et al., 2012). In a human genomic study variants in the A_1R gene have been associated with the development of posttraumatic seizures after a severe traumatic brain injury, suggesting that deficiency in A_1R signaling might be associated with posttraumatic epileptogenesis (Wagner et al., 2010). Together, these data suggest that dysregulation of A_1R signaling is intricately linked to the pathophysiology of epilepsy.

2.2. Adenosine $A_{2A}R$

The synaptic fraction of $A_{2A}Rs$ can mediate synaptotoxic effects of the synaptic pool of adenosine (Matos et al., 2012; Popoli et al., 2003; Silva et al., 2007), which is largely dependent on the neuronal release of adenosine or its precursor ATP (Lovatt et al., 2012). Thereby, neuronal hyperexcitability in epilepsy likely leads to enhanced synaptic $A_{2A}R$ activation, which could aggravate synaptotoxicity and thereby further the degeneration of normal circuitry contributing to the progressive course of epilepsy. Interestingly, genetic variants of the $A_{2A}R$ gene have been associated with acute encephalopathy with biphasic seizures and late reduced diffusion in children, suggesting that $A_{2A}R$ dysregulation promotes seizures and excitotoxic brain damage in those patients (Shinohara et al., 2013). In Wistar Albino Glaxo/Rijswijk (WAG/Rij) rats, a model of human absence epilepsy, increased expression of $A_{2A}Rs$ in epileptic rats, but not in pre-symptomatic animals has been described suggesting that increased $A_{2A}R$ expression in this model supports the epileptic phenotype (D'Alimonte et al., 2009). In line with a potentially pro-convulsive role of the $A_{2A}R$, $A_{2A}R$ knockout mice were partially resistant to limbic seizures. In conclusion, increased $A_{2A}R$ activation may promote the epileptic state.

2.3. Adenosine A_{2B} and A_3Rs

Little is known about the contribution of $A_{2B}Rs$ and A_3Rs in epilepsy. Using an *in vitro* system of tissue from human resected epileptogenic foci, which was microtransplanted into Xenopus