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Review article

Modulation of adenosinergic system and its application for the treatment of epilepsy

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ABSTRACT

Adenosine is present in all cells and is implicated in the control of the function of every tissue and organ. The elevated adenosine levels seem to play a significant role in a protection against cellular damage in the regions with increased metabolic demand and prevent the subsequent dysfunction of the affected organs. Furthermore, adenosine has been shown to play an important role not only in the regulation of pathophysiological processes, but also in the modulation of normal physiological processes, for example, the regulation of sleep and arousal as well as by impact on pre- or postsynaptic receptors involved in releasing neurotransmitters (*e.g.* glutamate, acetylcholine, norepinephrine, 5-hydroxytryptamine, dopamine, GABA and others).

Experimental studies provide evidence supporting the role of adenosine as an endogenous anticonvulsant agent. Numerous adenosine agonists acting through A_1, A_2 and A_3 receptors were proven as potent anticonvulsant compounds in a wide variety of animal models of epilepsy. However, despite their efficacy in such models, adenosine receptor agonists do not appear to be good candidates for successful clinical applications. The therapeutic range of systemically administered adenosine receptor agonists is very narrow and they often produce profound adverse events. It seems, therefore, that adenosine receptor agonists could only be used clinically when co-administered with other antiepileptic drugs or when used in local therapies, where their side effect profile is much more tolerable. An alternative strategy would be to enhance the natural adenosinergic feedback mechanism triggered by seizures by using adenosine uptake inhibitors. This approach seems very attractive as it would allow limiting the action only in the active areas such as seizure foci and thus, preventing the systemic side effects.

Contents

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Introduction

Many epileptic patients are not adequately treated with currently available antiepileptic drugs. It is estimated that seizures are intractable in as much as 35% of patients with partial complex seizures, which are the most frequent type of epilepsy in humans [1,2]. Non-pharmacological therapies, such as surgical resection, are applicable for only some patients as it is often extremely difficult or even impossible to localize the epileptic focus. In many cases, the epileptic focus is located in the close proximity of eloquent brain areas, which creates serious surgical risks [3]. Moreover, the potential for significant side effects caused by the drug actions in or outside of the brain limits the optimal systemic drug delivery in a high percentage of cases. There is, therefore, an unfulfilled need for alternative treatment strategies that would allow achieving improved efficacy in these drug resistant forms of epilepsy. Recently, several novel approaches are being investigated and a number of them concentrate on therapies that involve mechanisms of action different from those exhibited by the currently available antiepileptic drugs. The approach that seems to be particularly attractive and promising involves modulation of excitatory neurotransmission in the brain with agents suppressing neuronal activity, including the adenosinergic system.

Adenosine exists in all cells and it is implicated in the control of the function of every tissue and organ. Extracellular levels of adenosine rise during conditions involving increased metabolic demand and/or lack of oxygen. Such conditions occur during seizures, ischemia, stress, hypoglycemia, inflammation and trauma. The increased adenosine-5′-triphosphate (ATP) metabolism taking place in such conditions leads to the production of adenosine through the breakdown of ATP *via* adenosine-5′-diphosphate (ADP) and adenosine-5′-monophosphate (5′-AMP) [4]. The elevated adenosine levels seem to play a role in a protection against cellular damage in the regions with increased metabolic demand and prevent the subsequent dysfunction of the affected organs. Numbers of study reports available to date provide evidence that adenosine exerts a protective action throughout all organs of the body and its effects range from the amelioration of brain and heart injury caused by ischemia, suppression of inflammation and suppression of seizures. Furthermore, adenosine has been shown to play an important role not only in the regulation of pathophysiological processes, but also in the modulation of normal processes, especially, the regulation of sleep and arousal [5]. Adenosine is a natural sleep-promoting agent and its level increasing during periods of wakefulness and decreasing during sleep [6]. Adenosine is involved in the autoregulation of cerebral blood flow modulating vascular resistance and causing vasodilation, inhibits locomotor activity and motor coordination [7,8], causes sedation [9] and leads to depression of cardiovascular and respiratory functions (for review see Dunwiddie and Masino [10]).

Adenosine enters the extracellular space either following the dephosphorylation of adenine nucleotides or through a direct release from cells. This release does not appear to be calcium-dependent and takes place *via* facilitated diffusion nucleoside transporters, which are driven by adenosine concentration gradients. Active sodium-dependent adenosine transporters have also been identified, however, their importance is yet to be established [11].

Adenosine is removed from the extracellular space by reuptake transported to the cells (facilitated diffusion or active transport) or by inactivation with adenosine deaminase resulting in transformation to inosine [12,13,14].

Adenosine behaves as an extracellular signal molecule and affects synaptic transmission without being itself a neurotransmitter, and thus modulating the activity of the nervous system at cellular level. This modulation takes place either presynaptically by inhibiting or facilitating transmitter release or postsynaptically by depolarizing or hyperpolarizing neurons [15]. Stimulation of the adenosine receptors causes the inhibition of the release of the various neurotransmitters like glutamate, acetylcholine, norepinephrine, 5-hydroxytryptamine, dopamine, GABA and others [16,17]. The strongest inhibitory action of adenosine occurs in the excitatory glutamatergic system, where it is capable of completely blocking synaptic transmission. The action on the excitatory system is much stronger than that on the inhibitory modulation of inhibitory systems, therefore, in general the activation of adenosine receptors leads to reduced excitability of neurons [18].

Types of adenosine receptors

Adenosine exerts its effects by interacting with specific cell-surface G-protein coupled receptors. Activation of these receptors leads to the inhibition of calcium influx and opening of presynaptic potassium channels (GIRKs), which causes hyperpolarization and subsequent decrease in the release of excitatory neurotransmitters. So far, four adenosine receptors have been identified, cloned, pharmacologically characterized and classified into the following subtypes: A_1, A_{2A}, A_{2B} and A_3 [19]. The A_1 and A_3 receptors interact with G and G_0 proteins and inhibit adenyl cyclase, whereas the A_{2A} and A_{2B} receptors stimulate the adenyl cyclase through interaction with members of the G_s family of G proteins. A_1, A_{2B} and A_3 receptors can also activate phospholipase C, and this action is mediated by activation of G_q proteins [20].

Adenosine receptors show an uneven distribution with A_1 receptors widely presents throughout the brain, but particularly concentrated in the cerebral cortex, cerebellum, hippocampus, olfactory tubercles and ventral globus pallidus [21,22]. The A_1 receptors are also found in the heart, aorta, liver, kidney, bladder and eye. The high affinity A_{2A} receptors are present at high levels in only a few parts of the brain, such as the striatum [23], nucleus accumbens and olfactory tubercles [24]. However, a highly sensitive RT-PCR technique (reverse transcription-polymerase chain reaction) can detect low concentrations of A_{2A} receptor