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Neuromodulation and metamodulation by adenosine: Impact and subtleties upon synaptic plasticity regulation

*Ana M. Sebastião**, *Joaquim A. Ribeiro*

Instituto de Farmacologia e Neurociências, Faculdade de Medicina e Unidade de Neurociências, Instituto de Medicina Molecular, Universidade de Lisboa, Lisboa, Portugal

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ABSTRACT

Synaptic plasticity mechanisms, i.e. the sequence of events that underlies persistent changes in synaptic strength as a consequence of transient alteration in neuronal firing, are greatly influenced by the 'chemical atmosphere' of the synapses, that is to say by the presence of molecules at the synaptic cleft able to fine-tune the activity of other molecules more directly related to plasticity. One of those fine tuners is adenosine, known for a long time as an ubiquitous neuromodulator and metamodulator and recognized early as influencing synaptic plasticity. In this review we will refer to the mechanisms that adenosine can use to affect plasticity, emphasizing aspects of the neurobiology of adenosine relevant to its ability to control synaptic functioning.

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1. Introduction

Synaptic plasticity refers to events that lead to changes in synaptic strength that follow transient changes in neuronal activity, being widely accepted as a functional correlate of learning and memory. As detailed in several chapters of this issue, it may involve long- or short-lasting alterations of inhibitory and/or excitatory synapses, synapse weakening or reinforcement, functional or structural modifications of synapses. Being a consequence of and resulting in modifications of synaptic activity, plasticity is strongly influenced by modulators of synaptic activity.

Adenosine is an ubiquitous neuromodulator, released by neurons and glia and affecting the activity of synapses at the pre-, post- and non-synaptic levels through the activation of membrane-located G-protein coupled receptors (GPCR) (Sebastião and Ribeiro, 2009). It can be formed extracellularly from released ATP, ATP and adenosine being key molecules in

Abbreviations: ADK, adenosine kinase; cAMP, cyclic adenosine monophosphate; CNT, concentrative nucleoside transporter; ENT, equilibrative nucleoside transporter; LTD, long-term depression; LTP, long-term potentiation

*Correspondence to: Instituto de Farmacologia e Neurociências, Faculdade de Medicina, Universidade de Lisboa, Av. Prof. Egas Moniz, 1649-028 Lisboa, Portugal.

E-mail addresses: anaseb@medicina.ulisboa.pt (A.M. Sebastião), jaribeiro@medicina.ulisboa.pt (J.A. Ribeiro).

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tripartite synapse communication (Fields and Burnstock, 2006; Hamilton and Attwell, 2010). Challenging ideas on the way adenosine can set the stage for plasticity have been put forward recently (Dias et al., 2013a). We herein refer to the mechanisms adenosine can use to affect plasticity, emphasizing aspects of the neurobiology of adenosine relevant for its ability to control synaptic functioning. Importantly, adenosine can act to control the action of other modulators of synaptic functioning and in such way operate as a metamodulator of synaptic activity and plasticity (Ribeiro and Sebastião, 2010; Dias et al., 2013a). We will predominantly refer to the hippocampus, the brain area mostly studied in what concerns synaptic plasticity.

2. Neurobiology of adenosine

2.1. *Extracellular adenosine dynamics*

The levels of intracellular and extracellular adenosine are under the control of equilibrative nucleoside transporters (ENT) in the plasma membrane (Parkinson et al., 2011), which can either release or take up adenosine according to its concentration gradient across the membrane. Since there is an independent source of adenosine in the extracellular space, the catabolism of released adenine nucleotides (Fig. 1A), the synaptic concentration of adenosine is usually higher than the intracellular one. Therefore, the transport across ENTs is usually in the inward direction. It can, however, be reversed under conditions of high intracellular adenosine. ENTs are the most abundant nucleoside transporters in the brain, being expressed in neurons and glia; concentrative nucleoside transporters (CNTs) also exist but their expression in the brain is low (Parkinson et al., 2011). The possibility that CNTs may play a role in the sleep/wakefulness cycle was, however, advanced on the basis that sleep deprivation diminishes the amounts of CNT2 mRNA in the brain (Guillén-Gómez et al., 2004).

The intracellular concentration of adenosine depends on the activity of adenosine kinase (ADK) (EC 2.7.1.20), which converts adenosine into AMP with a Km value in the sub-micromolar range (Yamada et al., 1980). ADK in the adult brain is predominantly expressed in astrocytes (Studer et al., 2006). Alterations in the activity of ADK in astrocytes lead to marked changes in synaptic activity at the hippocampus (Diógenes et al., 2014), a strong indication of the involvement of adenosine release per se in the astrocytic to neuronal

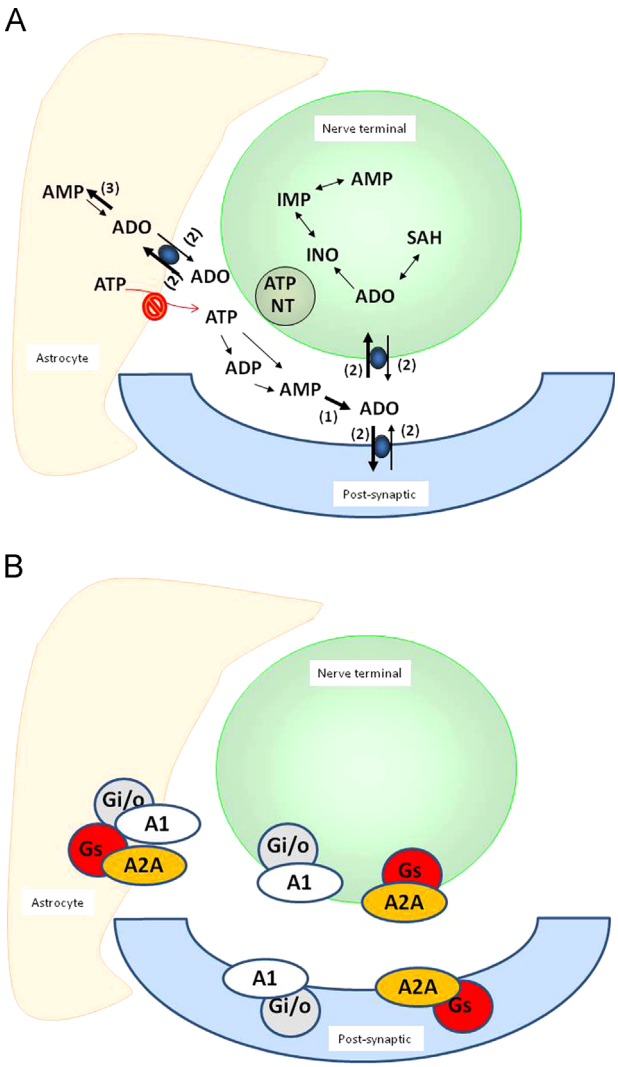

Fig. 1 – Schematic representation of the main molecules involved in the control of the action of adenosine at the tripartite synapse. (A) Main mechanisms involved in the control of extracellular levels of adenosine. Adenosine (ADO) can be formed extracellularly from the breakdown of released ATP through a cascade of ectoenzymes, the last step being hydrolysis of AMP by ecto-5'-nucleotidase (1). Adenosine is also released as such through equilibrative transporters (2). Adenosine kinase (3), present in astrocytes, efficiently converts adenosine into AMP. Inter-conversion of adenosine into S-adenosyl-homocysteine (SAH) or deamination into inosine (INO) also contributes to the low intracellular adenosine levels. Intracellular AMP also results from the action of phosphodiesterases over cyclic AMP, which in turn results from the action of adenylate cyclase upon ATP (not shown). ATP is released from the astrocytes through a mechanism not yet fully understood. ATP is also stored with neurotransmitters (NT) being released from the nerve terminal upon stimulation. See text for details and references. (B) Subtypes of high affinity adenosine receptors that modulate synaptic function. Once in the extracellular space, adenosine activates membrane-located G-protein coupled receptors. The A1 receptor is an inhibitory receptor, coupled with Gi/o proteins. The A2A receptor is an excitatory receptor, coupled with Gs proteins. Both receptors can be located at the tripartite synapse either at the nerve terminal, at the post-synaptic level or at the astrocyte, to control neuronal activity. The receptors in astrocytes can form A_1/A_{2A} heteromers, as directly assessed by BRET assays (Cristóvão-Ferreira et al., 2013). However, A1/A2A heteromers may also exist in nerve terminals (Ciruela et al., 2006). Moreover, this schematic representation does not intend to preclude the existence of non-heteromeric forms of the receptors in the astrocytes. For a recent discussion on the impact of receptor heteromerization for neuronal plasticity see Fuxe et al. (2014). See the text for details and further references.