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Different cellular sources and different roles of adenosine: A_1 receptor-mediated inhibition through astrocytic-driven volume transmission and synapse-restricted A_{2A} receptor-mediated facilitation of plasticity

Rodrigo A. Cunha *

Center for Neuroscience of Coimbra, Institute of Biochemistry, Faculty of Medicine, University of Coimbra, 3004-504 Coimbra, Portugal

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Abstract

Adenosine is a prototypical neuromodulator, which mainly controls excitatory transmission through the activation of widespread inhibitory A_1 receptors and synaptically located A_{2A} receptors. It was long thought that the predominant A_1 receptor-meditated modulation by endogenous adenosine was a homeostatic process intrinsic to the synapse. New studies indicate that endogenous extracellular adenosine is originated as a consequence of the release of gliotransmitters, namely ATP, which sets a global inhibitory tonus in brain circuits rather than in a single synapse. Thus, this neuron-glia long-range communication can be viewed as a form of non-synaptic transmission (a concept introduced by Professor Sylvester Vizi), designed to reduce noise in a circuit. This neuron-glia-induced adenosine release is also responsible for exacerbating salient information through A_1 receptor-mediated heterosynaptic depression, whereby the activation of a particular synapse recruits a neuron-glia network to generate extracellular adenosine that inhibits neighbouring non-tetanised synapses. In parallel, the local activation of facilitatory A_{2A} receptors by adenosine, formed from ATP released only at high frequencies from neuronal vesicles, down-regulates A_1 receptors and facilitates plasticity selectively in the tetanised synapse. Thus, upon high-frequency firing of a given pathway, the combined exacerbation of global A_1 receptor-mediated inhibition in the circuit (heterosynaptic depression) with the local synaptic activation of A_{2A} receptors in the activated synapse, cooperate to maximise salience between the activated and non-tetanised synapses.

Keywords: Adenosine; A_1 receptor; A_{2A} receptor; ATP; Nerve ending; Nerve terminal; Astrocyte; Synaptic plasticity; Modulation

1. Adenosine in the brain

Adenosine is a prototypic neuromodulator in the nervous system, which means it does not trigger direct neuronal responses but instead fine tunes on-going synaptic transmission. The impact of adenosine modulation is more evident in the control of excitatory rather than inhibitory synapses (reviewed in Dunwiddie and Masino, 2001). The most widely recognised effects of adenosine are operated through inhibitory A_1 receptors, one of the most abundant G protein-coupled receptors in brain tissue (Dunwiddie and Masino, 2001). A_1 receptors are mainly located in synapses (Rebola et al., 2003), in particular in glutamatergic synapses (Rebola et al., 2005a). They are located presynaptically where they inhibit glutamate release (as well as other neurotransmitters) and post-synaptically where they inhibit calcium influx through voltage-sensitive calcium channels and NMDA receptors and also inhibit potassium currents, leading to membrane hyperpolarization (reviewed in Fredholm et al., 2005). Altogether, these physiological functions of adenosine operated through A_1 receptors provide a compelling rationale for this modulation system to fulfil a neuroprotective role in situations of brain damage (reviewed in de Mendonça et al., 2000). Interestingly, although the activation of A_1 receptors prevents or attenuates neuronal damage (de Mendonça et al., 2000), evidence is accumulating to suggest that the neuroprotection afforded by activation of A_1 receptors might be unrelated to its synaptic

* Tel.: +351 239 820190; fax: +351 239 822776.
E-mail address: racunha@ci.uc.pt.
URL: http://cnc.cj.uc.pt/lab_lef/

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effects and probably results from its extra-synaptic effects, in particular the decrease brain metabolism (Håberg et al., 2000; Duarte et al., 2005) and eventually the control of glia cells (reviewed in van Calker and Biber, 2005).

There are 3 other adenosine receptors (A_{2A}, A_{2B} and A_3 receptors), but their density in brain tissue is lower than that of A_1 receptors. Little is still known about A_{2B} and A_3 receptors due to their low density in brain tissue and to the unavailability of drugs and antibodies selective for these receptors across different species (Fredholm et al., 2005). More work has been devoted to understanding the role of A_{2A} receptors in the brain, especially in the basal ganglia where they play a prominent role in the control of psychomotor behaviour (reviewed in Xu et al., 2005). A_{2A} receptors also play a key role in astrocyte endfeet controlling microcirculation in the brain since adenosine is an endproduct generated by astrocytes coupling increased neuronal activity with vasodilation (reviewed in Phillis, 2004), although other vasoactive substances are also involved in neurovascular coupling (reviewed in Haydon and Carmignoto, 2006). A_{2A} receptors are also present at low density in different brain areas, namely in cortical areas where they have a predominant presynaptic localization (Rebola et al., 2005b). Although A_{2A} receptors have been shown to enhance the release of different neurotransmitters such as glutamate, their physiological function in the control of brain circuits is still unclear (Fredholm et al., 2005). Recently, A_{2A} receptors have received broader attention because their blockade affords a robust neuroprotection in different chronic noxious brain conditions by mechanisms still to be resolved (reviewed in Cunha, 2005).

2. Effects of endogenous adenosine in brain circuits

Apart from the basal ganglia, the experience of the vast majority of researchers exploring adenosine modulation is that adenosine essentially fulfils an inhibitory role mediated by inhibitory A_1 receptors (reviewed in Dunwiddie and Masino, 2001). In particular, the seminal work of Tom Dunwiddie has revealed that there is an inhibitory tonus mediated by endogenous adenosine that results from the activation of A_1 receptors (Dunwiddie, 1980). This agrees with the general findings that the addition of exogenous adenosine to integrated brain preparations causes an inhibition of synaptic transmission and that no other effect is observed once inhibitory A_1 receptors are blocked or genetically ablated (e.g. Johansson et al., 2001; Sebastião et al., 1990). This clearly shows that A_1 receptors play by far the predominant role in modulation of brain circuits.

Nevertheless, some studies have revealed particular conditions where it is possible to show that adenosine can also facilitate the evoked release of neurotransmitters (reviewed in Cunha, 2001a). Thus, the release of neurotransmitters might be simultaneously controlled not only by inhibitory A_1 but also by facilitatory A_{2A} receptors (Cunha, 2001a). Indeed, A_1 and A_{2A} receptors can be located in the same synapse (Ciruela et al., 2006; Rebola et al., 2005a). These observations open the question of understanding the physiological reason directing the localization in the same synapse of two receptors with opposite function that are activated by the same ligand with similar affinities (see Fredholm et al., 2001). In the particular case of striatal glutamatergic terminals, A_1 and A_{2A} receptors form heterodimers that allow a concentration-dependent switch from A_1 receptor-mediated inhibition into A_{2A} receptor-mediated facilitation with increasing concentrations of adenosine (Ciruela et al., 2006). However, in other glutamatergic synapses, such as in the hippocampus, A_1 and A_{2A} receptors are located in the same glutamatergic synapses (Rebola et al., 2005a) and there is an insurmountable A_1 receptor-mediated inhibition of synaptic transmission with increasing concentrations of adenosine (Johansson et al., 2001; Sebastião et al., 1990). Thus, at these synapses, other mechanisms should be considered to understand when A_{2A} receptors will come into play and this review proposes that this may due to the dynamics of extracellular adenosine metabolism under different conditions of neuronal firing.

3. Source of endogenous extracellular adenosine

The source of endogenous extracellular adenosine during physiological conditions of neuronal firing has been one of the less studied aspects of adenosine neuromodulation. There are two potential metabolic sources able to generate extracellular adenosine: (1) release as such, or (2) extracellular formation from released adenosine nucleotides.

The formation of adenosine from released adenine nucleotides is based on the observation that most cell types in the brain can release ATP (reviewed in Fields and Burnstock, 2006) and are endowed with ecto-nucleotidases that are able to convert extracellular ATP into adenosine (see Cunha, 2001b; Zimmermann, 2000). As shall be detailed, there is now compelling evidence supporting an important role for this source of adenosine, at least under physiological conditions (Correia-de-Sá et al., 1996; Cunha et al., 1996a; Dale, 2002; Koizumi et al., 2003; Newman, 2003; Pascual et al., 2005; Zhang et al., 2003). The difficulties in highlighting the role of ecto-nucleotidases in the formation of endogenous extracellular adenosine are probably related to general lack of pharmacological tools to manipulate this large family of enzymes (Zimmermann, 2000) and to the inability to recognise that the ecto-nucleotidase pathway displays an abnormally efficient kinetic profile characteristic of fractal kinetics (Cunha et al., 1998; Cunha, 2001b; Dunwiddie et al., 1997). In fact, we know considerably more about the molecular biology of ecto-nucleotidases than about their localization and kinetic properties in native tissues that ultimately define their physiological role. A further major issue contributing for the inability to highlight the contribution of ecto-nucleotidases as a source of endogenous extracellular adenosine might be the different handling of preparations in order to avoid the massive extracellular accumulation of adenosine that occurs after different types of insults (reviewed in Latini and Pedata, 2001). The elegant work of Bruno Frenguelli and Nicholas Dale has clearly established that the hypoxia-induced build-up of extracellular adenosine is far larger than in normoxia and is independent of released ATP, in contrast to normoxia (Frenguelli et al., 2007).

The alternative possible metabolic source of extracellular adenosine is its release as such. Any situation in which tissue workload overtakes the availability of metabolic energy leads to the consumption of ATP (millimolar concentrations in cell), which causes a disproportionate increase of adenosine (nanomolar concentration in cells) (see Cunha, 2001a). This adenosine can then escape cells through bidirectional non-concentrative nucleoside transporters that are assumed to be present (still to be experimentally documented) in all cell types (reviewed in Kong et al., 2004). Although this is the most widely accepted hypothesis for the build-up of extracellular adenosine, it has only received episodic experimental confirmation (e.g. Cunha et al., 2000; MacDonald and White, 1985). Oddly, the effect of pharmacologically manipulating these nucleoside transporters is an increase of the extracellular levels of adenosine implying that their role is to take-up rather than release adenosine (see Fredholm et al., 2005). Thus, in integrated brain preparations under physiological conditions, there are no studies directly supporting the contention that adenosine is released as such through nucleoside transporters. This situation is different from stressful conditions, where recent careful studies were left with the remaining hypothesis that adenosine is released as such (Frenguelli et al., 2007; Martin et al., 2007; Pearson et al., 2001) through mechanisms still to be resolved, which may involve carrier systems (Sperlagh et al., 2003), but independently of nucleoside transporters.

In contrast to this still debated issue of the metabolic source of extracellular adenosine, there has been considerable advance in our understanding of the cellular source of endogenous extracellular adenosine. The classical view was that adenosine would fulfil a restricted synaptic role. Thus, adenosine would be locally generated in the synapse in amounts directly proportional to synaptic activity, and would act through inhibitory A_1 receptors as a feedback mechanism to restraint excessive synaptic activation (Dunwiddie and Masino, 2001). Two parallel mechanisms were considered to understand how the levels of synaptic adenosine would parallel synaptic activity: (1) adenosine would be formed extracellularly upon catabolism of released ATP originated from synaptic vesicles (reviewed in Sperlágh and Vizi, 1996); (2) adenosine would be released from the postsynaptic neuron as a consequence of the activation of ionotropic glutamate receptors (see Dunwiddie and Diao, 1994; Mitchell et al., 1993a). Irrespective of the source of synaptic adenosine, the predominance of A_1 receptor-mediated inhibition behaved as a homeostatic 'autocrine'-like role restricted to a particular excitatory synapse. However, this scenario suffers from a major caveat: it does not provide a proper rationale to understand how synapses could overcome A_1 receptor-mediated inhibition to undergo plastic changes (Mitchell et al., 1993b). In fact, the supra-maximal activation of A_1 receptors is able to block excitatory synaptic transmission. Since the strength of A_1 receptor inhibition should increase with increasing synaptic activity, then high frequency trains would generate sufficient extracellular adenosine to block synaptic transmission in a tetanised synapse (see Cunha et al., 1996a). Hence one would expect a synaptic block rather than an increase of synaptic efficiency as is known to occur upon application of different high frequency trains (Dunwiddie and Lynch, 1978).

A major twist was recently provided by the group of Phillip Haydon (Pascual et al., 2005). They generated a transgenic mouse with astrocytic over-expression of a dominant-negative form of synaptobrevin-2, which largely abrogates exocytotic release selectively from astrocytes (Zhang et al., 2004). They found that this lead to the disappearance of the tonic A_1 receptor-mediated inhibition on synaptic transmission in hippocampal slices (Pascual et al., 2005). This implies that the endogenous extracellular adenosine responsible for the tonic A_1 receptor-mediated inhibition of excitatory synaptic transmission is largely derived from astrocytes. Astrocytes release ATP (reviewed in Fields and Burnstock, 2006; Haydon and Carmignoto, 2006), which is then extracellularly metabolised into adenosine before activating synaptically located A_1 receptors (Koizumi et al., 2003; Newman, 2003; Pascual et al., 2005; Serrano et al., 2006; Zhang et al., 2003). Thus, there might actually be an astrocytic ''adenosine-cycle'' starting with the astrocytic vesicular release of ATP, its extracellular degradation to adenosine, its reuptake by equilibrative nucleoside transporters and its phosphorylation by adenosine kinase back into ATP (Boison, 2006). This ''adenosine-cycle'' would be compatible with findings that nucleoside transport inhibitors lead to an increase of extracellular adenosine, by preventing intracellular metabolism of adenosine by adenosine kinase, which would act as the driving force for the astrocytic reuptake of adenosine. These observations prompted a novel view on the physiological meaning of this tonic inhibition mediated by inhibitory A_1 receptors. In fact, astrocytes respond to neuronal activity with a time course considerably slower than neurons (tenths of seconds versus milliseconds; see Fellin et al., 2004) and promote broad volume transmission (reviewed in Halassa et al., 2007; Haydon and Carmignoto, 2006; Scemes and Giaume, 2006) thanks to their syncytium-like connectivity (D'Ambrosio et al., 1998; Latour et al., 2001; Wallraff et al., 2004) and to the number of synapses (near 10,000) contacted by each astrocyte (Bushong et al., 2003; Ventura and Harris, 1999). This means that astrocytic-derived adenosine can only be aimed at setting a global inhibitory tonus as a function of a time-averaged activity in a broad neuronal circuit. Thus, this astrocytic source of adenosine implies the concept of slow and global coordination of synaptic activity in a circuit (i.e. a 'paracrine'-like modulation) rather that a rapid 'autocrine'-like modulation restricted to the synapse, as implied by the classical view assuming a synaptic source of endogenous extracellular adenosine tonically activating A_1 receptors.

4. Adenosine as a hetero-synaptic modulator—A_1 receptors

Several groups noted that the blockade of ecto-nucleotidases decreases the extracellular levels of endogenous adenosine in brain slices (Pascual et al., 2005; Martin et al., 2007; Serrano et al., 2006). In particular, the innovative methodology devised by Nicholas Dale to quantify on-line the extracellular levels of

ATP and adenosine (Llaudet et al., 2005; Pearson et al., 2001) confirmed that the extracellular catabolism of ATP contributed for the basal extracellular levels of adenosine in slices stimulated at low frequency (<0.1 Hz) stimulation. Since this tonic adenosine level is derived from exocytotic release of gliotransmitters from astrocytes (Pascual et al., 2005), it is possible to assume that the endogenous extracellular adenosine is originated from ATP released from astrocytes (it should be noted that this conclusion is only an assumption still to be demonstrated: in fact, it remains possible that some gliotransmitter may indirectly cause the release of ATP and/or adenosine from neurons). Irrespective of the actual gliotransmitter that is indirectly responsible for the generation of endogenous extracellular adenosine, it should be pointed out that it is constitutively released in slices, albeit Ca^{2+} waves, indicative of astrocytic activation (Dani et al., 1992; reviewed in Halassa et al., 2007; Scemes and Giaume, 2006), are scarcely observed upon low frequency stimulation of adult brain preparations (Hirase et al., 2004; Newman, 2003; see also Grosche et al., 1999; Pasti et al., 1997). But from the functional point of view, this astrocytic-driven constitutive generation of endogenous extracellular adenosine has an important correlate: it means that the tonic A_1 receptor-mediated inhibition of excitatory synaptic transmission is likely designed to act globally in brain circuits to decrease noise in excitatory circuits.

This long-distance A_1 receptor-mediated inhibition operated by endogenous extracellular adenosine also fits beautifully with the idea that adenosine is the main messenger mediating heterosynaptic depression (Manzoni et al., 1994). This consists in the observation that a high frequency stimulation of a particular excitatory pathway causes a depression in nearby pathways (Lynch et al., 1977). When first described, this was proposed to depend on the recruitment on interneurons (Manzoni et al., 1994). This was confirmed in a recent elegant study which established that the high frequency stimulation of a set of Schaffer fibers in hippocampal slices led to the sequential activation of NMDA receptors in GABAergic interneurons and the GABA released would trigger astrocytic activation through $GABA_B$ receptors (Kang et al., 1998; Serrano et al., 2006); thanks to the long-range propagation of Ca^{2+} waves in astrocytic syncytium (up to 100 μm; reviewed in Halassa et al., 2007; Haydon and Carmignoto, 2006; Scemes and Giaume, 2006), the astrocytes could release ATP in sites facing distant non-stimulated synapses (Pascual et al., 2005; Serrano et al., 2006; Zhang et al., 2003), which, upon extracellular degradation by ecto-nucleotidases, would activate A_1 receptors in these distant non-stimulated synapses (Serrano et al., 2006). This heterosynaptic depression triggered in a group of neighbouring excitatory synapses as a result of the high-frequency stimulation of a particular synapse has an important physiological role: it is designed to increase contrast between activated synapses undergoing plastic changes and non-tetanised synapses (Lynch et al., 1977; Serrano et al., 2006). One expected correlate is that the decrease of this A_1 receptor-mediated heterosynaptic depression might facilitate synchronization of neuronal activity, which has been proposed to cause seizures (see Halassa et al., 2007).

5. Adenosine as a synaptic modulator—A_{2A} receptors

This 'paracrine'-like role of adenosine acting broadly in large groups of synapses in a non-synaptic (Vizi, 1984) or volume transmission-like manner (Agnati et al., 1986) should not underscore a complementary role fulfilled by adenosine as an 'autocrine'-like signalling molecule restricted to a particular synapse. In fact, there is ground to propose that the role of adenosine in the control of synaptic plasticity might not only be limited to the 'paracrine'-like action of inhibitory A_1 receptors, but is supplemented by an 'autocrine'-like role of facilitatory A_{2A} receptors restricted to activated synapses (reviewed in Ferré et al., 2005). In fact, several studies have shown that stimulated nerve terminals can directly release ATP, which is stored in synaptic vesicles (reviewed in Sperlágh and Vizi, 1996). However, this stimulation-evoked release of ATP from nerve terminals seems to differ from the release of classical neurotransmitters (Farinas et al., 1992; Magalhães-Cardoso et al., 2003; Rabasseda et al., 1987; Santos et al., 1999; see also Coco et al., 2003). In particular, this release of ATP is disproportionally larger at higher frequencies of nerve stimulation (Cunha et al., 1996a; Wieraszko et al., 1989). We have recently confirmed that this release of ATP from hippocampal nerve terminals required greater intensities of stimulation than these required to trigger the release of glutamate, GABA or acetylcholine and also involves the recruitment of L-type calcium channels rather than N- or P-type calcium channels (Rodrigues et al., 2004). Also, we have found that the extracellular catabolism of released adenine nucleotides in synapses is not associated with the activation of inhibitory A_1 receptors, but rather with the activation of facilitatory A_{2A} receptors (Cunha et al., 1996b). Furthermore, we have shown that the activation of A_{2A} receptors can down-regulate A_1 receptors via different mechanisms: in hippocampal synapses, A_{2A} receptor activation operate a protein kinase C-dependent pathway to down-regulate A_1 receptors (Lopes et al., 1999); in contrast in cortico-striatal glutamatergic nerve terminals, A_1 and A_{2A} receptors form heterodimers and A_{2A} receptor activation by increasing concentrations of adenosine down-regulates A_1 receptor-mediated responses (Ciruela et al., 2006). Finally, we also found that the activation of these A_{2A} receptors by endogenous adenosine is required to sustain NMDA receptor-dependent synaptic plasticity in hippocampal synapses (Costenla et al., 2004; Rebola et al., 2006), the same occurring in the basal ganglia (D'Alcantara et al., 2001).

This support a role for an 'autocrine'-like facilitation operated by A_{2A} receptors that are activated by adenosine formed from neuronally released ATP (see Cunha, 2001a). This facilitation is restricted only to tetanised synapses where extracellular ATP is generated in sufficient amounts to activate A_{2A} receptors (Almeida et al., 2003). This might only occurs upon high-frequency stimulation, characteristic of long-term potentiation. Thus, this local stimulation of A_{2A} receptors restricted to the tetanised stimulated synapses has a double importance: it directly promotes the NMDA receptor-mediated plastic changes triggered by high-fre-

quency stimulation and it simultaneously down-regulates A_1 receptor-mediated inhibition. Therefore, it is a local mechanism to facilitate the implementation of synaptic plasticity.

6. An integrated view of adenosine modulation

Overall, the 'paracrine'-like role of A_1 receptor-mediated inhibition and the 'autocrine'-like facilitatory role of A_{2A}

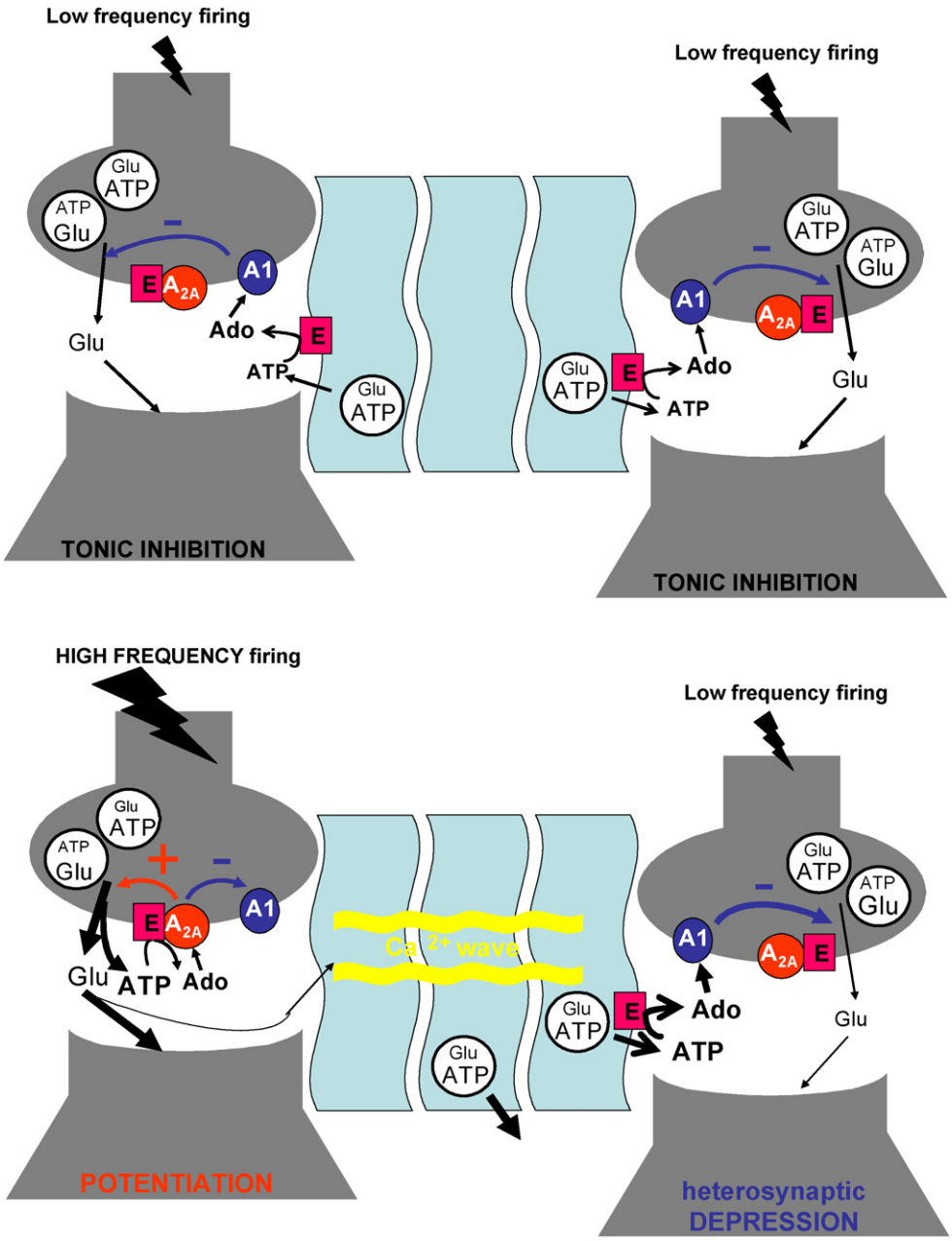

Fig. 1. In resting conditions, astrocytic-derived extracellular adenosine maintains a tonic A_1 receptor-mediated inhibition of excitatory transmission to decrease noise in excitatory circuits (upper panel). When a synapse is activated by tetanisation, the A_1 receptor-mediated heterosynaptic depression further decreases activity of non-activated synapses and A_{2A} receptors are selectively recruited in the activated synapse to locally shut-down A_1 receptors and promote the potentiation of this synapse. The upper panel illustrates a resting condition of functioning of a neuronal circuit, where two synapses (in grey) are connected by an astrocytic syncytium (in blue). The astrocytes tonically release vesicular ATP, which is extracellularly catabolised by ectonucleotidases (E, in violet) forming adenosine that activates A_1 receptors (in blue) to tonically inhibit both excitatory, releasing glutamate (Glu). The lower panel illustrates a condition where one of the synapses (in the left) is activated by a burst of high-frequency firing. In this synapse, high-frequency stimulation now leads to the release of presynaptic vesicles containing ATP. This ATP is degraded by synaptic ecto-nucleotidases forming adenosine that is directed to the activation of facilitatory A_{2A} receptors (in red). These A_{2A} receptors facilitate glutamate release and down-regulate A_1 receptors. The overall result is a potentiation of this activated synapse. In parallel, glutamate triggers a heterosynaptic depression. This starts by an NMDA receptor-dependent activation of interneurons (not presented) to trigger a calcium wave in astrocytes (in yellow). This leads to a greater release of ATP in distal non-activated synapses. As described for the upper panel, this ATP is catabolised by ecto-nucleotidases and activates A_1 receptors to further depress this non-activated synapse. Therefore, the combined action of A_{2A} receptors in the activated synapse and of A_1 receptors in non-activated synapses increase salience of information processing during a high-frequency train. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

receptors work in tandem to guarantee a maximal salience between stimulated and non-tetanised synapses (Fig. 1). At low frequencies of nerve stimulation (used in the majority of studies), it is only possible to highlight a role of A_1 receptors, which impose a global tonic inhibition of excitatory transmission designed to decrease noise (Fig. 1, upper panel). Facilitatory A_{2A} receptors only come into play when frequency-coded information arrives at a given synapse in the form of a high frequency train of action potentials. In the tetanised synapse, ATP is released and catabolised to activate A_{2A} receptors which play a double role: they facilitate synaptic plasticity and they down-regulate A_1 receptors selectively in the activated synapse. In parallel, through the recruitment of an interneuron-astrocytic network, there is a global increase of extracellular adenosine implementing a heterosynaptic depression in all neighbouring synapses (Fig. 1, lower panel). This cooperation between the activation of A_{2A} receptors in activated synapses and A_1 receptors in non-activated synapses may be a fine-tuning mechanism increasing salience of information processing in activated versus non-tetanised pathways in brain circuits.

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