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Perspective

How astrocytic ATP shapes neuronal activity and brain circuits

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Abstract

Astrocytes play a key role in processing information at synapses, by controlling synapse formation, modulating synapse strength and terminating neurotransmitter action. They release ATP to shape brain activity but it is unclear how, as astrocyte processes contact many targets and ATP-mediated effects are diverse and numerous. Here, I review recent studies showing how astrocytic ATP modulates cellular mechanisms in nearby neurons and glia in the grey and white matter, how it affects signal transmission in these areas, and how it modulates behavioural outputs. I attempt to provide a flowchart of astrocytic ATP signalling, showing that it tends to inhibit neural circuits to match energy demands.

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Introduction

Astrocyte networks spread over the whole brain, and they are commonly known for their role in supporting neurons: they maintain a steady environment by controlling extracellular potassium concentration and by removing neurotransmitters released at synapses, and they control energy supply by regulating blood flow and providing lactate to neurons [1]. They are ideally organised to fulfil these tasks, as each astrocyte covers a distinct volume and has many processes that potentially contact all cell types at various subcellular localisations. Astrocytes essentially do not overlap with other neighbouring astrocytes, but neighbouring astrocytes are connected with gap junctions which allow Ca^{2+} waves to propagate [2]. More recently, there has been a broad interest in the role of astrocytes in synaptic transmission, in particular to understand how they actively participate in brain information processing. Although it is becoming evident that astrocytes are essential for regulating cognition and behaviour [3–8], the cellular and molecular mechanisms underlying these processes are unclear, because astrocytes release several gliotransmitters such as glutamate, γ-aminobutyric acid (GABA), D-serine and adenosine triphosphate (ATP), that act differently on neuronal receptors expressed at sites responsible for integrating and generating signals [9].

To understand these signalling pathways, it is important to dissect each of them separately. In this review, I will focus on the role of a unique modulatory molecule, ATP, which was originally known for its role in providing energy to cells, and only many decades later was shown to act as a transmitter in the brain [10]. It may prove to be a challenging task to interpret experimental data involving ATP's general aspects as a modulatory molecule because it is generated by, and thus can be released by, any cell type and it targets many receptors that trigger either opposite or redundant effects within the purinergic receptor family or other types of receptors [11,12]. Based on recent literature investigating astrocytic ATP signalling from the molecular to the behavioural level, I will attempt to simplify astrocytic ATP-mediated regulation of neuronal activity and its impact on brain circuits and behavioural outputs, focusing on advances in understanding the role of astrocytic ATP near excitatory and inhibitory synapses, and near axons in the grey and white matter. I will conclude by speculating on how astrocytic ATP signalling may reshape functional circuitry within and between brain areas during different brain states and according to energy status.

Influence of astrocytic ATP on synaptic transmission

Influence on excitatory synapses

Astrocytes play an integral part in synaptic communication, as they interact with both the pre- and post-synaptic compartments, forming the so-called "tripartite synapse" [13]. Their role in modulating excitatory synaptic gain has been widely documented [13]. ATP is released from astrocytes onto many targets via

membrane channels and Ca^{2+}-dependent exocytosis (see below and review [14]). ATP activates ionotropic P2X and metabotropic P2Y receptors found at presynaptic compartments to regulate glutamate release [15,16] and at post-synaptic compartment can control the function and the number of NMDA and AMPA receptors [17,18] (Figure 1a). ATP is converted by ecto-ATPases into adenosine in the extracellular space. Adenosine also modulates synaptic activity by activating A1 and A2a receptors expressed at glutamatergic synapses. These receptors counterbalance each other's activity via changes in cAMP level (which is lowered by A1 and raised by A2a receptors) to regulate information transmission at excitatory synapses [19–24], however the dominant effect is a reduction of excitatory transmission by presynaptic adenosine receptors [25,26].

Influence on inhibitory inputs

ATP/adenosine signalling at inhibitory (GABAergic) neurons has been less studied than at their excitatory counterparts, perhaps because the vast majority of neurons and synapses (about 85%) are glutamatergic [27,28]. However, this should not detract from the potential importance of ATP-mediated modulation of inhibition, as inhibitory inputs in neural circuits are crucial for brain computation [29]. It is therefore essential to understand how astrocytic ATP affects inhibitory synapses. Only recently, it was shown that ATP release from astrocytes, via postsynaptic A1R activation at GABAergic synapses, upregulates the inhibition mediated by somatostatin-expressing (SST) interneurons onto pyramidal neurons in the CA1 hippocampus and layer II/III visual cortex [30,31] (but not the inhibition mediated by parvalbumin-expressing (PV) interneurons [30]). Astrocyte-derived ATP also upregulated cholecystokinin-expressing interneuron activity in the hippocampal CA1 area, but not PV interneuron activity, following P2Y1R activation and subsequent K2P K^+ channel blockade [32]. Thus, although still elusive, recent literature indicates that astrocytic ATP upregulates at least some inhibitory inputs.

Impact on circuit output and behavioural consequences

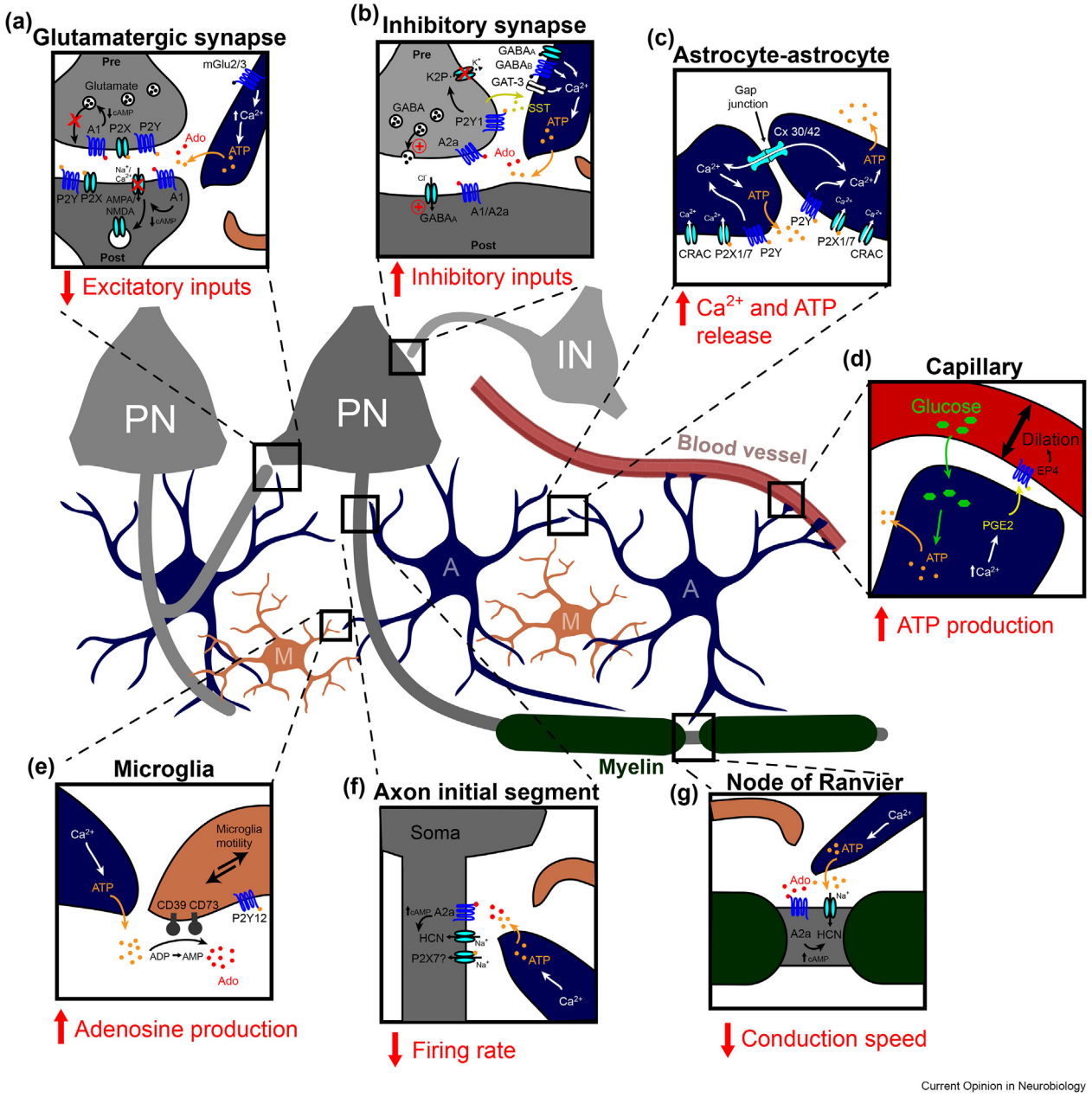
Tan et al. [32] showed that, while potentiating inhibitory neurons as described above, astrocytic ATP depressed the activity of excitatory pyramidal neurons via A1Rs and subsequent opening of GIRK K^+ channels. Yet, it should be noted that this study used optogenetics to induce Ca^{2+} activity at astrocytes, which is expected to increase the extracellular K^+ concentration and engender many non-specific effects [33]. A similar type of regulation, where astrocyte-derived ATP acts in synergy to potentiate inhibitory neurons and depress excitatory neurons, has also been described in the amygdala. There, astrocytic ATP/adenosine depressed excitatory synapses via A1R activation and enhanced inhibitory synapses via A2aR activation, which reduced fear expression in mice [34]. This differential regulation may take place in other brain areas, as depression of excitatory synapses via activation of A1Rs by astrocytic ATP/adenosine is also observed in the nucleus accumbens, which is involved in the dopaminergic brain reward system [35,36], and in the hypothalamic arcuate nucleus, where astrocytic ATP inhibits AGRP neurons via A1R or ATP-sensitive potassium (K_{ATP}) channel activation, thereby dampening food intake [37–39]. In sleep, the decrease in neuronal activity is also mediated by A1Rs via astrocytic ATP release in the cortex and the basal forebrain [40], and the disinhibition of sleep-promoting GABAergic projection neurons via A1R activation in the ventrolateral preoptic nucleus may contribute to this [41] (although unspecific optogenetic stimulation of astrocytes was used here as well [33]). Although A1R-mediated effects seem to be predominant (particularly at glutamatergic synapses), postsynaptic A2aRs at inhibitory synapses may play an important role during development, as these receptors are transiently overexpressed to regulate the number of active GABAergic synapses [42]. Thus, the expression of purinergic receptors at synapses mainly dictates how ATP/adenosine regulates synaptic transmission. Overall, it appears that inhibition of neural circuits dominates the effects mediated by astrocytic ATP across different areas via: (i) inhibition of excitatory inputs via A1Rs and (ii) activation of inhibitory inputs (although the predominant mechanisms mediating the latter remain unclear), thereby shaping various behavioural outputs [3].

Mechanisms potentiating astrocytic ATP signalling

Local feedback mechanisms

ATP release from astrocytes is controlled by synaptic activity, in mechanisms that also lead to a depression of neuronal activity. Glutamate release from excitatory neurons raises astrocytic Ca^{2+} via mGluR2/3 glutamate receptors expressed on the astrocytes [43]. Increasing the activity of GABAergic neurons induces Ca^{2+} transients via $GABA_A$ [44] and $GABA_B$ receptors expressed on astrocytes [44–47], as well as via the astrocytic GABA transporter GAT-3 which co-transports GABA and Na^+ into astrocytes and thus in turn promotes Ca^{2+} influx via Na^+/Ca^{2+} exchange [30,47,48] and via Ca^{2+} release-activated Ca^{2+} (CRAC) channels [49]. Interestingly, Mariotti et al. showed that SST interneuron stimulation raised astrocyte $[Ca^{2+}]_i$ more robustly than PV interneuron activity, indeed repetitive stimulation of PV interneurons depressed astrocyte Ca^{2+} rises while stimulation of SST interneurons potentiated them due to the release of somatostatin [46] (Figure 1b). Astrocytes further support the inhibition of neuronal circuits via paracrine and autocrine ATP signalling, as ATP released by the same astrocytes or by nearby cells can raise astrocyte $[Ca^{2+}]_i$, and thus release more ATP. Astrocytes

Figure 1



Cellular mechanisms and functions mediated by astrocytic ATP. Astrocyte (A) processes contact many targets, and release onto them ATP and adenosine (Ado), resulting in an overall dampening of brain activity. They release ATP/adenosine onto excitatory synapses to reduce presynaptic glutamate release and postsynaptic AMPA/NMDA currents, and enhance the internalisation of AMPA/NMDA receptors (inset a). Astrocytic release of ATP/adenosine potentiates presynaptic GABA release and postsynaptic GABA currents in inhibitory synapses, particularly the ones formed by interneurons (IN) expressing and releasing somatostatin (SST) (inset b). Astrocyte processes also interact with axons at sites of spike generation of excitatory pyramidal neurons (PN): at the axon initial segment, ATP/adenosine reduces the firing rate of highly active neurons (inset f), while at nodes of Ranvier it slows down the axonal conduction speed, as it increases HCN currents at these sites (inset g). Effects mediated by astrocytic Ca^{2+}-dependent ATP/adenosine release are amplified by: (i) Ca^{2+} waves propagating between astrocytes linked by gap junctions, and via autocrine/paracrine astrocytic ATP signalling enhancing $[Ca^{2+}]_i$ rises (inset c); (ii) astrocytic Ca^{2+}-dependent vasodilation, increasing glucose supply and thus ATP production by astrocytes (inset d); (iii) interactions between astrocytes and microglia (M), as ATP attracts microglial processes expressing CD39 and CD73, enzymes that catalyse adenosine production (inset e). Microglia contact synapses and sites of spike generation (insets a, b, f and g), although less commonly than astrocytes.

express ionotropic P2X7 receptors [50], which facilitate influx of Ca^{2+}, and metabotropic P2YRs that release Ca^{2+} from intracellular stores [14] (Figure 1c). Altogether, these feedback mechanisms may serve to reinforce and sustain inactivation of local circuits.

Participation of microglia

Another key player at synapses are microglia, the brain's main immune cells. They are known for pruning non-functional synapses during development [51,52]. Although they are not considered an integral component of the synaptic structure as much as astrocytes, their highly motile processes may be recruited to the vicinity of synapses in response to high neuronal activity. ATP release from astrocytes can activate P2Y12Rs, the receptors in charge of microglial targeted motility to synapses and neuronal somata [53–55]. As microglial processes are recruited to the proximity of synapses, they amplify the production of extracellular adenosine because they express the ectonucleotidases CD39 and CD73 on their membrane [56,57] (Figure 1e). Pharmacological blockade of P2Y12R, CD39 and CD73 reduced neuronal inhibition induced by A1Rs in the striatum and the cortex [56]. This effect exacerbated neuronal response to neurostimulants, implying that microglia might be involved in preventing aberrant hyperexcitability or excitotoxicity rather than in processing brain information *per se*. In line with these findings, microglial deletion of P2Y12R increased the excitability of hippocampal CA1 pyramidal neurons [58]. P2Y12 microglial knock-out also enhanced innate fear behaviour [58], consistent with the decrease in fear expression mediated by astrocytic Ca^{2+}-derived ATP release in the amygdala [34]. Thus, microglia may regulate ATP/adenosine levels in the synaptic environment and similarly near axons (see below).

Link between neuronal activity and brain energy status

Astrocytic ATP release is tightly linked to brain energy status**.** Blood vessels provide energy to the brain as glucose and oxygen. Glucose is converted into ATP (via glycolysis and mostly via oxidative phosphorylation in mitochondria) that will be used for many intracellular processes consuming energy. Blood supply and neuronal activity are coupled, as ATP is in particular needed for synaptic transmission which is highly demanding energetically [59,60]. Astrocytes contact both synapses and blood vessels at their end-feet, and are thus perfectly suited to mediate neurovascular coupling [61]. Indeed, ATP released at synapses during high neuronal activity activates astrocytic P2X1Rs and raises $[Ca^{2+}]_i$ which leads to the release of prostaglandin E2 on capillaries and vasodilation via EP4 receptors, ultimately increasing blood supply [62] (Figure 1d). In parallel, astrocytes, via Ca^{2+} rises, release ATP/adenosine onto synapses to dampen neuronal activity in a negative feedback manner. When the brain is energy-deprived, intracellular adenosine accumulates as ATP production is limited, and equilibrative nucleoside transporters (ENT) release adenosine from the cells driven by the concentration gradient of adenosine [63] (adenosine's extracellular concentration can rise 100-fold in an ischaemic brain [64]). Thus, the energy status molecules ATP and adenosine secreted by astrocytes may be able to adjust blood supply to power neuronal activity, and vice versa (i.e., astrocytes may be able to adjust neuronal activity to regulate blood supply). Microglial recruitment to synapses might contribute to this because microglial contacts with neurons increase when the activity of neuronal mitochondria is high [55]. By supplying glucose and oxygen, and thus ATP to brain areas, blood vessels do not only provide the main substrates for energy supply but also allow generation of two crucial modulators of neuronal activity (ATP and adenosine).

Influence of astrocytic ATP on axonal conduction

Astrocytes have mainly been investigated for their impact on synapses, but, as they cover all the areas of the brain, their processes contact other subcellular structures. The axon initial segment (AIS), where action potentials are generated, is an area prone to extrinsic modulation by externally-released molecules [65–67]. A2a receptor activation at the AIS of cortical layer V pyramidal neurons, via astrocyte Ca^{2+} rises, prevented high-frequency firing in response to robust stimulations [68] (Figure 1f). In another study, P2X7 receptor activity disrupted the AIS structure and reduced the excitability of pyramidal CA3 hippocampal neurons and layer V cortical neurons [69], although it is unclear whether the effect was mediated by P2X7 receptors on neurons, or at least partially via P2X7 receptors on astrocytes, which would raise astrocytic Ca^{2+} levels and in turn release ATP/adenosine [50]. ATP and adenosine released by astrocytes may also regulate signal propagation along axons. Astrocyte Ca^{2+} rises near unmyelinated axons of hippocampal CA3 pyramidal neurons broadened the action potentials and strengthened downstream synaptic transmission [70]. This was mediated by glutamate release and depolarisation of the axonal membrane via AMPA receptor activation. However, intriguingly, blocking axonal A1 receptors mimicked the glutamate-evoked effects in an independent manner, implying that basal adenosine levels were sufficient to dampen axonal excitability and the generation of downstream excitatory post-synaptic currents (EPSCs).

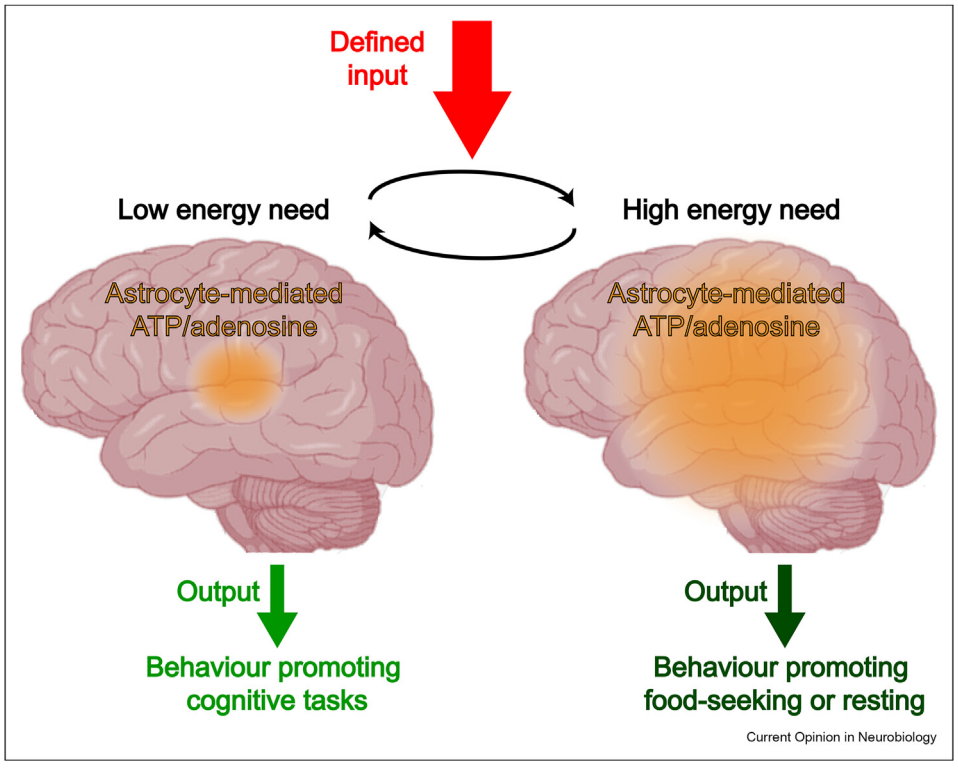
Astrocytes are found in abundance in the white matter, which constitutes half of the human brain and where synapses are mainly lacking. Although astrocytes were found decades ago in the vicinity of myelinated axons, in particular contacting nodes of Ranvier [71] (where action potentials are regenerated along myelinated axons), their

impact on axonal propagation has been surprisingly understudied. A cellular mechanism was recently discovered by which, as near the AIS, astrocyte release of ATP/adenosine onto nodes of Ranvier activated A2a receptors. This raised the cAMP concentration and depolarised the nodal membrane by activating HCN (Ih) channels, thus reducing the conduction speed of myelinated axons extending from layer V pyramidal neurons [68] (Figure 1g). This modulation may not occur along axons extending from inhibitory neurons [68]. The node of Ranvier and AIS are also contacted by microglia, which might contribute to rises in local adenosine levels, as near synapses. Thus, although its role is still elusive, astrocytic ATP release along axons in the white matter may share similarities with its effects at synapses in the grey matter, in that it regulates neuronal excitability and signal transmission, promoting depression of brain activity.

Why is astrocyte-mediated ATP signalling needed?

What are the advantages of regulating neuronal networks via astrocytic ATP/adenosine signalling? In appearance, it offers much less specificity as ATP and adenosine can be potentially released by all the cells and target many receptors which mediate various effects, in contrast to the much more defined roles of molecules that can similarly modulate neuronal activity, such as GABA and glutamate. In addition, astrocytic secretion is more diffuse, likely to target many cells and many receptor types concurrently, in contrast to the confined release of transmitters from presynaptic terminals within synaptic clefts. Additionally, the astrocyte network does not provide much sophistication in its function since these cells are not as spatially polarised as neurons. The power of the astrocyte network may in fact lie in this apparent functional crudeness. Calcium transients in a single astrocyte process affect the function of nearby structures (e.g. a few synapses or a few nodes of Ranvier), while a robust calcium rise would rather lead to ATP/adenosine secretion near all the structures the astrocyte contacts (e.g., a single astrocyte can contact about 140,000 synapses on different neurons [72], many nodes of Ranvier on different axons, many AISs, and blood capillaries). Astrocytes are linked by gap

Figure 2



Perspective on how astrocytic ATP may shape neural circuitry and behavioural outputs. Depending on the energy status of the brain, and thus on the level of astrocyte-mediated ATP/adenosine, a defined input is expected to promote different behavioural outputs. When the brain energy need is low (*left*), ATP/adenosine-mediated concentration is low, and outputs will promote the completion of cognitive tasks. When the brain energy need is high (*right*), ATP/adenosine concentration accumulates via feedback mechanisms described in this review, and outputs will promote behaviour linked to food-seeking or resting. Therefore, astrocytic ATP reshape neural circuitry functionally by providing a different "context" to a received input, thereby matching behaviour linked to arousal to brain energy demands.

junctions via connexin 30 and connexin 43 [2], so that Ca^{2+} waves can propagate long distances in the brain (travelling hundreds of microns in cell cultures, although conclusive data *in vivo* on whether astrocytic Ca^{2+} waves occur and on how far they propagate is still lacking) [73–75]. By these means, astrocytes may synchronise neuronal activity locally and across different brain areas. Thus, although brain computation is unarguably complex, the astrocyte network via ATP/adenosine signalling offers a relatively straightforward solution to orchestrate brain neuronal activity and couple it to brain energy status.

The slow rate of astrocytic ATP signalling implies that it does not act to resolve the immediate demands of the brain. While synaptic transmission and spike generation at the AIS and nodes occur within a few milliseconds, mechanisms mediated by astrocyte Ca^{2+} occur in seconds to minutes (although calcium transients in astrocytic microdomains can occur faster [76]). The interconversion of ATP and adenosine, the lack of restriction to spatially constrained domains (as opposed to synaptic release) and most effects being mediated by intracellular signalling cascades downstream to metabotropic receptor activation further accentuate the slow timescale of these mechanisms. In regard to regulation across different areas, the time delays between neuron-neuron and astrocyte-neuron communication will be even more pronounced: the propagation speed of intercellular Ca^{2+} waves in astrocytes ranges between 10 and 60 μm/s [73,75], about 10^5 times slower than the conduction speed along myelinated axons in the brain's white matter (about 3 m/s [77]). Assuming that an neuronal EPSC and astrocytic Ca^{2+} transient occur together at a synapse, the evoked action potential would reach a node of Ranvier located one centimetre down the axon in 3 ms (for a speed of 3 m/s), while the Ca^{2+} wave would reach the same node up to 5.5 min later (for a speed of 30 μm/s) (assuming that astrocyte processes run parallel to myelinated axon [68]). Some areas in the human brain are several centimetres distant, thus ATP released during astrocyte Ca^{2+} waves does not provide a solution for fast information processing, but it is likely to be involved in slower mechanisms such as those controlling food intake and sleep. Adenosine levels build up with extended wake time and with energy deprivation [40,64,78]. During sleep, transitions from non-REM to REM sleep characterised by different neuronal activities and oscillatory patterns are linked to changes in astrocytic ATP levels [74,79,80]. Food deprivation decreases ATP use and AMPAR currents, thereby impairing coding precision in the visual cortex [81]. Thus, during states reflecting brain energy status, information processing in the brain is altered. Indeed, cognitive tasks and behavioural outputs are generally affected when one experiences tiredness or hunger. Gradually, increasing ATP or adenosine levels and their effects mediated via feedback mechanisms described above will alter the functional circuitry and the behavioural outputs in response to a defined stimulus (Figure 2). This may have evolved as a way to match behaviour linked to arousal to brain energy needs (for example by prioritising food-seeking or resting over cognitive tasks).

Conclusions

Astrocyte control of brain activity by ATP provides a different "context" to a received input and will in practice reshape the neural circuitry functionally. Thus, the ATP-mediated effects discussed above will need to be taken into consideration when exploring brain circuity and related behaviours. Astrocyte ATP signalling acts, as a rule of thumb, as a local inhibitor of neural networks, which can expand its repressive actions to distant brain areas. Astrocytic ATP and adenosine signalling at synapses has been widely studied and, as it was also demonstrated to be crucial in tuning the information flowing along axons, it will be important in future studies to understand how it orchestrates brain activity as a whole.

Conflict of interest statement

Nothing declared.

Data availability

No data was used for the research described in the article.

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- •• of outstanding interest

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