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Monoaminergic control of cellular glucose utilization by glycogenolysis in neocortex and hippocampus

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Abstract

Brainstem nuclei are the principal sites of monoamine (MA) innervation to major forebrain structures. In the cortical grey matter, increased secretion of MA neuromodulators occurs in response to a wealth of environmental and homeostatic challenges, whose onset is associated with rapid, preparatory changes in neural activity as well as with increases in energy metabolism. Blood-borne glucose is the main substrate for energy production in the brain. Once entered the tissue, interstitial glucose is equally accessible to neurons and astrocytes, the two cell types accounting for most of cellular volume and energy metabolism in neocortex and hippocampus. Astrocytes also store substantial amounts of glycogen, but non-stimulated glycogen turnover is very small. The rate of cellular glucose utilization in the brain is largely determined by hexokinase, which under basal conditions is more than 90% inhibited by its product glucose-6-phosphate (Glc-6-P). During rapid increases in energy demand, glycogen is a primary candidate in modulating the intracellular level of Glc-6-P, which can occur only in astrocytes. Glycogenolysis can produce Glc-6-P at a rate higher than uptake and phosphorylation of glucose. MA neurotransmitter are released extrasynaptically by brainstem neurons projecting to neocortex and hippocampus, thus activating MA receptors located on both neuronal and astrocytic plasma membrane. Importantly, MAs are glycogenolytic agents and thus they are exquisitely suitable for regulation of astrocytic Glc-6-P concentration, upstream substrate flow through hexokinase and hence cellular glucose uptake. Conforming to such mechanism, Gerald A. Dienel and Nancy F. Cruz recently suggested that activation of noradrenergic locus coeruleus might reversibly block astrocytic glucose uptake by stimulating glycogenolysis in these cells, thereby anticipating the rise in glucose need by active neurons. In this paper, we further develop the idea that the whole monoaminergic system modulates both function and metabolism of forebrain regions in a manner mediated by glycogen mobilization in astrocytes.

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Disclosure/Conflict of interests

The authors declare no conflict of interest.

Keywords

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Introduction

The brain depends on continuous supply of nutrients from the blood stream, namely oxygen and carbohydrates. With the exception of certain monocarboxylates, which accumulate in the blood during conditions associated with e.g. hyperketonemia or hyperlactatemia, glucose is the sole blood-borne metabolic substrate of adult brain cells [1]. It is estimated that nearly 75% of the glucose entering the neocortex and hippocampus in awake resting state is utilized for signaling functions, with the remaining 25% supporting basal metabolism (e.g., turnover of proteins, nucleotides and phospholipids) [2]. Neurons and protoplasmic astrocytes (hereafter termed just astrocytes) together account for most of tissue cellular volume in cortical grey matter (approximately 45–55% for neurons and 15–25% for astrocytes) [3]. Glucose is taken up from the circulation and translocated to brain parenchyma through endothelial glucose transporter (GLUT) proteins. Although cerebral vasculature is almost completely covered by astrocytic endfeet [4], it has been convincingly demonstrated that interstitial glucose is equally accessible to both neurons and astrocytes [5–8]. With respect to glucose uptake, the anatomical proximity between perivascular astrocytic processes and blood capillaries is likely compensated by the considerably lower glucose transport capacity of astrocytic GLUT1 compared with neuronal GLUT3 carrier isoform [9, 10]. The metabolic rates of neurons and astrocytes, in terms of glucose and oxygen utilization, roughly reflect their cellular volume fractions (i.e. these cell types have comparable energy expenditure per unit volume) [11]. Whereas neuronal energetics fuels rapid changes in membrane potential of axons, synapses and dendrites, astrocytic energetics likewise fuels rapid removal of neuroactive compounds (essentially glutamate and K^+) from extracellular space [12].

The accomplishment of these important stages of ionic movements and transmitter cycling hinges on a high degree of cell specialization and requires large capacity for ATP turnover. The neocortex and hippocampus maintain elevated rates of ATP turnover ($\sim 12 \mu\text{mol g}^{-1} \text{min}^{-1}$ in humans; more than double of this value in rodents) [13]. Therefore, it is necessary that substrate delivery closely matches demand in time and space. Because of ADP recycling mechanism in mitochondria, it is unlikely for cells to largely uncouple the cytosolic glucose processing to pyruvate by glycolysis from the mitochondrial pyruvate channeling into tricarboxylic acid (TCA) cycle and subsequent oxidative phosphorylation (Figure 1) [for a review, see 14]. Neuronal expression of both cytosolic and mitochondrial creatine kinase (CK) ensures ADP recycling [15] by rapid signaling from the sites of ATP hydrolysis (i.e., membranes) to mitochondria. ADP recycling is reinforced by mitochondria-bound kinases including the glycolytic enzymes hexokinase (HK) [16] and phosphofructokinase [17], the latter directly disinhibited by the transient drop in ATP level brought about by the mitochondrial CK. Since phosphorylation by HK commits glucose to cell metabolism, overall the above-mentioned processes result in increased glucose utilization. Glucose uptake is facilitative and, as such, it is driven by intracellular substrate flow through HK (note that glucose delivery to the brain is in excess of demand, see [18]). Astrocytes do not

express the mitochondrial CK enzyme [19, 20] and therefore ADP signaling from membranes to mitochondria is likely to be slower in these cells than in neurons. The lack of CK in astrocytic mitochondria can be interpreted as a mechanism to circumvent competition for glucose with neurons in conditions of fast energy needs [14]. However, astrocytes also are required to operate quickly; therefore, their energy metabolism needs to be upregulated accordingly. Astrocytes can meet this requirement as they specifically contain glycogen, the only endogenous glucose reserve of the brain [21]. Astrocytic glycogen can be mobilized faster compared with uptake and phosphorylation of glucose [21, 22]. Furthermore, during rises in energy demand glycogen provides substrate to sustain glycolysis in already phosphorylated form [12]. In particular, glycogen phosphorylase (GP), the enzyme that cleaves the bond linking a terminal glucose residue to the polysaccharide, yields glucose-1-phosphate [reviewed by 23]. The latter metabolite is in equilibrium with the phosphorylated product of glucose processing by HK, namely glucose-6-phosphate (Glc-6-P). Glc-6-P is a primary branch-point in many anabolic and catabolic pathways including glycolysis, gluconeogenesis, glycogenesis, glycogenolysis and pentose phosphate pathway.

Importantly, Glc-6-P and other hexose mono- and bisphosphates are strong regulators of the flow of glucose through cellular metabolic pathways [24]. For example, Glc-6-P causes the detachment of HK from mitochondria, a process that also alters the enzyme functionality towards lower activity [see 25 and references therein]. In kinetic terms, Glc-6-P is a non-competitive inhibitor of HK with a K_I that in the brain is approximately one tenth of its steady-state concentration ($\sim 100 \mu\text{mol/L}$), which means that in basal conditions HK is more than 90% product-inhibited. Since glycogenolysis is the most powerful source of cellular Glc-6-P, only astrocytes are *de facto* capable of the above-mentioned regulation of HK activity [26]. The other source of hexose monophosphate (besides HK) in both neurons and astrocytes, namely fructose-1,6-bisphosphatase, is much slower and less active in the brain to account for important rises in Glc-6-P levels [27]. Overall, astrocytes contribute to the control of cellular glucose uptake.

Role of the monoaminergic system in behavior and its relevance to brain energy metabolism

Besides being energetically expensive [28], intracortical network activity underlying stimulus processing takes time, and the latency between the time of alerting stimuli, perception and behavioral response can be a significant constraint for the performance and survival of an organism. As an illustration, for many trigger stimuli processing delays are circumvented because they are detected by “innate” survival circuits consisting of genetically specified synaptic arrangements [29]. Based on studies of the human visual system, it has been proposed that the brain constantly applies a perceptual compensation to the sensory information in order to generate a perception of the present [30]. This ongoing, short-term task entails that the brain possesses a high anticipatory/preparatory capacity, a feature that eventually leads to view brains as “prediction machines” [31]. Error-correction is an integral part of this predictive coding strategy for both the accurate propagation of representations and the adjustments to model structure. The monoaminergic system is exquisitely implicated in error processing and awareness of performance errors, which is

especially important for adaptive goal-directed behavior [32, 33]. The major monoamine (MA) neuromodulators include histamine (HA), the catecholamines norepinephrine (NE) and dopamine (DA), and the indoleamine 5-hydroxytryptamine (5-HT) [34]. Our choice of not including acetylcholine (ACh) among MA neuromodulators is motivated by the distinct chemical structure of ACh (absence of aromatic ring) as well as by important differences in ACh metabolism (synthesis and degradation pathways and corresponding enzymes) and transport (vesicular and plasmalemmal carriers) compared to MA neuromodulators. As far as neocortex and hippocampus are concerned, these MAs originate primarily from several brainstem nuclei that are reciprocally interconnected, including tuberomammillary nucleus (TMN), locus coeruleus (LC), ventral tegmental area (VTA), and Raphe nuclei (RN), respectively (Figure 2). Through long-range projections, monoaminergic nuclei control the release of MA neuromodulators in neocortex and hippocampus, where the processing of information about internal and external environment does occur. Accordingly, these nuclei take part in a plethora of behavioral states including arousal, attention, stress, vigilance, drive, motivation, reward, addiction, appetite, mood, wakefulness/sleep and circadian rhythms, which in turn influence cognitive processes such as focused attention, learning, memory and perception [35]. Environmental as well as homeostatic challenges activate the neuromodulatory monoaminergic systems to prepare the organism to a behavioral (re)orienting response [36]. The latter is achieved by optimizing the temporal resolution and the signal-to-noise ratio of incoming electrical signals by transiently inhibiting (i.e. resetting) the activity of neural networks in forebrain regions [see, for example 37]. Describing the experimental evidence for the predictive design of monoaminergic systems is beyond the scope of this paper. To mention just a few sparse examples, activity of brainstem nuclei anticipate the transition from sleep to wakefulness/arousal [38], the anxiety (necessary for panic inhibition) towards potentially aversive consequences during avoidant behavior [39], the rewards (necessary for motivation) during appetitive behavior (e.g., food, sex or even abstract rewards) [40].

Axons arising from the monoaminergic nuclei in the brainstem provide widespread innervation to cortical grey matter, and terminate as conventional synapses but more often (~80% of cases) as varicosities that release MAs extrasynaptically [41]. This mechanism of action, called volume transmission, allows for diffusion of MAs through the extracellular fluid and paracrine stimulation of both neurons and astrocytes. Neuromodulators can thus contact a large number of cells opposite to what classical neurotransmitters do at the synapse within the point-to-point, wired intercellular communication. The efficacy of volume transmission depends not only on the density of receptors on the cell plasma membrane but also on the total exposed surface of cellular elements. Importantly, astrocytes express virtually all monoaminergic G-protein coupled receptors as neurons, and in some cases, the astrocytic expression of certain MA receptors is predominant [42, 43]. For example, adrenergic receptors are more concentrated in astrocytes than in neurons [44–47]. Moreover, due to the lamellar nature of their fine peripheral processes astrocytes have a much higher local surface-to-volume ratio compared with neurons, especially in humans [48, 49]. Since astrocytes express MA transporters as well as the metabolic machinery to catabolize MA neuromodulators, they can also regulate the extracellular concentration of MA levels [50]. It is likely that part of the above-mentioned “preparatory” mechanism exerted by brainstem

nuclei on forebrain regions depends on astrocytic responses mediated by MA receptor signaling. Indeed, the removal of neuroactive compounds from the extracellular space by astrocytes contributes to the MA-induced inhibition of neocortical and hippocampal neurons. For example, NE and 5-HT have been found to stimulate preferentially the astrocytic Na^+/K^+ -activated adenosine triphosphatase (NKA) [51–53], which supports the increased clearance of K^+ from the extracellular space by astrocytes [45, 54, 55]. In these cells, MA-mediated signal transduction can also elicit Ca^{2+} -dependent stimulation of mitochondrial dehydrogenases and oxidative metabolism [see discussion in 56 and references therein]. This in turn may channel more glutamate into the TCA cycle and accelerate extracellular glutamate uptake, as clearly demonstrated for NE [57] and conceivably also for DA and 5-HT [58]. Based on the specific ability of LC-NE projections to induce astrocytic Ca^{2+} signaling, a recent study even suggested that astrocytes might represent the primary target of NE in the neocortex [59]. Overall, astrocytes support the functional changes brought about by monoaminergic systems in anticipation of increased glutamatergic neuronal activity and associated energy demand.

Metabolic and homeostatic effects of monoamines: activation of glycogenolysis and regulation of cellular glucose uptake

The critical supportive astrocytic functions discussed above are energetically expensive *per se* and as such, they have metabolic consequences. This means that, in addition to the functional effects on neuronal activity, astrocytes also prepare the neurochemical environment for the forthcoming processing of information in sensory, motor, association and memory areas of neocortex and hippocampus. A compelling argument supporting a common metabolic outcome to monoaminergic signaling is that MAs are potent glycogenolytic agents (Table 1). Stimulation of glycogen breakdown induced by MA neuromodulators is mediated by metabotropic G-protein coupled receptors (see also Figure 2). In particular, cAMP- as well as Ca^{2+} -dependent intracellular signaling cascades result in activation of glycogen phosphorylase [23]. The studies summarized in Table 1 support the involvement of both second messengers in the glycogenolytic effect of MAs. Values for half-maximal response (EC_{50}) are typically in the order of $\mu\text{mol/L}$, which is similar to that of glutamate at NMDA receptors and much smaller than that of glutamate at AMPA receptors [60]. Such low EC_{50} values mean that the glycogenolytic response to MAs is very powerful and can efficiently extend to a large number of astrocytes during paracellular diffusion of the MA neuromodulators from the point of release. The action of MAs on glycogen is likewise rapid, and estimates for the initial rates of MA-induced glycogenolysis (range $0.07\text{--}5.0 \mu\text{mol g}^{-1} \text{min}^{-1}$, Table 1) match or exceed astrocytic metabolic rate of glucose ($0.3\text{--}0.5 \mu\text{mol g}^{-1} \text{min}^{-1}$, estimated as half of resting cerebral metabolic rate of glucose). Such high glycogenolytic rates entail that the product of glycogen mobilization, namely Glc-6-P, is produced faster than is consumed and thus transiently accumulates inside astrocytes.

As the MA-induced glycogen breakdown in astrocytes is a short-term response [61, 62], it can be envisaged that it belongs to the rapid preparatory events taking place in grey matter after activation of the monoaminergic systems. Since the repercussions of increased glycogenolysis may influence the uptake of glucose in cellular compartments (see above), it

is tempting to speculate that, through MA neuromodulators, the brainstem contributes to control glucose channeling in the neocortex and hippocampus. Accordingly, Gerald A. Dienel and Nancy F. Cruz have recently suggested that during alerting signals “catecholamine-evoked glycogen mobilization would shift metabolism of blood-borne glucose away from astrocytes to neurons in a large volume of forebrain” [63]. In the following, we identify a number of findings that would support such mechanism by focusing on the LC-NE system, which is arguably the most studied and well-characterized monoaminergic system in the literature.

The clearance of extracellular K^+ by astrocytes, a key factor underlying neuronal inhibition during MA receptor signaling, is reciprocally associated with glycogenolysis [53, 64, 65]. In particular, β -adrenergic stimulation activates the astrocytic but not neuronal NKA, and this process is glycogenolysis-dependent [53]. Remarkably, the effect only occurs at non-elevated (or modestly elevated) extracellular K^+ , in agreement with the notion that the preparatory action of NE due to alerting stimuli involves unstimulated tissue, independent of energy demand. Support to the significance of glycogen in NE signaling comes from animal studies of unilateral LC destruction. Specifically, in the hemisphere depleted of adrenergic input fibres glycogenolysis is found to be substantially impaired, as evidenced by the higher amount of the polysaccharide retained in the ipsilateral cortex after enhanced activity [66, 67]. Failure to mobilize glycogen in NE-depleted hemisphere accompanies abnormalities in oxidative metabolism under stimulated conditions, which eventually results in reduced metabolic capacity to respond to increased energy demand [68, 69] and possibly in altered K^+ homeostasis [see discussion in 53 and references therein]. These findings indicate that the glycogenolytic effect induced by the catecholamine is relevant for the brain to provide an adequate functional and metabolic adaptation to incoming stimuli. A role for NE in modulating glucose availability to brain cells is suggested by the inverse relationship between activity of LC neurons and blood glucose levels reported by studies on insulin-induced hypoglycaemia [70]. Although systemic effects are likely to be involved, an increased release of NE in forebrain regions resulting from rise in activity of LC neurons at decreasing glycaemia points to a glucose-sparing effect for NE. Interestingly, unilateral or bilateral lesions in LC are found to increase cortical glucose consumption, especially in response to metabolic challenges [71–74]. These results have been often interpreted as reflecting the decline of inhibitory action of NE on cortical neurons. However, they are also consistent (and possibly overlapped) with the compensatory increase of glucose utilization reported in many cortical areas after blockade of glycogenolysis in astrocytes [75]. In other words, any loss of NE-induced glycogenolytic response would increase glucose utilization in the compensatory (but possibly unsuccessful) attempt to gather the required substrates for energy metabolism from the blood. Finally, the proposed NE-induced inhibition of astrocytic glucose uptake is consistent with the finding that NE varicosities are preferentially associated with perivascular astrocytic endfeet [76–78]. Thus, the increased glycogenolysis and production of Glc-6-P can make these processes transiently “impermeable” to glucose, favouring paracellular diffusion of the sugar through interstitium and neuronal uptake. The concept of “permeability” to sugar responding to changes in glucose phosphorylation is actually anything but new [79; see below].

Since pharmacological adrenergic (but also serotonergic) stimulation increases extracellular glucose levels in neocortex and hippocampus [80–82] with possibly unchanged or decreased tissue glucose uptake [83], it can be inferred that glycogenolysis exerts a glucose-sparing effect in these brain regions. The increase in extracellular glucose indicates that monoaminergic signaling *per se* has no or little effect on neuronal glucose uptake, while it clearly stimulates glycogen mobilization in astrocytes. Whether glycogenolysis and the associated rise in Glc-6-P levels actually represents the mechanism responsible for inhibition of astrocytic glucose uptake remains to be demonstrated. Indirect support to this hypothesis is provided by studies on insulin-stimulated glucose uptake in muscle. In particular, epinephrine and NE antagonize the receptor-mediated actions of insulin in activating glucose uptake and glycogen storage [see 84 and references therein]. Blockade of β -adrenergic receptors drastically reduces the effectiveness of epinephrine and NE to inhibit insulin-stimulated glucose uptake [84–87]. Importantly, the inhibition of insulin-stimulated glucose uptake by epinephrine and NE is accompanied by a substantial increase in intracellular Glc-6-P (and glucose) levels, which is completely prevented by β -adrenergic (not α -adrenergic) antagonists [84, 85, 88]. Notably, glycogen breakdown and increase in Glc-6-P concentration induced by epinephrine in muscle occur independently of insulin [79, 89]. In the brain, both neurons and astrocytes are endowed with insulin receptors, but only astrocytes respond to insulin by increasing glucose uptake and glycogen synthesis, whereas insulin does not affect neuronal glucose uptake [90–93]. Overall, these findings suggest that glycogenolysis and suppression of glucose phosphorylation by HK identify some of the effects of noradrenergic signaling.

Conclusions and perspectives

In this paper, we have developed the idea (illustrated in Figure 2) that monoaminergic systems might control cellular glucose uptake [63] based on the potential of astrocytic glycogenolysis to modulate glucose channeling to brain cells in a Glc-6-P-dependent manner [26]. Our discussion can be summarized as follows.

1. Alerting stimuli induce activation of brainstem nuclei and MA release in forebrain regions including the neocortex and hippocampus. MAs act by volume transmission on receptors located in both neurons and astrocytes. MAs have a functional inhibitory effect on neuronal activity designed to increase signal-to-noise ratio for subsequent neural processing. Astrocytes take part in this mechanism by removing neuroactive compounds from extracellular space. Overall, this preparatory mechanism occurs in anticipation of subsequent behavioral responses.
2. MAs have a metabolic effect as well, involving astrocytic MA-stimulated glycogenolysis and associated increase in intracellular Glc-6-P level. High Glc-6-P concentration in astrocytes reduces substrate flow through HK via product-inhibition. In turn, this decrease in glucose phosphorylation diminishes extracellular glucose uptake by astrocytes and thus leaves more glucose available for neuronal utilization. In this respect, the rapid chain of events underlying this preparatory mechanism fits the view that “astrocytes are good scouts: being prepared also help neighboring neurons” [94].

Unfortunately, generalization on the metabolic effects of MAs is difficult because experimental (especially *in vivo*) studies suffer from the high degree of redundancy existing within and between monoaminergic systems. Furthermore, the determinations of brain glycogenolysis and corresponding changes in intracellular Glc-6-P are experimentally challenging, which adds to their conceivable dependence on the distinct stages of a stimulatory event (i.e., alerting, onset, progression, and recovery), let alone their interactions with systemic hormonal and nutritional status. Future research may focus on the relation between the failure of monoamines to induce glycogenolysis and the development of certain brain disorders. For example, studies dating back to several decades ago [95 and references therein] have suggested that an impaired capacity of NE to mobilize glycogen can result in epileptic manifestations [see also 96, 97]. Interestingly, the methionine sulfoximine rat epilepsy model exhibits increase glycogen and decrease in catecholamine (both NE and DA) levels [98].

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Abbreviations

5-HT	5-hydroxytryptamine (serotonin)
AK	adenylate kinase
CK	creatine kinase
DA	dopamine
Glc-6-P	glucose 6-phosphate
GLUT	glucose transporter
GP	glycogen phosphorylase
HA	histamine
HK	hexokinase
LC	locus coeruleus
MA	monoamine
NE	norepinephrine (noradrenaline)
NKA	Na ⁺ /K ⁺ -activated adenosine triphosphatase
RN	Raphe nucleus
TCA	tricarboxylic acid
TMN	tuberomammillary nucleus
VTA	ventral tegmental area

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Figure 1. Schematic diagram for the ADP recycling mechanism in mitochondria

Rapid ADP signaling from plasma membrane NKA to mitochondria occurs in neurons because of expression of mitochondrial creatine kinase (mCK). In astrocytes, creatine buffer remains confined to cytosol (note that both neurons and astrocytes express cytosolic creatine kinase). Neuronal oxidative metabolism is thus rapidly up-regulated. Mitochondria-bound kinases, including HK and mCK (see text), maintain substrate availability for F₀-F₁ ATP synthase. Continuous recycling of ADP ensures the maintenance of mitochondrial membrane potential (ψ_m), which otherwise hyperpolarizes and accelerates electron leak

and associated production of reactive oxygen species (ROS) within the electron transport chain (ETC). Glucose processing through HK is hypothesized to be necessary for neurons as these cells have very high rates of mitochondrial respiration and are exceptionally sensitive to oxidative stress (see [14] for details). ANT, adenine nucleotide translocator (ATP/ADP antiporter); GLUT, glucose transporter; VDAC, voltage-dependent anion channels (porin).

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Figure 2. Summary of the effects of main MA neuromodulators on intracellular signaling, glycogenolysis and cellular glucose uptake

Ascending monoaminergic axons innervating the neocortex and hippocampus terminate primarily as varicosities that release MAs extrasynaptically. MAs diffuse paracellularly through the extracellular space and activate G-protein coupled receptors (GPCRs) located on both neuronal and astrocytic plasma membrane. In neurons, MAs eventually concur to dissipate postsynaptic depolarization (e.g., via hyperpolarization-activated cyclic nucleotide-gated channels, not shown) and thus contributing to the inhibitory effect underlying the increase in signal-to-noise ratio. The same outcome is brought about by astrocytes due to uptake of extracellular K⁺ and associated neuronal hyperpolarization. Stimulation of astrocytic MA receptors initiates intracellular signaling cascades involving production of cAMP by adenylyl cyclase (AC) and subsequent stimulation of protein kinase A (PKA), and/or entry of Ca²⁺ into cell cytosol from endoplasmic reticulum after activation of phospholipase C (PLC) and inositol 1,4,5-trisphosphate receptors (IP₃Rs). In turn, PKA and Ca²⁺ ions stimulate phosphorylase kinase (PhK) by phosphorylation or through allosteric mechanism, respectively. Finally, PhK phosphorylates glycogen phosphorylase (GP), the enzyme responsible for mobilization of glycogen, which produces (after isomerization)

phosphorylated glucose in the form of Glc-6-P. Since the rate of glycogenolysis, and hence that of Glc-6-P production, is relatively high (see Table 1) there is substantial product-inhibition of hexokinase (HK). Decreased consumption (i.e. phosphorylation) of glucose by HK results in reduced concentration gradient of the sugar across the plasma membrane, thereby also reducing the substrate flow through gradient-driven glucose transporter 1 (GLUT1) isoform. Uptake of extracellular glucose is therefore shifted away from astrocytes, while in neurons it proceeds normally through high-capacity GLUT3 carriers. Overall, energy metabolism (downstream HK) is equally supported in neurons (with carbons coming from glucose) and astrocytes (with carbons coming from glycogen). This means that the switch between glucose and glycogen as carbon source is not expected to change the intercellular fluxes of lactate/pyruvate (not shown), consistent to what we previously found through kinetic analysis [26]. Inset (bottom) shows the approximate location of monoaminergic brainstem nuclei and their projections to forebrain regions. Note that other afferent and efferent projections, including mutual interconnections, are not reported in the figure. Only the dorsal Raphe nucleus (the largest serotonergic nucleus projecting to the forebrain) is shown.

Table 1

Monoaminergic receptor-mediated stimulation of brain glycogenolysis.

Ref.	System	MA	Receptor*	EC ₅₀ (μmol/L)	Glycogenolysis Rate** (μmol/g/min)
[99]	chick brain	HA	H ₂ (Gα _s)		1.4 (35% in 5–10 min, 80 μg/Kg HA i.v.)
[100]	rat astrocytoma cells	HA NE	H ₁ (Gα _{q/11}) β (Gα _s)		
[101]	human astrocytoma cells	HA	H ₁ (Gα _{q/11})	2.0	2.0 (30% in 3 min, 300 μmol/L HA)
[102]	cultured rat astrocytes	HA	H ₁ (Gα _{q/11}) H ₂ (Gα _s)	0.4 (H ₁) 3.3 (H ₂)	0.5 (50% in 20 min, 100 μmol/L HA)
[103]	mouse cortical slices	HA	H ₁ (Gα _{q/11})	3.4	0.33 (25% in 15 min, 100 μmol/L HA)
[104]	guinea-pig hippocampal slices	HA	H ₁ (Gα _{q/11})		
[105]	mouse cortical slices	HA NE 5-HT	– β (Gα _s) –	0.5 (β)	
[106]	leech segmental ganglia	HA NE DA 5-HT	– – – –		
[107]	cultured chick astrocytes	NE	β (Gα _s) α ₂ (Gβγ)		0.08 (25% in 60 min, 100 μmol/L NE)
[108]	cultured mouse astrocytes	NE	β (Gα _s) α ₁ (Gα _{q/11})	0.02	0.75
[109]	cultured mouse astrocytes	NE		0.05	
[110]	cultured rat astrocytes	NE	β (Gα _s)		
[111]	cultured mouse astrocytes	NE	β (Gα _s) α ₂ (Gβγ)	0.046	0.3–0.7
[112]	chick brain	NE	β (Gα _s)		
[113]	mouse cortical slices	NE	β (Gα _s)	0.36	
[114]	rainbow trout brain	NE	–		0.17 (25% in 30 min, ~170 μg/Kg NE i.c.v.)
[115]	cultured chick astrocytes	NE	β (Gα _s)		
[116]	rat olfactory bulb	NE	β (Gα _s) α (Gα _{q/11} , Gβγ)	0.02	
[117]	mouse brain	NE DA	β (Gα _s) –		3.0–4.0 (20% in 1 min, ~100 μg/Kg NE i.c.v.; 30% in 2 min, ~200 μg/Kg DA i.c.v.)

Ref.	System	MA	Receptor*	EC ₅₀ (μmol/L)	Glycogenolysis Rate** (μmol/g/min)
[118]	cultured cortical astrocytes	NE DA	β (Gα _s) D ₁ (Gα _s)		1.0–2.0 (50% in 5 min, 100 μmol/L NE; 25% in 5 min, 100 μmol/L DA)
[119]	cultured rat astrocytes	NE 5-HT	β (Gα _s) α (Gα _{q/11} , Gβγ)		
[120]	rat hippocampus	DA	D ₂ (Gβγ)		
[121]	mouse brain	5-HT	–		5.0 (25% in 1 min, ~200 μg/Kg 5-HT i.c.v.)
[122]	rainbow trout brain	5-HT	5-HT _{1,2} (Gα _{q/11})		0.4 (40% in 20 min, 12.8 μg/Kg 5-HT i.c.v.)
[123]	mouse cortical slices	5-HT	5-HT ₂ (Gα _{q/11}) 5-HT ₇ (Gα _s)	20.0	
[124]	cultured mouse astrocytes	5-HT	–		n.d. (25% in 24h, 100 μmol/L 5-HT)
[125]	leech segmental ganglia	5-HT	–		0.07 (20% in 60 min, 100 μmol/L 5-HT)
[126]	rat brain	5-HT	5-HT ₂ (Gα _{q/11})		0.23 (35% in 30 min, 2mg/Kg 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane, i.p. or 10 mg/Kg mescaline i.p.)
[127]	cultured rat astrocytes	5-HT	5-HT ₂ (Gα _{q/11})	5.0	
[128]	cultured mouse astrocytes	5-HT	5-HT ₁	1.0	
[129]	cultured mouse astrocytes	5-HT	5-HT ₂ (Gα _{q/11})		0.3 (15% in 10 min, 10 μmol/L fluoxetine)

* The type of receptor implicated in the glycogenolytic response has been determined experimentally or, where possible, inferred by the relevant effector pathway. The corresponding G protein isoform is indicated in parenthesis. Gα_{q/11} is coupled to phospholipase C and Ca²⁺ signaling. Gα_s is positively coupled to adenylylate cyclase and cAMP signaling. Gβγ subunits regulate a variety of effectors including phospholipases, cyclases and protein kinases, whose outcomes can overlap with those brought about by α subunits. Stimulation of glycogen degradation (but also of glycogen turnover) occurs through regulation by phosphorylation of GP after Ca²⁺ and/or cAMP signaling pathways [23] (see also Figure 1).

** The rate of glycogenolysis is estimated in individual studies or alternatively here on the basis of the amount of glycogen mobilized at the time of assay, assuming a basal glycogen concentration in astrocytes of 20 μmol/g [130, 131]. This value is determined either by taking an average whole-brain glycogen content of 5 μmol/g and an astrocytic volume fraction of 25%, or by considering an average glycogen content of ~120 nmol/mg protein in cultured astrocytes (with 160 mg protein/g wet weight). Where relevant, the concentration of the MA used in the experiments is also shown (for in vivo studies: i.v., intravenous injection; i.c.v., intracerebroventricular injection; i.p., intraperitoneal injection). Note that the rate of glycogenolysis (especially peak rate, see Table 3 in [21]) is possibly underestimated when calculated from studies that assayed changes in glycogen content after long exposure/incubation periods.

Only studies directly reporting MA-induced decreases of glycogen content in astrocytes of forebrain structures are included.