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Beta2-Adrenergic Receptor and Astrocyte Glucose Metabolism

Jun-hong Dong · Xin Chen · Min Cui · Xiao Yu · Qi Pang · Jin-peng Sun

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Abstract Astrocyte glucose metabolism functions to maintain brain activity in both normal and stress conditions. Dysregulation of astrocyte glucose metabolism relates to development of neuronal disease, such as multiple sclerosis and Alzheimer's disease. In response to acute stress, beta2-adrenergic receptor is activated and initiates multiple signaling events mediated by Gs, Gi, arrestin, or other effectors depending on specific cellular contexts. In astrocytes, beta2-adrenergic receptor promotes glucose uptake through GLUT1 and accelerates glycogen degradation via coupling to Gs and second messenger cAMP-dependent pathway. Beta2-adrenergic receptor may regulate other steps in astrocyte glucose metabolism, such as lactate production or transduction. Inappropriate regulation of beta2-adrenergic receptor activity can disrupt normal glucose metabolism, and leads to accelerate neuronal disease development. It was demonstrated that the absence of beta2-adrenergic receptor in astrocytes occurred in multiple sclerosis patients, and the increased beta2-adrenergic receptor activity relates to Alzheimer's disease. A clear view of beta2-adrenergic receptor-mediated signaling pathways in regulating astrocyte glucose metabolism could help us to develop neuronal diseases treatment by targeting to the beta2-adrenergic receptor.

Keywords Beta2-adrenergic receptor · Astrocytes · Glucose metabolism · G protein-coupled receptors

J.-h. Dong · J.-p. Sun (✉)
Key Laboratory for Experimental Teratology of the Ministry of Education, Department of Biochemistry and Molecular Biology, Shandong University School of Medicine, Jinan, Shandong 250012, People's Republic of China
e-mail: sunjinpeng@sdu.edu.cn

X. Chen · Q. Pang · J.-p. Sun
Provincial Hospital Affiliated to Shandong University, Jinan 250021, People's Republic of China

M. Cui · X. Yu
Department of Physiology, Shandong University School of Medicine, Jinan, Shandong, People's Republic of China

J.-h. Dong
Weifang Medical University, Weifang, Shandong, People's Republic of China

Introduction

Astrocytes are star-shaped brain glial cells with important functions including physical structuring of the brain, blood–brain barrier formation, modulation of synaptic transmission, and nutrient support to adjacent neurons. Residing close to microvasculature and neuronal axons, astrocytes are poised ideally to supply axons with metabolic intermediates, such as glutamate, GABA, and probably lactates, which are essential for neuron function under normal or stress conditions. In resting state, the brain consumes 20 % of total body oxygen in contrast to its 2 % relative weight, suggesting the importance of oxidative phosphorylation in glucose metabolism of both astrocytes and neurons (Genc et al. 2011). However, in response to detrimental factor or urgent situation, such as hypoxia condition with reduced oxygen in blood, astrocytes can also switch to anaerobic pathway and produce then transfer lactate to around axons. Both oxidative and aerobic glucose metabolism in astrocytes are tightly regulated by concerted actions of neuronal transmitter, nutrient, and other factors, and dysfunction of glucose metabolism regulation may lead to development or acceleration of many neuronal diseases, such as multiple

sclerosis, Parkinson's disease, and Alzheimer's disease (AD, Hunt et al. 2007; Laureys et al. 2010).

Beta2-adrenergic receptor (β_2AR) is one of the major receptors of endogenous "fight or flight response hormone," norepinepherine, which regulates multiple steps of glucose metabolism in astrocytes (Cohen et al. 1997; Carnevale et al. 2007). Numerous studies have shown expression of beta-adrenergic receptor in both gray and white matters by radioligand binding and immunohistochemistry, in which β_2AR is the dominant component of human white matter astrocytes (Aoki 1992; Sutin and Shao 1992; Zeinstra et al. 2000). A recent research with specific receptor subtype knockout mice, with radio ligand binding together with RT-PCR, also demonstrated expression of all three types of beta-adrenergic receptors in astrocytes (Liu et al. 1992; Salm and McCarthy 1992; Shao and Sutin 1992; Mantyh et al. 1995; Zeinstra et al. 2000; Catus et al. 2011).

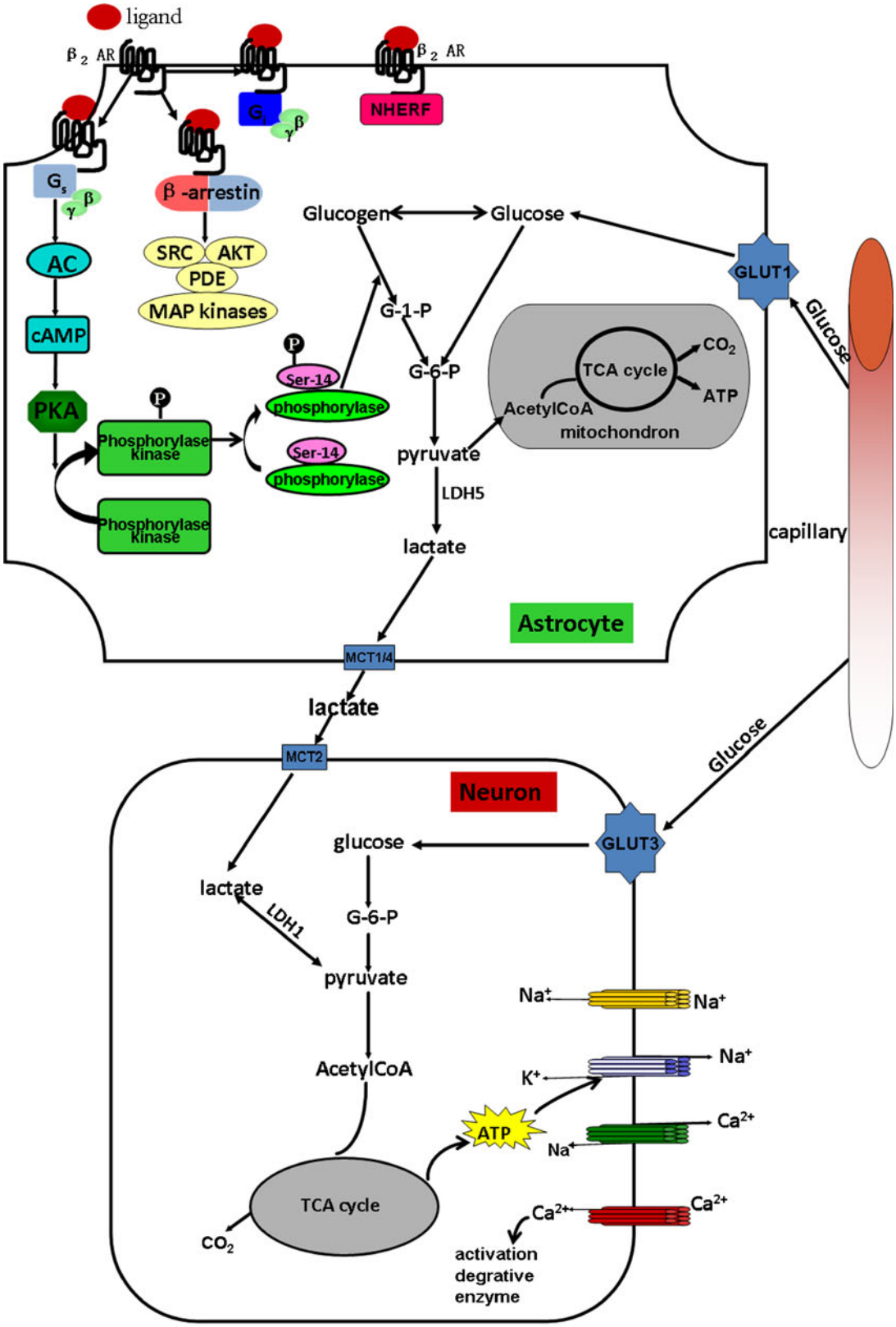
Being the first radiolabeled and cloned other than rhodopsin, β_2AR is the best characterized G protein-coupled receptor in signaling and biochemical studies, which is highlighted by recent advanced works such as crystal structure of β_2AR–Gs protein complexes, multiple conformations of β_2AR with different ligands, and its numerous downstream signaling at cellular level (Robishaw et al. 1986; Daaka et al. 1997; Hall et al. 1998; Xiao et al. 2010; Hara et al. 2011; Kahsai et al. 2011; Kobilka 2011; Rasmussen et al. 2011). Generally, with endogenous ligand norepinepherine stimulation, β_2AR primarily couples to Gs proteins, successively activates adenylyl cyclase, and produces cAMP (Robishaw et al. 1986). The increased cellular concentration of cAMP functions as the "second messenger"; activates cascade connection, such as PKA and CREB; and results in a "first wave" of biological effects (Fig. 1). The activated PKA conversely phosphorylates β_2AR, uncoupled it from Gs then switches the receptor to couple to Gi (Daaka et al. 1997; Xiao et al. 1999). The switching mechanism of β_2AR from Gs to Gi during persistent agonist stimulation has important anti-apoptotic effects in cardioprotection (Zhu et al. 2001; Xiao et al. 2006).

Concurrent with its phosphorylation by PKA, β_2AR is also phosphorylated by one or two specific GRKs on its c-terminal or intracellular third loop depending on its specific cellular contexts (Wilkins and Scolding 2008). The phosphorylated receptor recruits beta-arrestins, terminates Gs signaling at one side, and initiates a "second wave" of signaling by scaffolding different downstream molecules, such as Src, ERK, and PDE (Lin et al. 1999; Luttrell et al. 1999; Perry et al. 2002; Nelson et al. 2008). The arrestin-mediated β_2AR signaling regulates multiple cellular activities, which is signified by recent research in β_2AR regulation of DNA damage in stress response pathway (Hara et al. 2011). Unless general G or arrestin mediated pathway for all GPCRs, it is also reported that specific downstream signals are initiated by β_2AR in specific physiological conditions. β_2AR can directly interact with NHERF through its c-terminal, regulating Na^+/H^+ exchange (Hall et al. 1998). In recent research of Alzheimer's disease, activated β_2AR interacts with presenilin-1, stimulates γ-secretase activity, and accelerates amyloid plaque formation (Ni et al. 2006). Thus, as the most important endocrine receptor, β_2AR may regulate distinct cellular functions due to variation in the abundance of its downstream effectors in specific organs or cell types. In this minireview, we will examine current knowledge of β_2AR function and in regulating astrocyte glucose metabolism and its relevance to neuronal disease, which may shed light for future studies.

β_2AR Regulate Glucose Transport Through GLUT1

Glucose is regarded as the main carbon source of brain energy metabolism. During rest conditions astrocytes and neuron uptake glucose from the blood with similar rate. After being taken up by astrocytes, glucose can be metabolized through glycolysis or be stored via glycogen synthesis. Once there is intense neuronal activity or stress signal, astrocytes increase glucose uptake rate while the neuron does not change, suggesting a tight regulation of glucose transport in astrocytes (Pellerin et al. 2007; Chuquet et al. 2010).

β_2AR first regulates glucose transport from the blood vessel cells into astrocytes (Fig. 1). As early as 1990, Hsu et al. observe a marked increase of ^{14}C-labeled glucose transport induced by beta2 and beta3 adrenergic receptor agonist isoproterenol after 30 min incubation, accompanied with an activation of adenylyl cyclase (Hsu and Hsu 1990). Further studies with specific β_2AR agonist zinterol and beta3 adrenergic receptor agonist CL316243 revealed that beta3 adrenergic receptor regulates early time points while β_2AR functions at later time of glucose transport (Sato et al. 2007; Gibbs et al. 2008). The fact that two adenylate cyclase inhibitors DDA and SQ22536 block β_2AR-mediated glucose transport suggests that β_2AR regulates glucose transport through coupling to Gs and activation of adenylate cyclase pathway. Just recently Catus et al. did a thorough research on three beta-adrenergic receptor functions in regulation of glucose transport with subtype specific receptor knockout animals. They demonstrated that activation of beta2 receptor upregulated glucose transport (Catus et al. 2011). Application of GLUT inhibitor cytochalasin B blocks beta-adrenergic receptor-mediated glucose transport, suggesting that β_2AR likely regulate glucose transport through directly affecting GLUT1 activity. Neurons express GLUT3, while astrocytes mostly express GLUT1 (Pellerin et al. 2007; Genc et al. 2011). This glucose subtype specificity determines their different regulatory property, which may explain the glucose uptake rate change occurring in astrocytes



SRC： Sarcoma
AKT： Protein kinase
PDE： phosphodiesterase
TCA cycle： tricarboxylic acid cycle
G-6-P： Glucose-6-phosphate
MCT： monocarboxylic acid transporter
AC: adenylate cyclase
GLUT: glucose transporter
PKA: protein kinase A
LDH: lactate dehydrogenase
cAMP: cyclic adenosine monophosphate
MAP kinases： Mitogen-activated protein kinases

◀ **Fig. 1** Signaling cascade by beta2 adrenergic receptor and its regulation on astrocyte glucose metabolism

but not neurons under stress. Whether do β_2AR regulate GLUT1 function through phosphorylation, membrane anchoring, or protein expression needs further scrutinized inspection.

β_2AR in Astrocyte Glycogenesis and Lactate Metabolism

Astrocytes are the primary glycogen stores in the brain, and 40 % glucose taken up by astrocytes enters into glycogen synthesis (Prebil et al. 2011), which is majorly promoted by alpha adrenergic receptor (Hertz and Gibbs 2009; Hutchinson et al. 2011) in physiological conditions. Neurons can also synthesize glycogen while this activity is inhibited to prevent the harmful effects of glycogen to these cells. Thus, astrocyte glycogen is the only glycogen source in the brain and is necessary to maintain neuronal activity in case of energy deprivation, hypoxia, ischemia, or too much neuronal activity. With a low blood glucose concentration or stress condition, glycogen stored in astrocytes undergoes glycogenlysis in response to glucagon or epinephrine, not only providing energy for it own consumption but also generating glucose or lactate to supply peripheral axon demand. Binding of β_2AR in astrocytes either by norepinephrine or isoproterenol leads to coupling the receptor to Gs and activation of adenylyl cyclase (Fig. 1). The activated adenylyl cyclase increases intracellular cAMP and promotes glycogenlysis through a PKA-mediated phosphorylation cascade (Brown et al. 2003, 2005; Dienel et al. 2007). The PKA activates phosphorylase kinase, which, in turn, phosphorylates glycogen phosphorylase b at Ser14, rearranges residues region 10-22 into a stable alpha helical conformation, increases phosphorylase activity up to 25 %, and enhances further AMP activation. The activated phosphorylase cleaves glycogen at α-1-4 position and substitutes with a phosphoryl group, generating glucose-1-phosphate (G1P). The conversion of phosphorylase b to phosphorylase a by PKA controls the rate-limiting step of glycogen degradation to monomers (Johnson et al. 1978; Sorg and Magistretti 1991; Fillenz et al. 1999; Magistretti and Pellerin 1999; Allaman et al. 2000; Wender et al. 2000; Zaccolo et al. 2006; Brown and Ransom 2007; Walls et al. 2009).

G1P is isomerized to glucose-6 phosphate (G6P) by phosphoglucomutase. Most of G6P are converted to pyruvate via glycolysis as the concentration of glucose-6-phosphatase is quite low in astrocytes (Dringen and Hamprecht 1993; Magistretti and Pellerin 1999). Pyruvate can either go through oxidative phosphorylation in the mitochondria to provide ATP for astrocytes' usage or be converted to lactate through anaerobic metabolism. The significance of anaerobic metabolism as energy supply is highlighted by the fact that 50 % glucose versus 5 % oxygen increase is taken up by astrocytes under stress condition (Fox et al. 1988). Astrocytes express specific LDH5 which prefers converting pyruvate to acetate whereas neurons only have LDH1 that favors the reverse reaction. There is an astrocyte–neuron lactate shuttle hypothesis (ANLSH model) that lactate generated by astrocytes can be provided to adjacent neurons for emergent demands. Although several computational studies questioned the efficiency of the glucose utilization in the process, experimental and computational evidence supports the functional importance of the hypothesis (Jolivet et al. 2010; Mangia et al. 2011; Bouzier et al. 1998; Genc et al. 2011; Newman et al. 2011). For example, exogenous lactate serves as the main substrate for C6 glioma cell oxidative metabolism monitored by NMR (Bouzier et al. 1998); the MCT inhibitor that blocks the lactate transport impairs learning memory and in silico preference of ANLSH model in hypoxia-induced condition (Bouzier et al. 1998; Genc et al. 2011; Newman et al. 2011).

β_2AR has been identified to regulate anaerobic metabolism and lactate production. With human exercise test, it is found that infusion of epinephrine increases blood lactate concentration. The nonselective beta-adrenergic receptor blocker propranolol attenuates oxygen–carbohydrate index while beta1 adrenergic receptor antagonist metoprolol has no effect. These results suggest that β_2AR not beta1 adrenergic receptor regulates this nonoxidative metabolism (Seifert et al. 2009). β_2AR probably regulates lactate production by accelerating glycogenlysis, while it is also possible that it can directly regulate LDH or lactate transport. It is reported that both of β_2AR agonists isoproterenol and clenbuterol elevate LDH4 and LDH5 expression in ventricular myocytes (Kaundal et al. 2007). Whether or not a similar effect of beta2 adrenergic receptor functions in regulation of astrocyte specific LDH expression is never examined. It is also not known whether LDH can be phosphorylated downstream of β_2AR activation, which provide another level of potential β_2AR regulatory mechanism in lactate production.

The lactate produced by astrocytes will be transported outside of the astrocytes through monocarboxylate transporters (MCTs). Astrocytes are abundant with MCT1 and MCT4 while neurons are enriched with MCT2. It is known that MCT1 and MCT4 prefer to releasing lactate outside while MCT2 prefer uptaking lactate, which supports the ANLSH model (Pellerin et al. 1998; Bergersen 2007; Genc et al. 2011). In neurons, norepinepherine stimulates MCT2 expression through PI3K/Akt pathway. Conversely, the same stimulation may also increase the expression of MCT1 or MCT4 in astrocytes through β_2AR. Such hypothesis is waiting for further evidences (Chenal and Pellerin 2007).

Dysregulation of β_2AR in Astrocyte Glucose Metabolism Relates to Development of Multiple Sclerosis and Alzheimer's Disease

There are signs indicating the association of astrocyte glucose metabolism dysfunction with neuronal diseases, such as multiple sclerosis, Alzheimer's disease and Parkinson's disease(Steele and Robinson 2012; Alexander 2002; Freemantle et al. 2006; Maragakis and Rothstein 2006). As perhaps the most important neuronal transmitter receptor, β_2AR regulates the transition of astrocytes from rest to active state to respond to acute stress, and to accomplish the fine-tuning metabolic interactions between astrocytes and around neurons. In most cases, astrocyte β_2AR expression is upregulated in areas of the CNS or optic nerve injury (Mantyh et al. 1995; Hodges-Savola et al. 1996). However, clinical studies revealed that β_2AR is absent in plaques and alba of multiple sclerosis patients' postmortem brain sections compared with nonneurologic disease patients, through both immunohistochemistry and quantitative autoradiography with [^{3}H]-labeled dihydroalprenolol (De Keyser et al. 1999; Zeinstra et al. 2000). This observation indicates that β_2AR may involve in a rescuing mechanism during neuronal injury, and the lack of β_2AR in astrocyte cells may cause or accelerate multiple sclerosis development.

Inflammatory cell infiltration, glial cell hyperplasia plaque formation, axon damage and loss are all involved in multiple sclerosis development (Frohman et al. 2005; Wilkins and Scolding 2008). β_2AR has been extensively reviewed by several recent papers for its importance in immune inflammatory astrocyte responses (Laureys et al. 2010). Yet, recent research found that drugs suppressing the inflammatory response, such as IFN-beta and CD52, were unable to prevent chronic neurological damage in multiple sclerosis (Coles et al. 1999; Kidd et al. 1999; Confavreux et al. 2000). These results suggest that other mechanisms, such as glucose metabolism disorder, also play important roles in multiple sclerosis development. When hypoglycemia or nerve activity becomes strong, glycogenolysis in astrocytes plays as an important energy supplier for axons (Fillenz et al. 1999). Extending away from their cell bodies, axons depend on local production of ATP to maintain ion gradients and sustain energy supply. In the white matter, primary axonal energy metabolism takes place at abut of astrocytes and Ranvier nodes (Brown 2007). Lack of β_2AR in multiple sclerosis patients causes disorder of astrocyte glucose transportation and glycogenlysis, and decreases the energy supply to axons. The energy deprivation of axons will decrease its ATP synthesis, yielding insufficient energy to fulfill Na^+–K^+ pump requirements. The failure of Na^+–K^+ pump finally leads to excessive Na^+ influx and uncontrolled depolarizations, followed by the opening of voltage-sensitive Ca^{2+}channels and reverse operation of the Na^+–Ca^{2+} exchanger, namely intake Ca^{2+} and the discharge Na^+. The rise in axonal Ca^{2+} then leads to microtubule breakdown and unwanted apoptosis (Gaskin et al. 1975; Ransom and Fern 1997; Stys and Jiang 2002). Thus deficiency of β_2AR in astrocytes causes dysregulation of astrocyte glucose metabolism, and finally contributes to progressive axonal degeneration and multiple sclerosis development.

Dysregulation of glucose metabolism may also contribute to neuron degeneration of Alzheimer's disease. Positron emission tomography studies demonstrate that glucose uptake is impaired in Alzheimer's disease patients (Minoshima et al. 1994; Freemantle et al. 2006). The observation that disruption of glucose metabolism precedes the amyloid plaque formation suggests a relation of astrocytes glucose metabolism in AD development (Small et al. 2000).

As environmental factors such as acute stress are important risk factors of Alzheimer's disease, there is no doubt that dysregulation of β_2AR has important impact on Alzheimer's disease development. It was initially identified that both β_2AR and β_1AR showed smaller but significant (25 %) increases in aggressive Alzheimer's disease subjects versus both nonaggressive Alzheimer's disease patients and controls (Russo-Neustadt and Cotman 1997). In neurons, activation of β_2AR associates with presenilin-1, enhances γ-secretase activity, and promotes amyloid plaque formation (Ni et al. 2006). Conversely, amyloid beta can directly interact with β_2AR, induces PKA-dependent AMPA receptor hyperactivity, and promotes β_2AR internalization and degradation (Wang et al. 2010, 2011). All these results indicate that hyperreactive β_2AR relates to AD and β_2AR selective blockers have therapeutic potential for Alzheimer's disease treatment. The concept is supported by a recent study that beneficial effects are seen from β_2AR selective antagonist application with an induced acute stress mouse model (Yu et al. 2010).

The hyperreactive β_2AR in neurons seems to contradict to the observation of hypometabolic glucose state in the brain of Alzheimer's disease patients (Wang et al. 2011). A possible explanation is that acute stress induces significant β_2AR downregulation in neurons and astrocytes. After activation, β_2AR should be phosphorylated by GRKs or PKA, binding to beta arrestin and internalized. Some internalized receptor will be recycled to the cell membrane, while some will be targeted to lysozyme for degradation. A superactive receptor may also have rapid inactivation kinetic, and a long-term stress may induce more receptor degradation that can account for lowered glucose activity in the brain of Alzheimer's disease patients. Till now, two polymorphisms of β_2AR are identified to associate with sporadic late onset of Alzheimer's disease. One is G16R, and the other is Q27E (Yu et al. 2008). The R16 polymorphism has enhanced agonist-mediated desensitization, and E27 polymorphism displays increased agonists signaling in the vasculature. As β_2AR signaling and desensitization are cell specific and also depend on intracellular regulators'

abundance, such as PKA, GRK, and arrestin, a thorough study of the effects of these mutations on β_2AR degradation and desensitization in astrocytes is in need. The impact of β_2AR internalization on glucose metabolism and its relation to Alzheimer's disease should also be examined.

Conclusions and Perspective

The "fight or flight hormone receptor" β_2AR play important roles in regulating astrocyte glucose metabolism in acute stress. Together with other factors, dysregulation of β_2AR will disrupt fine-tuning glucose metabolism in astrocytes and may contribute to the development of neuronal disease such as multiple sclerosis and Alzheimer's disease. In astrocytes, β_2AR is demonstrated to be an important regulator of glucose uptake and glycogen degradation. Lack of β_2AR in multiple sclerosis patients may destroy energy supply from astrocytes to axons, contributing to neuronal degeneration and multiple sclerosis development. While in Alzheimer's disease, hyperactivity of β_2AR or desensitized β_2AR polymorphism is identified in promoting amyloid beta formation and neuronal degeneration. Studies of β_2AR and its polymorphism in desensitization and downregulation in astrocytes likely elucidate its function relevance, which may reconcile the contradiction of observed less glucose metabolism with higher β_2AR activity in the brain of Alzheimer's disease patients.

β_2AR has been demonstrated to regulate cellular activity through coupling to different effectors, such as Gs, Gi, beta arrestin, NHERF, and presenilin, depending on specific cellular contexts. Compared with the heart and skeletal muscle systems, the combination signaling and function of β_2AR in astrocyte cell glucose metabolism are less investigated. The β_2AR molecular regulatory target of glucose transport in astrocytes and whether or not β_2AR involves in lactate transport and aerobic oxidation through regulation of LDH expression and activity of MCTs await further investigation. Current available tools of B2AR accumulated in the past three decades of research, including specific receptor knockout and trans-gene models, multiple ligands with different receptor activation properties, and knowledge of the fine-tuning downstream regulatory mechanisms, provide good opportunities for a better understanding of its function in astrocytes glucose metabolism and relation to neuronal disease. Such understanding will lay out the foundation for further development and usage of specific beta2 receptor ligands in preventing or therapeutic treatment of neuronal disease, such as multiple sclerosis and Alzheimer's disease.

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