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OVERVIEW

Astrocytes as GABA-ergic and GABA-ceptive Cells

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Abstract GABA (gamma-aminobutyric acid) is considered to be the major inhibitory neurotransmitter that is synthesized in and released from GABA-ergic neurons in the brain. However, recent studies have shown that not only neurons but astrocytes contain a considerable amount of GABA, which can be released and activate the receptors responsive to GABA. In addition, astrocytes are themselves responsive to GABA by expressing GABA receptors. These exciting new findings raise more questions about the origin of GABA, whether it is synthesized or taken up, and about the role of astrocytic GABA and GABA receptors. In this review, we propose several potential pathways for astrocytes to accumulate GABA and discuss the evidence for functional expression of GABA receptors in astrocytes.

Keywords Astrocyte · Glial GABA · Tonic inhibition

Introduction

Recent experimental evidence suggests that glial cells interact closely with neurons and participate in the regulation of synaptic transmission in a manner not assumed previously. At the synapse, astrocytes make direct contacts with neurons via a structure that has been defined as the tripartite synapse where the astrocytic process is associated with the presynaptic and postsynaptic elements [1]. Indeed, astrocytes play an active role in the brain by expressing various receptors for neurotransmitters and releasing various transmitters and neuroactive molecules, just like neurons [2–4]. Among several gliotransmitters released by astrocytes, glutamate, ATP, adenosine, and D-serine have received much attention [5, 6]. Moreover, some suggest taurine as a gliotransmitter [7, 8]. In contrast, the possibility of GABA as a gliotransmitter had not been widely studied previously. Recently, some exciting findings report that in rodent brain the non-neuronal, astrocytic release of GABA can cause tonic inhibition in several brain regions including the thalamus and cerebellum [9, 10]. The amount of astrocytic GABA is variable depending on the brain regions and is positively correlated with the degree of tonic inhibition in CA1 and cerebellum [11]. In addition cultured human astrocytes were shown to be capable of releasing GABA [12]. The next question is then, "how do astrocytes acquire GABA in the first place?"

With regard to the source of astrocytic GABA, we can ask whether astrocytic GABA is synthesized or taken up. If astrocyte has its own synthetic mechanism, the amount of astrocytic GABA must be modulated by various molecular components. On the other hand, if the source of astrocytic GABA is solely the uptake of extracellular GABA, it would be insufficient to explain the varying amount of astrocytic GABA depending on the brain regions, because GABA transporters are widely expressed in astrocytes throughout the whole brain. Therefore, we can assume that multiple pathways might be involved in synthesis and modulation of astrocytic GABA. There are several

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potential pathways for astrocytic GABA. A classical pathway is to synthesize via glutamate decarboxylase (GAD)—a well-known GABA synthesizing enzyme in neurons [13]. In addition, there is an alternative pathway leading to GABA synthesis that utilizes putrescine [14]. The amount of astrocytic GABA can be regulated by GABA metabolizing enzyme GABA-a-ketoglutaric acid aminotransferase (GABA-Transaminase or GABA-T) and GABA uptake proteins, GABA transporter (GAT). Through these potential pathways, astrocytes might contain a significant amount of GABA [15] and release it to mediate tonic inhibition [10].

It has been known for many years that astrocytes help to terminate inhibitory synaptic transmission via GABA uptake mechanisms [16]. In addition, various GABA receptors have been found in astrocytes, suggesting that these cells not only support but also respond and contribute to synaptic transmission [17]. The properties of astrocytic GABA receptors are remarkably similar to their neuronal counterparts. In this review, we provide insightful clues to uncover the possible functions of astrocytic GABA and GABA receptors.

GABA Synthetic Pathway

GABA can be synthesized via two different pathways in the brain. The classical pathway relies on the expression and activity of GAD enzyme, which removes the carboxyl group of glutamate to produce GABA, and the second pathway is through monoacetylation of putrescine, leading to production of GABA.

GAD

There are two different forms of GAD. The gene of 67-kDa form, referred to as GAD1, is located in human chromosome 2, while the gene of 65-kDa form, GAD2 is located in chromosome 10 [18]. Most neurons have been reported to express both of these forms, but the ratios appear to differ depending on the brain region, as well as the type of neuron, and the subcellular compartment involved. GAD67 is mainly devoted to the synthesis of GABA for general metabolic activity while GAD65 seems to be devoted to synthesis of GABA related with synaptic transmission [19].

Wilson et al. [20] used biochemical assays to compare the level of GAD enzymatic activity between neuronal and non-neuronal cell lines. By incubating the cells with radioactive glutamic acid and counting the scintillation of GAD products obtained from cell homogenates, they concluded that GAD activity was detectable in glia, although it was significantly lower than in neurons. Using similar techniques, Schrier and Thompson [21] observed the production of GABA in rat glial tumor cells. GAD67 was present in glial cells of neonatal rats, but its expression diminished with development and interestingly, GAD65 was not expressed in these cells [22]. A recent study reported a positive immunostaining of GAD67 in cultured human astrocytes [15]. In this study the astrocytes were negative for GAD65, while cortical interneurons were positive. Therefore, this GAD based GABA synthetic pathway appears to be involved in astrocytes, but more molecular and functional evidence is needed to make a definitive conclusion.

Putrescine

Putrescine, a precursor of spermidine and spermine, is first acetylated to monoacetyl putrescine and further degraded to GABA by monoamine oxidase pathway [20]. GABA synthesis from putrescine was first described in bacteria [14]. Then, more reports have shown that GABA may be formed from putrescine in the vertebrate CNS [23, 24]. Also, GABA immunoreactivity preceded that of GAD in ganglion cell and inner nuclear layers in the developing rat retina [25]. In addition, O2A glial progenitors of the optic nerve in culture are capable of synthesizing GABA from putrescine. These cells have no detectable GAD expression by immunocytochemistry, but show a strong immunohistochemical staining with GABA antiserum. HPLC data also showed that the quantity of GABA in these cells was much higher in putrescine-enriched medium than in control [26]. More recently, this alternative GABA production pathway using putrescine was observed in the neuroblasts of the subventricular zone at the early stages of rat embryonic development, when the GAD activity was not detected [27]. This GABA synthetic pathway via putrescene is also evident in pathological conditions. The rate of GABA production from radioactive putrescine in astrocytes was four times higher in epileptic DBA/2J mice than normal C57BL/6J mice [28]. Therefore, this putrescine based GABA synthetic pathway appears to play an important role under distinct physiological and pathological conditions.

GABA Modulating Pathway

Astrocytes are important for the clearance of remaining neurotransmitters in the synaptic cleft. They use different transporters to take up and maintain the basal levels of glutamate and GABA in the extracellular space. Astrocytes also metabolize the taken-up neurotransmitters. GABA, in particular, is rapidly and efficiently catalyzed into glutamate by GABA-T.

GABA-Transaminase

GABA is metabolized by GABA-T, also known as 4-aminobutyrate aminotransferase (ABAT). It is a mitochondrial enzyme, which converts GABA into glutamate. GABA-T is more widespread than GAD and highly expressed in astrocytes. In cultured human astrocytes, immunostaining with a polyclonal antibody to GABA-T demonstrated positive staining of Purkinje cells and apparently stronger staining of astrocytes [12]. In hippocampal co-culture of neurons and glia, GABA efflux was increased by the inhibition of GABA-T using vigabatrin [29]. They measured postsynpatic $GABA_A$ receptor mediated current, which was blocked by bicuculine. This current represented spontaneous tonic non-vesicular GABA release. In response to vigabatrin treatment, GABA efflux increased in a time dependent and dose dependent manner. Also, vigabatrin enhanced tonic current in hippocampal neuron [30]. These studies suggested that decreased activity of the GABA-T can increase GABA in astrocyte and release more GABA. Indeed, intracellular GABA levels were enhanced by other GABA-T inhibitor, gabaculine, in addition to vigabatrin [12].

GABA Transporter

GABA transporters are members of a large family of Na^+- and Cl^--dependent neurotransmitter reuptake proteins. Among the three subtypes of GABA transporters, GAT1 and GAT3 are highly expressed in astrocytes. To know the effect of blocking GABA transporter on tonic GABA current, Rossi et al. used GABA transporter inhibitors to conclude that inhibition of GAT-1 by a specific inhibitor SKF-89976A did not affect the tonic current, but instead produced an inward current, even in the presence of 1 μM TTX. This is due to GABA accumulating rapidly in the extracellular space and acting on $GABA_A$ receptors. Thus, GAT-1 does not appear to release GABA but, rather actively takes up GABA from the extracellular space. Also, pre-loading β-alanine, a GAT3 inhibitor, did not reduce, but instead doubled the bicuculline-sensitive tonic GABA current relative to control slices [31]. The compromised GABA uptake in GAT1 knockout mice increased $GABA_A$ receptor-mediated tonic conductance in both cerebellar granule and Purkinje cells [32].

However, a few studies have reported that GABA transporters can release GABA from astrocytes under certain conditions [12, 33]. Although they showed possibility that GABA transporters can involve or revert for GABA release, these were tested in cultured astrocyte or non-physiological conditions. Therefore, GABA transporters appear to take up GABA from the extracellular space, instead of directly releasing by reverse mode under physiological condition. At the least, those studies suggest that GABA transporters can modulate the accumulation of GABA in astrocyte.

Function of GABA-ergic Astrocytes

In conclusion, astrocytes are able to synthesize and release GABA into the extracellular space and activate GABA receptors located on neurons. It was recently found that GABA release from glial cells mediates tonic inhibition [10]. Compared to the activation of tonic $GABA_A$ receptor by astrocytic GABA, activation of $GABA_B$ receptors by glial GABA is not defined. Therefore, it is needed to be investigated whether GABA release from astrocyte affect $GABA_B$ receptors in particular those located on neuronal presynaptic terminals, in which case astrocytic GABA could modulate the release of neurotransmitters.

$GABA_A$ Receptors

Despite the fact that some studies failed to describe the presence of $GABA_A$ receptors on cultured astrocyte using autoradiographic [34, 35] and biochemical experiments [36], other studies reported the presence of $GABA_A$ receptors in cultured astrocytes from hippocampus [37, 38], retinal slices [39], Bergmann glia in cerebellar slices [40, 41], and acutely isolated astrocytes [42].

Expression of $GABA_A$ Receptor in Astrocytes

Although immunocytochemical studies generally failed to identify $GABA_A$ receptor expression in astrocyte, $GABA_A$ receptor containing $\alpha 1$ and $\beta 1$ subunits was detected in acutely isolated hippocampal astrocytes using immunohistochemical and fluorescent benzodiazepine binding techniques [37]. Recently, $GABA_A$ receptor containing $\alpha 2$ and $\gamma 1$ subunits was detected in Bergmann glia in cerebellar slices using electron microscopy [41]. This receptor was localized on the plasma membrane of Bergmann glia processes that wrap Purkinje cell soma, dendritic shafts, and dendritic spines.

In cultured cerebellar astrocytes, mRNA for almost all subunits of $GABA_A$ receptor was quantified by competitive polymerase chain reaction assay [43]. It was found that $\alpha 1$ and $\alpha 2$, $\beta 1$ and $\beta 3$, and $\gamma 1$ subunits were prominent in astrocytes. However, the total amount of $GABA_A$ receptor subunit mRNA in astrocytes was two orders of magnitude lower than in neuronal cells [43].

Most convincing evidence showing the presence of $GABA_A$ receptors was obtained using electrophysiological experiments. The activation of $GABA_A$ receptors caused an efflux of Cl^- [44, 45] and led to a membrane

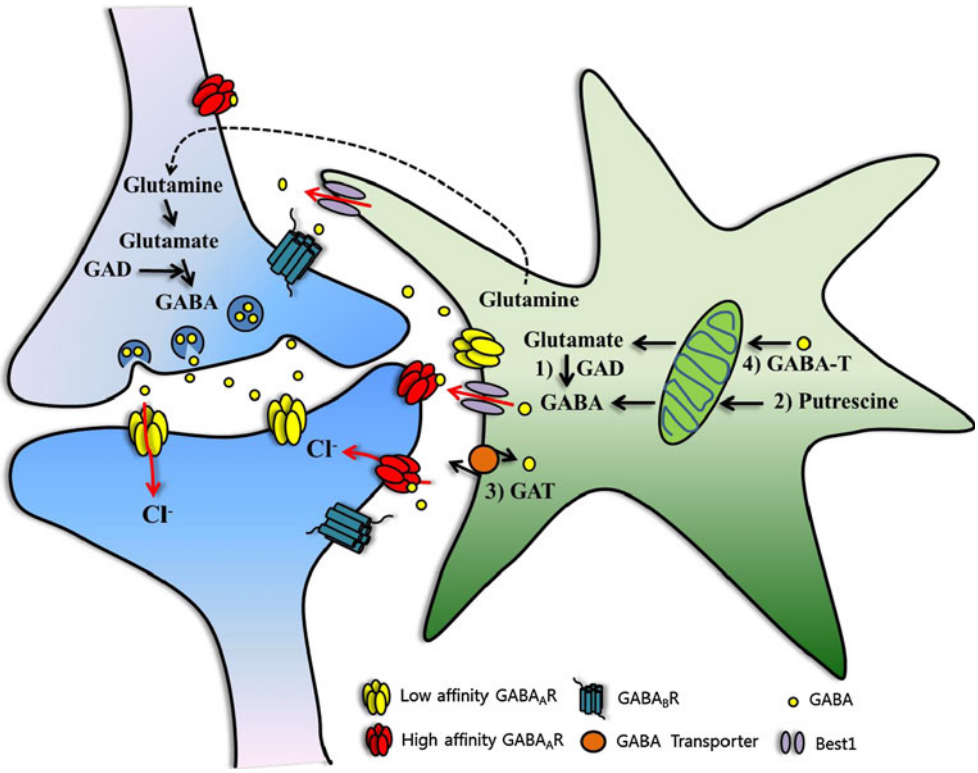

Fig. 1 The model of sources and regulation for GABA-ergic astrocytes. This figure describes the four possible pathways for production and regulation of GABA in astrocytes; (*1*) production of GABA from glutamate via glutamate decarboxylase (GAD), (*2*) synthesis of GABA from putrescine via monoamine oxidation, (*3*) GABA transporter taking up extracellular GABA into astrocyte, (*4*) GABA transaminase converting GABA into glutamate in astrocyte

depolarization of about 40 mV in cultured astrocytes, where the Cl^- equilibrium potential can be as positive as −35 mV [35, 46, 47]. This GABA-induced response was mimicked by muscimol, a $GABA_A$ receptor agonist and blocked by bicuculline, $GABA_A$ receptor antagonist [37].

Function of $GABA_A$ Receptor in Astrocytes

The expression of $GABA_A$ receptors in retina, hippocampus, and cerebellum suggested that $GABA_A$ receptor expression may be important for development [38]. It has been proposed that $GABA_A$ receptors expressed in the Bergmann glia and other astrocyte are linked to GABA-ergic synaptic transmission, synapse formation and stabilization [48, 49]. Because of the GABA-induced depolarization, it has been proposed that glial $GABA_A$ receptor could be involved in intracellular Cl^- homeostasis [45] and extracellular pH and K^+ homeostasis during synaptic transmission [37, 50].

The $GABA_A$ receptor-induced membrane depolarization could open voltage-activated Ca^{2+} channels identified in cultured and acutely isolated astrocytes [51, 52]. And, other groups reported an increase in intracellular Ca^{2+} from ER by $GABA_A$ receptor activation through unknown mechanism [53]. The GABA-induced increase in intracellular Ca^{2+} could subsequently release gliotransmitters such as glutamate and ATP, possibly affecting synaptic transmission [5, 54].

$GABA_B$ Receptors

The first evidence that astrocytes express $GABA_B$ receptor was obtained by measuring Ca^{2+} flux [55]. Using autoradiography, the expression of $GABA_B$ receptor was detected in cultured astrocytes from the cerebellum, spinal cord, and brain stem [35]. Moreover, the membrane hyperpolarization was observed by application of baclofen, a $GABA_B$ receptor agonist. This was inhibited by saclofen, $GABA_B$ receptor antagonist [35]. It has been reported that glial cells, namely astrocytes and microglia from the CNS exhibit $GABA_B$ receptor immunoreactivity [56]. Recently, by measuring the adenylyl cyclase activity, functional $GABA_B$ receptor was confirmed in cultured astrocyte from the cerebral cortex. Astrocytes are shown to express $GABA_BR1$ and $GABA_BR2$ subunits [57].

In some studies, it has been shown that activation of $GABA_B$ receptor by baclofen reduced basal Ca^{2+} flux in cultured cortical astrocytes [58]. However, in other studies, Ca^{2+} rise after activation of $GABA_B$ receptor has been reported in cultured astrocytes and hippocampal slices [17, 59]. Interestingly, the $GABA_B$ receptor-mediated Ca^{2+} responses were abolished in Ca^{2+} free solution [17]. However, the precise molecular mechanism is not known. The role of astrocytic $GABA_B$ receptor on synaptic transmission was proposed in this study. Activation of astrocytic $GABA_B$ receptor potentiated the inhibitory transmission in hippocampal slices, probably through the release of

gliotransmitter, especially glutamate, after $GABA_B$ receptor-mediated Ca^{2+} rises [17].

Concluding Remarks

In summary, several studies concerning the expression of GAD and putrescine pathway in astrocytes suggest that they might produce GABA themselves in addition to accumulating GABA through uptake mechanism. Glial cells can use two distinct pathways of GABA synthesis: the classical pathway using GAD enzymes to catabolize glutamate and an alternative pathway via degradation of putrescine (Fig. 1). It is important to note that biochemical analyses of GABA producing pathways in glial cells have been performed only on cultured cells and that in vivo experiments are still lacking and therefore future work is needed. After decades of studying GABA receptors on astrocytes, it is now accepted that astrocytes express some subunits of $GABA_A$ and $GABA_B$ receptors (Fig. 1). However, the physiological and functional significance of GABA receptor activation on astrocytes remains to be investigated in the future. The recent findings of astrocytic GABA and GABA receptors bring new excitement in the fields of glial biology and glia-neuron interaction. Future studies on the role of glial GABA and GABA receptors will shed light on inhibitory functions of these glial cells, which were once thought to be the "passive glue in the brain."

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