GABA-driven excitatory neurotransmission: gene regulation by excitatory GABA and its possible role in the developing brain

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Introduction

γ-Aminobutyric acid (GABA), a major inhibitory neurotransmitter in the nervous system, functions as an excitatory neurotransmitter in the developing nervous systems [1, 2, 3, 4]. The excitatory and inhibitory responses of neurons to GABA have been attributed to the differential expression of two Cl− transporters between immature and mature neurons, the Na+−K+−2Cl− co-transporter NKCC1 and K+−Cl− co-transporter KCC2 (Fig. 1) [5, 6, 7]. Since GABAergic neurotransmission operates before glutamatergic neurotransmission [4, 8], GABA, instead of glutamate, plays a central role in excitatory neurotransmission in the early development of the brain. On the other hand, neuronal activity-dependent gene expression, which is evoked by excitatory neurotransmissions, contributes to the expression of various neuronal functions including cell survival [9, 10, 11], dendritic growth [13, 14, 15], and long-term memory [16]. These findings strongly indicate that activity-dependent gene expression is operated by the excitatory action of GABA in developing neurons, thereby promoting neural development. We recently demonstrated that excitatory GABA activated transcription of the gene encoding brain-derived neurotrophic factor (BDNF). Since BDNF plays a fundamental role in the expression of various functions by the nervous system, the excitatory GABA-induced expression of the BDNF gene may be important for the neural development of the brain. In this review, we summarized the mechanisms underlying the excitatory GABA-induced expression of the BDNF gene, and proposed the possible roles of its regulation in the early development of the brain, an impairment in which may cause the abnormal development of the brain.

Keywords: GABA; BDNF; CREB; gene expression; neural development

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-VIII, and -IX) exist upstream of each exon (Bdnf exon-I, -II, -III, -IV, -V, -VI, -VII, -VIII, and -IX) (Fig. 2). Because of multiple splicing donor sites, a single splicing acceptor site, and two polyadenylation signals (Fig. 2), a large number of Bdnf transcripts, all of which share a common coding region, can be produced [22]. Among these alternative Bdnf promoters, Bdnf promoter-I, -IV, and -IX were previously shown to be activated in response to neuronal activity [23, 24].

Neuronal activity-responsive transcription factors participating in the activity-dependent regulation of Bdnf have already been identified (Fig. 2) and cAMP-response element-binding protein (CREB) and neuronal PAS domain protein 4 (NPAS4) were found to be commonly involved in the activity-dependent transcription of Bdnf promoter-I, -IV, and -IX [24].

Excitatory GABA-induced Bdnf expression in immature neurons

As shown in Figure 1, since the intracellular concentration of Cl⁻ ([Cl⁻]i) is low in mature neurons, activation of the ionotropic GABA_A receptor causes the influx of Cl⁻ into neurons and membrane hyperpolarization, resulting in its inhibitory action [5, 6, 7]. On the other hand, activation of the GABA_A receptor induces Cl⁻ efflux due to the higher [Cl⁻], in immature neurons and consequently membrane depolarization [1]. These developmental changes in [Cl⁻], and excitatory/inhibitory GABA responses have been attributed to changes in the expression of two cation-chloride co-transporters, the chloride accumulator NKCC1 and chloride extruder KCC2 [3]. Using fura-2 fluorescence ratio imaging to monitor changes in the intracellular concentration of Ca^{2+} ([Ca^{2+}]), we found that [Ca^{2+}] transiently increased upon the specific stimulation of GABA_A receptors with GABA at 4 DIV, an increase in which was due to the entrance of extracellular Ca^{2+} into neurons via L-type voltage-dependent calcium channel (L-VDCC) [17]. On the other hand, a prolonged culture of cortical cells caused a synchronized Ca^{2+} oscillation at 14 DIV, which could be spontaneously generated at later stages of the culture due to the maturation of synapses in culture [25, 26]. This oscillation was abolished by the addition of N-methyl-D-aspartate (NMDA) receptor antagonist or GABA, in accordance with changes in the expression levels of Nkcc1 and Kcc2 during the culture [17]. Thus, it is possible, at least in part, to monitor the process of the cellular differentiation of neurons in primary culture of rat cortical cells.

A previous study demonstrated that the excitatory action of GABA induced the mRNA expression of genes, such as c-fos and Bdnf, in immature neurons [27]. Obrietan et al. (2002) also showed that excitatory GABA induced the expression of Bdnf via the mitogen-activated protein kinase (MAPK)-CREB pathway, because, in addition to an increase
in Bdnf mRNA expression, the phosphorylation of MAPK and CREB was induced by the treatment of cultured cells with GABA and concomitantly suppressed by inhibition of the MAPK pathway with U0126 [28]. However, it currently remains unknown whether and how transcriptional activation is involved in the excitatory GABA-induced expression of Bdnf in immature neurons. In our recent study [17], we addressed the mechanisms underlying the excitatory GABA-induced expression of Bdnf using a primary culture of rat cortical cells at 4 ~ 5 DIV, in terms of transcription regulation.

Mechanisms underlying Bdnf promoter activation by excitatory GABA actions

By focusing on the transcriptional regulation of Bdnf promoter-IV, one of the activity-regulated Bdnf promoters, we demonstrated that GABA activated Bdnf promoter-IV through multiple Ca\(^{2+}\) signaling pathways including not only MAPK, but also Ca\(^{2+}\)/calmodulin-dependent protein kinase (CaMK) and calcineurin, the activation of which was mainly evoked via L-VDCCs and partially via NMDA receptors [17]. Although multiple cis-regulatory elements, to which transcription factors such as CREB [19], upstream stimulatory factor (USF) [29], Ca\(^{2+}\)-responsive factor (CaRF) [30], nuclear factor of activated T-cell (NFAT) [31], and nuclear factor kB (NFkB) [32] specifically bind, were previously shown to be involved in the activity-dependent transcription of Bdnf, the mutation of CRE in Bdnf promoter-IV or overexpression of dominant negative A-CREB was sufficient to almost completely suppress GABA-induced promoter activation [17], indicating that multiple Ca\(^{2+}\) signaling pathways evoked by the excitatory action of GABA converge on CREB to activate Bdnf promoter-IV (Fig. 3).

We demonstrated that the GABA-induced activation of Bdnf promoter-IV was dependent on both the phosphorylation of CREB at Ser133 and nuclear localization of CREB-regulated transcriptional co-activator 1 (CRTC1) [17]. CRTC1s were initially shown to regulate CREB-dependent transcription independently of the phosphorylation of CREB at Ser133 [33] and, furthermore, were involved in memory formation [34, 35]. The phosphorylation of CREB at Ser133 recruited its co-activator, CREB-binding protein (CBP)/p300, which possesses histone acetyltransferase (HAT) activity [36]. CBP itself is also phosphorylated by CaMKIV in order to participate in activity-regulated CREB-dependent transcription [37]. On the other hand, CRTC1 is released from 14-3-3 protein and translocates from the cytoplasm to the nucleus, in which it activates CREB-dependent transcription when dephosphorylated by calcineurin [38]. Recent studies indicated that CRTC1 was involved in the activity-dependent expression of immediate early genes [34, 39]. Heinrich et al. (2013) proposed that the KIX domain of CBP, which can interact with the kinase-inducible domain (KID) of CREB,
increased CRTC1 binding to phosphorylated CREB [40]. Thus, two distinct co-activators of CREB may cooperatively activate CREB-dependent transcription, in the case of the excitatory GABA-induced expression of Bdnf.

Using immunostaining with anti-CRTC1 antiserum, we found that CRTC1 translocated from the cytoplasm to the nucleus with the GABA treatment and was involved in the excitatory GABA-induced activation of Bdnf promoter-IV [17]. On the other hand, we also showed the involvement of the phosphorylation of CREB in the GABA-induced transcriptional activation using Gal4-CREB, in which the Gal4 DNA-binding domain was fused to the transcriptional activation domain of CREB by deleting the basic leucine-zipper DNA binding domain of CREB. Due to this deletion, CRTC1 was unable to access the Gal4-CREB. Nevertheless, excitatory GABA-induced Gal4-CREB-dependent transcription was significantly suppressed by the inhibition of calcineurin with FK506 [17]. A previous study reported that calcineurin was involved in the dephosphorylation of CREB at Ser133 by protein phosphatase 1 (PP1) following a brief neuronal stimulation, but not a longer one [41]. Calcineurin was also reported to contribute to neuronal activity-regulated CREB-dependent transcription [42]. Further investigations are needed in order to clarify how calcineurin participates in the activation of CREB-dependent transcription with and/or without the translocation of CRTC1, including not only the phosphorylation of CREB at Ser133 but also other factors including the other phosphorylation sites of CREB [43] and phosphorylation of the CREB co-activator CBP [37].

Possible role of excitatory GABA-regulated Bdnf expression in neural development

Concerning the excitatory GABA-induced expression of Bdnf in neural development, Wang and Kriegstein (2011) used bumetanide, an inhibitor of NKCC1 that raises [Cl-], thereby contributing to GABA-induced excitation during early development (Fig. 1), and observed decreases in dendritogenesis and spinogenesis in the cortical neurons of 4-week-old mice treated with bumetanide during early development (from embryonic day 15 to postnatal day 7) [44]. The early termination of GABA excitation by the forced expression of KCC2, which excluded Cl- and, thereby, contributed to GABA-induced inhibition in mature neurons (Fig. 1), also significantly impaired the morphological maturation of cortical neurons [45]. Ageta-Ishihara et al. (2009) demonstrated that excitatory GABA-induced activation of the CaMKK/CaMKIα pathway controlled cortical axon elongation, and BDNF was mainly involved in promoting dendritogenesis via CaMKIγ [46, 47]. These findings supported excitatory GABA contributing to the morphological development of cortical neurons through activation of the CaMKK/CaMKIα pathway and induction of BDNF/CaMKIγ one.

Excitatory GABA also plays an important role in driving adult neurogenesis, which can be observed in the dentate gyrus of hippocampus and in the olfactory bulb [48]. Tozuka et al. (2005) previously reported that the stimulation of GABAergic excitation promoted neuronal differentiation in adult hippocampal progenitor cells [49]. Jagasia et al. (2009) also demonstrated that GABA-mediated neuronal excitation contributed to the survival of newly born hippocampal neurons in the adult dentate gyrus through the phosphorylation of CREB [50]. Since BDNF is widely known to be involved in neuronal survival and differentiation [21], excitatory GABA-induced Bdnf expression could participate in enhancing the survival and differentiation of newborn neurons in the adult brain. Ren et al. (2015) recently reported that the late stage survival of neurons, dendritic complexity, and spine maturation of newborn neurons in dentate granule cells were reduced in GABA_A receptor-deficient mice (γ2−/− mice), which is now considered to be a model of major depressive disorder [51]. Furthermore, the expression of BDNF was slightly lower in γ2−/− mice than in wild type mice [51]. Thus, these findings also support GABA-induced Bdnf expression via CREB-dependent transcription playing an important role in the control of neuronal differentiation (Fig. 4).
Excitatory GABA actions may affect the structure of chromatin

The mechanisms underlying the regulation of Bdnf expression by membrane depolarization, which can be caused by elevations in the concentration of KCl in the culture medium, could reflectthose by excitatory GABA, because, as far as we detected, the intracellular signaling pathways involved in controlling the expression of Bdnf exon-IV mRNA by excitatory GABA was similar to those by KCl. We already showed that the activation of Bdnf promoter-I was remotely suppressed by repressor element-1 (RE1) in Bdnf exon II [52], which can bind RE-1-silencing transcription factor (REST)/neural restrictive silencer factor (NRSF) [52, 53]. This repressive activity was attributed to the recruitment of histone deacetylase (HDAC), which is associated with the epigenetic regulation of gene expression, to RE-1 and the level of its repression competed with the neuronal activity caused by membrane depolarization [52]. Taken together, these findings indicate that excitatory GABAergic inputs into neurons affect the chromatin state to make neuron-specific genes more readable in neurons, which may, at least in part, contribute to promoting the cellular differentiation of neurons. This notion also suggests that the stronger the excitatory GABA action, the more relaxed the chromatin structure; that is, the expression levels of neuron-specific genes differed among neurons according to the strength of excitatory GABA during development.

Impairment of excitatory GABA-induced gene regulation may affect the process of early development of the brain

GABAergic and BDNF actions are known to be involved in controlling the critical period for development of the visual cortex [54]. The overexpression of BDNF by transgenic mice or enhancements in the functions of GABA by the administration of benzodiazepine to gestating females shifted the critical period to an earlier time [55, 56], and could, conversely, be delayed by preventing GABAergic functions through the gene-targeted disruption of glutamic acid decarboxylase 65 (Gad65) [56]. Previous studies reported that the production and secretion of BDNF were important for inhibitory GABAergic development [57, 58, 59]. Thus, functional interactions between GABA and BDNF may be important for neuronal plasticity determining the critical period as well as the development of inhibitory GABAergic systems.

Schneider and Przewtocki (2005) reported that the offspring of female rats injected with valproic acid (VPA), an acidic chemical compound, on the 12.5 day of gestation exhibited behavioral aberrations that resembled those found in autistic patients [60]. VPA is clinically used as an anticonvulsant and mood-stabilizing drug, and raises the levels of GABA in synaptic clefts by inhibiting GABA degradative enzymes such as GABA transaminase. Therefore, the administration of VPA to gestating females enhances the activity of excitatory GABA actions, possibly shifting critical periods in the developing brain. On the other hand, VPA is also known to inhibit HDAC [61]. The administration of VPA to cultured rat cortical neuronal cells altered gene expression, in which Bdnf mRNA expression markedly increased [62], and this may have resulted in the overexpression of BDNF in the developing brain. Hong et al. (2008) directly demonstrated that the introduction of a subtle knock-in mutation into the CRE (or CaRE3) of mouse Bdnf...
promoter-IV resulted in the sensory-dependent induction of Bdnf mRNA expression being disrupted in the cortex, with the formation of fewer inhibitory synapses [57], which suggested that the impairment in BDNF expression by disruption of excitatory GABA actions was likely to retard the development of inhibitory synapses in the developing brain. Thus, the aberrant expression of BDNF may affect the excitatory-inhibitory balance of synapses, leading to neurodevelopmental disorders such as autism spectrum disorder [63].

Conclusion

The excitatory action of GABA plays a crucial role in the early development of the brain. Excitatory GABA has the ability to induce the neuronal activity-dependent expression of BDNF in immature neurons, which can be induced by glutamatergic neurotransmission in mature neurons. The effects of excitatory GABA on the early development of the brain may be mediated by the induction of Bdnf. Conversely, the dysregulation of BDNF expression by a disruption in the excitatory actions of GABA in immature neurons may cause abnormal neural development, potentially resulting in neurodevelopmental and psychiatric disorders.

Conflicting interests

The authors have no conflicts of interest to declare.

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