Ischemic Injury of Cortical GABAergic Neurons: Vulnerability, Mechanism and Pathological Impacts

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【**ABSTRACT**】 Cerebral ischemic stroke is a common neurological disease in senior individuals. Therapeutic strategies include anticoagulation, thrombolysis, neuroprotection and anti-inflammation. These efforts have not shown to fully improve stroke patients. Although studies have provided valuable insights for early interventions in neuroprotection, searching mechanisms underlying ischemic stroke is critically needed. Cerebral GABAergic neurons have been found to be vulnerable to pathological situations, such as ischemia, oxidative stress, acidosis and toxic molecules. The high consumption of cellular energy and the low volume of cellular buffer system make GABAergic neurons being vulnerable to the hazard internal environment. Insufficient blood flow initiates ischemic processes in brain cells, especially in GABAergic neurons and astrocytes. These changes activate intracellular signaling pathways and influence membrane components in GABAergic neurons. Moreover, an ischemic failure for astrocytes to reuptake glutamates exacerbates the dysfunction of GABAergic cells. Their dysfunctions in encoding spikes and transmitting synaptic signals may shift neural balance toward the excitotoxicity, which leads to the ischemic stroke of nerve cells. The studies of mechanisms underlying GABAergic cell vulnerability to toxic environments should provide the clues for developing therapeutic strategies in the protection of neuronal functions from ischemic injury.

【**KEY WORDS**】 ischemia; GABA; neuron; synapse; glia cell; brain

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大脑皮层 GABA 能神经元缺血性损伤:易损性,机制和病理影响

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【**摘要**】 大脑缺血性中风是老年人常见的神经疾病,其治疗策略包括抗凝、溶栓、神经保护和抗炎等,但疗效并非达到完全治愈。因而研究缺血性脑中风的新的病理机制和新的防治策略尤为重要。大脑 γ 氨基丁酸(gamma aminobutyric acid,GABA)能神经元因细胞活跃、代谢旺盛及其缓冲能力低下,对缺氧、氧化应激和毒素敏感,因而易受环境因素的影响而损伤。脑血流降低首先导致大脑星形胶质细胞和 GABA 能神经元缺血性病理变化,GABA 能神经元的损伤诱导大脑兴奋和抑制的失平衡,导致兴奋毒性神经损伤和缺血性神经细胞死亡。因而,澄清 GABA 能神经元易损性的机制将有助于发现新的保护神经元功能而防治脑损伤的策略。

【**关键词**】 缺血;γ 氨基丁酸;神经元;突触;神经胶质细胞;大脑

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Cerebral ischemic stroke is the most common disease and the third reason for disability in senior individuals[1-7]. Therapeutic strategies include anticoagulation, thrombolysis, neuroprotection and anti-inflammation[8-18]. Based on preclinical studies about ischemia-related molecules and biochemical reactions in brain cells, many approaches to interrupt injurious cellular and molecular processes were applied to clinical trials[19-21]. These methods have not shown the fully improvement of stroke patients[19-20,21-22]. The study of other mechanisms underlying ischemic stroke is critically needed.

Cerebral ischemia leads to the pathological changes of neurons[23-25] and the deficiency of neurovascular unit, neuron-astrocyte-endothelium[26-28]. Their ischemic malfunctions are usually ahead of their morphological impairments[29-35]. In general, the malfunction of these cells makes unable to maintain their structure, and their structural collapse leads to a complete loss of cellular functions. Therefore, the elucidation of the mechanisms underlying the dysfunctions of the brain cells in an early stage of ischemic stroke appears to be more important.

Although multiple signaling pathways in ischemia interactively initiate an impairment of nerve cells[36-38], neuronal excitotoxicity in its early stage is presumably a major reason to drive brain cells into injury. The evidences for this assumption include an elevated glutamate action because of its high release and/or injured reuptake[35,39-42], an elevated excitatory synaptic transmission[43-44], an increased neuronal excitability at cortical pyramidal neurons[35] and a decreased function of inhibitory interneurons[35,41,45-47]. As GABAergic cells are active in the central nervous system[48-50], they are vulnerable to the shortage of oxygen/glucose and the accumulation of waste products in ischemia. A study indicates that the dysfunction of cortical inhibitory neurons appears ahead of pyramidal neurons in an early phase of ischemia and that this inhibition vulnerability to ischemia facilitates neuronal overexcitation[35]. Therefore, the elucidation of the mechanisms underlying the vulnerability of inhibitory neurons during ischemia is critical for neuronal protection. The protection of inhibitory neurons from ischemic vulnerability is likely therapeutic strategy to prevent brain cells from ischemic stroke.

It is pointed out that molecular processes and signaling cascades, such as an activation of Ca^{2+}-permeable glutamate receptors[51-53], an increase of intracellular Ca^{2+}[54-57] and a production of intracellular toxic molecules[58-60] that lead to ischemic neuronal excitotoxicity, are present in GABAergic neurons[61-64]. Whether these processes are involved in ischemia-induced dysfunction of GABAergic neurons remains to be studied.

These studies indicate that the impairment of GABAergic neurons is likely an important step for neuronal excitotoxicity in the early phase of ischemic stroke, subsequently leading to brain cell death. In order to facilitate the development of therapeutic strategies via securing GABAergic neurons, we focus on reviewing current knowledge related to the ischemic injury of cerebral GABAergic neurons in terms of their functional impairment, molecular mechanisms and pathological consequence.

1 The characteristics of ischemic impairment in different types of brain cells

The neurons, glia cells and vascular endothelium cells in the brain constitute a neuron-astrocyte-endothelium unit[65-67] to maintain neuronal spike encoding[68-70]. Their ischemic impairments lead to clinical neuropathy[71-72]. As ischemic brain tissues are limited to be obtained from humans, the ischemia-induced injury of the brain cells is studied in animal models by bilateral carotid artery occlusion (BCAO) or middle cerebral artery occlusion (MCAO).

1.1 Morphological changes of brain cells during ischemia

In terms of morphological impairments in brain cells, the study by magnetic resonance imaging (MRI) shows the dilation of lateral ventricles after ischemia, indicating the shrink of brain tissues[73]. Under the light microscope, the densities of cortical neurons and white matter in ischemic animals are lower than those in controls, and small vessels are dilated. These results indicate that cerebral ischemia impairs the neurons and glia cells[72-75]. Moreover, the studies by scanning and transmission electron microscopy show that the veins and arteries appear the generalized vasoconstriction 10 min after ischemia, such as the reshuffle of smooth

muscle cells, the thickness of vessel base-membrane and the increase of endothelium microfilament. This vasospastic change may worsen the ischemic injury of brain cells [76-77].

Ischemic neural impairments are characterized as apoptosis and subsequent necrosis of brain cells [22,38,78-81]. Ischemia induces the upregulation of phosphorylated c-Jun in a proportion of morphologically intact hippocampal neurons and the subsequent apoptosis-like change, such as the increases of TUNEL-positive cells and caspase-3 activation [33,82-85]. These data indicate that neuron death in hippocampus after transient forebrain ischemia may be initiated via c-Jun N-terminal kinase activation and apoptosis-mediated pathways. Apoptosis-like change contributes to the subsequent necrosis of brain cells [86].

To temporal changes in the ischemic injuries of different types of cerebral neurons, the studies by morphology and biochemistry indicate that a generalized arrest of protein synthesis occurs shortly after ischemia. The arrest and recovery of protein synthesis appear more quickly in hippocampal interneurons than pyramidal cells [87]. An investigation by labeling GABAergic interneurons shows that transient cerebral ischemia leads to severe structural abnormality in hippocampal interneurons and delayed pyramidal cell degeneration, which is prevented by diazepam [88]. Therefore, hippocampal inhibitory neurons are likely vulnerable to cerebral ischemic damage, compared with pyramidal neurons.

1.2 Functional impairment of brain cells during ischemia

Well-organized brain functions are based on the coordinated activity of neurons and glia cells in cerebral networks. These cells and their synapses cost much energy to maintain membrane potentials, signal generation and transmission. The shortage of O_2 and nutrients and the accumulation of metabolic products in ischemia rapidly influence synaptic signal transmission and neuronal spike coding. Although the attenuation of neural activities lowers energy needs to maintain minimal metabolism for cell survival, this minimization can only be sustained for a few minutes. A prolonged ischemia may lead to progressive membrane depolarization and synapse dysfunction, which then elevates intracellular Ca^{2+} via influx and internal store release. Before it reaches a critical level to trigger irreversible processes for cell death, the restore of energy supply may reactivate the membrane pumps to reestablish normal ionic gradients and membrane potentials, which facilitates the return of synaptic and neuronal functions. The protection of brain cells from immediate ischemic dysfunctions and the promotion of their reversible recovery through elevating irreversible threshold and delaying irreversible cascades should be the future efforts.

The functional injury of nerve cells occurs quickly in a range of minutes after ischemia [89], compared with their morphological changes [90], which is consistent with the following facts. The brain functions in humans impair immediately after ischemic stroke. Neuronal functions supported by ionic channels and transporters are quite sensitive to the changes of biochemical reactions, especially the processes for adenosine-5'-triphosphate production. Therefore, the aims to measure the functions of brain cells during ischemia and to address the mechanisms underlying their dysfunction are critically important [91]. The pharmacological treatments to such early events may be the most effective approach to control ischemia and to attenuate long-term neurological deficits [92]. Recent studies about ischemia suggest a wide spectrum of agents potentially capable of delaying or even preventing irreversible outcomes of brain ischemia [93].

The functional measurements of brain cells in the study of ischemia include neuronal excitability, synaptic transmission and glutamate transporter by electrophysiology. In addition to permanent functional impairment by ischemic structure changes, ischemia in the minutes leads to prominent functional injuries including membrane depolarization, inhibitory synaptic depression and excitatory synaptic enhancement [30,94-98]. These processes are likely the trigger signals for neuronal excitotoxicity, irreversible cellular dysfunction and cell death [35]. This complexity in functional changes requires an early and broad spectrum of interventions at different ligand-activated receptors and voltage-dependent channels for the neuroprotection before neuronal damage expands to intact regions [92]. However, these studies did not compare what kinds

of cerebral neurons wee functionally vulnerable to ischemia.

2 Temporal changes among the different types of brain cells during ischemia

Neural excitotoxicity is presumably an early event to initiate neural injury during ischemic stroke [54,56,99]. Its molecular mechanisms include the malfunction of glutamate transporters to elevate glutamate actions [39-40,42,46,100-101] and the glutamate-dependent elevations of intracellular Ca^{2+} and free radicals [57,72,81,102-104]. In terms of processes for neuronal excitotoxicity, the enhancements of signal transmission at excitatory synapses [43-44] and neuronal excitability at cortical pyramidal neurons [35] as well as the attenuation of GABAergic neuron functions [35,45-46,105] are presumably involved. That is, an excessive release of excitatory amino acids and a reduced neuronal inhibition occur in brain ischemia. However, the temporal changes of these processes have not been addressed well.

2.1 Ischemic injury of GABAergic neurons

The functions of the neurons in the central nervous system include the reception of signals from presynaptic inputs, the integration of multiple synaptic signals, the generation of sequential spikes and the output of these digital spike codes to influence their downstream cells [70,106]. The analyses for the functions of GABAergic cells should include their sensitivity to excitatory synaptic input, the ability of encoding spikes and the output of inhibitory synaptic activity on the downstream neurons.

To examine ischemia-induced alternations in the output ability of GABAergic neurons, inhibitory postsynaptic potentials (IPSPs) are measured on their postsynaptic neurons. GABAergic IPSPs on cortical [35] or hippocampal [94] pyramidal cells are depressed rapidly after ischemia within a few minutes. On the other hand, in an *in vivo* model of transient cerebral ischemia, GABAergic IPSPs on large aspiny neurons are enhanced due to an increase of presynaptic release in 3~24 hours after ischemia, and lowered 24 hours after ischemia [107]. This early depression of GABAergic synapses may be related to the initiation of neuronal excitotoxicity, whereas an enhancement of inhibitory synapses is likely due to the *in vivo* intracranial anastomotic circulation or the compensatory processes in the brain. These data indicate that ischemia leads to an inability of GABAergic neurons to send their inhibitory outputs. This indication has been granted by examining ischemic changes in GABA synthesis, release, reuptake, $GABA_AR$ expression in *in vitro* and *in vivo* models of ischemia [97].

The sensitivity of GABAergic neurons to their synaptic inputs and the ability of encoding spikes are examined on their somata. Ischemia attenuates both neuronal spike encoding and excitatory synaptic transmission on cortical GABAergic neurons [46]. This indication is consistent with other studies. For instance, ischemia reduces the ability of firing spikes at cortical GABAergic neurons through elevating spike thresholds and prolonging refractory periods [35,45]. Cerebral ischemia makes the excitability of hippocampal CA1 interneurons declined by raising action potential threshold and shifting input-output curve rightward. Such changes are associated with the ischemic inactivation of voltage-gated Na^+ channel (Nav) and the reduction of Nav1.1 subunit expression at parvalbumin-coexpressed GABAergic neurons [108]. These results present a diagram that ischemia leads to the dysfunction of GABAergic neurons in aspects of the reception of signals from presynaptic inputs, the ability of encoding spikes and the output of controlling their downstream cells.

The role of GABAergic dysfunction in ischemia-induced neuronal death is to drive the balance between inhibition and excitation toward neuronal excitotoxicity, and then initiate the signal pathways for cerebral ischemic stroke [35,97]. This hypothesis is also supported by seeing the neuroprotective effects, when GABAergic neurotransmission is strengthened by preventing GABA reuptake and analytic metabolism or increasing $GABA_A$ receptor activities [47,88,97,109-110]. In addition, antiepileptic drugs by acting on the presynaptic and postsynaptic GABAergic synapses to enhance neuronal inhibition are proved to counteract abnormal brain excitability in ischemia. These experimental studies utilizing global or focal ischemia in rodents bring the insights into possible neuroprotective action of inhibition enhancers [111].

2.2 Ischemic injury of glutamatergic neurons

The influences of ischemia on the excitability and synaptic transmission of excitatory neurons are analyzed by approaches similar to the functional studies at inhibitory interneurons. Ischemia increases the

excitability of cortical pyramidal neurons, including the attenuation of spike thresholds and the elevation of firing sequential spikes [35]. In animal models of *in vivo* transient cerebral ischemia, hippocampal pyramidal neurons appear a raised membrane input resistance and time constant, which is associated with a decrease of hyperpolarization-activated cationic currents (Ih). The Ih enhancement by pharmacological approach immediately after ischemia attenuates the ischemic loss of CA1 neurons [30]. The results indicate that transient cerebral ischemia increases the intrinsic excitability of pyramidal neurons by upregulating voltage-gated sodium channels (VGSCs) and downregulating Ih. The raised excitability of cortical and hippocampal pyramidal neurons in ischemia exacerbates glutamatergic excitotoxicity and subsequent neuronal loss.

Ischemia-induced changes in glutamatergic neurotransmission have received widespread attention [97]. Early indication for an enhanced glutamate release during ischemia is from the measurement of excitatory neurotransmitter by micro-dialysis. The extracellular concentration of glutamates and aspartate is elevated in the hippocampus and cortex after transient cerebral ischemia [96,112]. This indication is also examined by measuring the excitatory postsynaptic potentials (EPSP), in which spontaneous glutamate release is spike-dependent and spike-independent processes. In the progress of ischemia, the patterns of spontaneous glutamate release in hippocampus change from spike-independent release to large amplitude spike-dependent release [35,42]. Glutamates in spike-dependent release increase may be due to neuronal hyper-excitability during ischemia, which act onto NMDA receptors and metabotropic receptors to raise neuronal excitability. Therefore, the increases of neuronal hyper-excitability and glutamate release may synergistically accelerate the development of neural excitotoxicity.

The involvement of metabotropic glutamate receptors (mGluR) in ischemic neural excitotoxicity has been received a great attention. The antagonists of mGluRs, such as MCPG for mGluR1/5, AIDC and LY367385 for mGluR1, and MPEP for mGluR5, are used to examine the effect of mGluRs on ischemic stroke. The blockade of mGluR5 activation lowers the volume of ischemic infarct [113]. The activation of mGluR5 triggers the release of free radicals for neuronal death after transient ischemia [114]. The blockade of mGluR1 activation reduces the volume of ischemic infarction by lowering PKCγ/Src signal pathway, PI3K-Atk pathway and NMDAR phosphorylation [115-117]. As we known, an activation of group I mGluR activates G-protein coupled-phospholipase C to release 1,2-diacylglycerol and activate protein kinase C. These results suggest that mGluR1/5 in the brain is involved in NMDAR phosphorylation via PKCγ/Src family kinase cascade for neural excitotoxicity after transient ischemia.

On the other hand, the agonists of mGluR1/5, such as CHPG and DHPG, are used to examine the effect of these receptors on ischemic stroke. CHPG reduces infarct volume and neurological deficit [113]. The application of DHPG leads to diverse effects on cortical neurons. DHPG potentiates NMDA-induced neuronal death in cultured cortical neurons by elevating glutamate release [118]. DHPG enhances neuronal injury under oxygen-glucose deprivation (OGD) to cortical and hippocampal cultures [119]. However, DHPG reduces OGD-induced neurotoxicity by inducing ischemic tolerance in organotypic rat hippocampal slices [120].

The reasons for these controversies about the role of mGluR in ischemia may be followings. The preparations used for experiments are different, such as *in vivo*, acute slices and tissue-cell culture. The conditions to induce neuronal injury are variable, such as the applications of NMDA, OGD, lower ACSF perfusion and blood vessel occlusion, which may act onto cellular targets differently regulated by group I mGluRs. The patterns of applying reagents are variable. For example, the study demonstrates that DHPG amplifies NMDA-induced neural injury, but two consecutive uses of DHPG produce neuroprotection, indicating that group I mGluR is an endogenous switch for a "neuroprotective mode", and mGluRs are subjected to activity-dependent switch in regulating excitotoxic neuronal death [121]. In addition, the study with *in situ* hybridization indicates that mGluR1 mRNA level is lower in ischemic animals, but mGluR5 mRNA appears a relatively high expression. The difference in mGluR expression during ischemic stroke indicates that these receptors play different functions in neuronal excitotoxicity [122].

The dysfunction of GABAergic neurons and the

enhancement of excitatory cellular functions in an early phase of cerebral ischemia may shift the balance between excitation and inhibition toward hyper-excitation for subsequent neuronal excitotoxicity. This indication remains to be systemically examined in a single experiment in terms of their spatial and temporal changes [35] to determine the time sequence of treatments to protect different kinds of brain cells.

2.3 Ischemic functional injury of glia cells

The astrocytes regulate ionic homeostasis and extracellular glutamate levels through their Na^+/K^+ ATPase pumps that consume ATP. On the other hand, the astrocytes have substantial oxidative capacity, compared to the neurons, to upregulate glycolysis by its powerful activator, which endows the astrocytes to sustain ATP production [123]. Therefore, the astrocytes are essential for neuronal survival and function, as well as are vulnerable to ischemia and oxidative stress. It is proposed that there is an interaction between glia cells and neurons in ischemia [124], and that the astrocytes play the diverse and important role in ischemic brain damage [125]. In addition to the ischemic injury of neuronal functions, the astrocytes undergo the ischemic dysfunction for destructions of brain tissues [126]. For instance, the astrocytes store glycogen that protects the brain against hypoglycemic damage, but aggravates brain damage during ischemia due to an enhanced lactic acidosis. The astrocytes release substances (such as glutamate, D-serine and adenosine) for ischemic brain damage. The gap junctions in astrocytic networks may spread the molecules to healthy regions leading to infarct expansion in stroke.

The GFAP-negative astrocytes in gray matter are presumably more sensitive to ischemia than the neurons *in vivo*. They undergo the programmed cell death in ischemia, acidosis and oxidative stress via the upregulation of caspases, since the astrocyte survival is improved by inhibiting caspase-dependent and polyADP-ribose-1 cell death pathways [79]. To the molecular targets for ischemic astrocyte dysfunction, the investigations for the ability of the astrocytes to reuptake glutamates with *in situ* hybridization and immunohistochemistry demonstrate that GLT1-mRNA and -proteins are decreased after cerebral ischemia. There is a positive correlation between the number of pyramidal neurons and the expression of GLT1-mRNA/protein. These data indicate that the expression of GLT1 in hippocampus is downregulated in response to ischemia [127]. In terms of the mechanisms of ischemic astrocyte injury, the disruption of Ca^{2+} homeostasis, the generation of free radicals and the depolarization of mitochondrial membrane are involved in to apoptotic astrocyte death [123].

The ischemic attenuation of ATP production reduces the clearance of glutamates from synaptic cleft by their transporters located in neurons and glia cells. The failure of glutamate removal results in glutamate accumulation and subsequent neuronal excitotoxicity. Such a scenario is associated with brain ischemia and hypoglycemia due to the prompt decline in ATP level. The contribution of glial vs. neuronal glutamate transporters and the involvement of distinct glutamate transporter subtypes in ischemic damage remain to be addressed [40].

The vulnerability of oligodendrocytes to ischemia may contribute to the malfunction of central white matter. The studies with LV-MBP-GFP labeled oligodendrocytes show a progressive loss of GFP+ oligodendrocytes in white matter 24 hours after ischemia. One week after stroke, the restoration of GFP+ oligodendrocytes is seen in ischemic white matter. These results indicate transient structural deterioration in oligodendrocyte cell bodies and myelinating processes in ischemia [128].

It is noteworthy that these studies do not indicate the time sequence of functional injury in these types of nerve cells, such that we are not able to estimate what kinds of nerve cells change early or late during ischemia and to determine what kinds of nerve cells should be protected in time windows. We have studied the functions of astrocytic glutamate transporters and GABAergic neurons during ischemia. As showed in a recent study [89], glutamate transporter currents at the astrocytes decrease significantly one minute after ischemia, whereas synaptic currents and intrinsic spikes at GABAergic cells significantly decrease three minutes after ischemia. That is, the dysfunction of glutamate transporters at the astrocytes is ahead of the deterioration of intrinsic property and synaptic transmission on GABAergic neurons. These results indicate the importance in an early protection of astrocytes during ischemia.

3 The impairment characteristics of GABAergic neurons during ischemia

As one group of function-specific neurons[48,63,70,129-133], GABAergic inhibitory interneurons receive and integrate signals from their presynaptic inputs, encode neuronal spikes and inhibit their downstream nerve cells. The analyses of functional changes in GABAergic neurons during ischemia include their sensitivity to excitatory synaptic inputs (i.e., excitatory postsynaptic potential), the ability of encoding spikes (spike pattern) and the output of inhibitory synaptic activity (i.e., inhibitory postsynaptic potentials and GABA release) on their downstream neurons.

3.1 The ischemic changes of active intrinsic properties

The parameters used to present the active intrinsic properties of GABAergic neurons include the ability of converting synaptic inputs into output spikes, the intervals of inter-spike or frequency as well as the threshold and refractory periods of sequential spikes[68,134]. These active membrane properties are essentially controlled by VGSCs[135-136]. VGSC activities are regulated by intracellular Ca^{2+} signals and protein kinases[137-138], which are elevated during ischemic stroke[56,138-141].

The studies with *in vitro* ischemia demonstrate that cerebral ischemia for five minutes impairs the ability of cortical GABAergic neurons to produce sequential spikes[35]. Cerebral ischemia makes the excitability of hippocampal interneurons declined, which is associated with shifting input-output curve toward right[108], i.e., reducing their ability of encoding spikes. This ischemic impairment in producing spikes is due to the elevation of spike thresholds and the prolongation of refractory periods at GABAergic neurons[35,45], as well as the inactivation of VGSCs and the reduction of Nav1.1 subtype expression at parvalbumin-coexpressed GABAergic neurons[108]. Thus, ischemia impairs GABAergic neurons in terms of their encoding spikes, such that they are unable to inhibit their downstream nerve cells, leading to neuronal hyper-excitability.

In addition, the sensitivity of cerebral GABAergic neurons to their presynaptic inputs is impaired during ischemia. For instance, ischemia reduces excitatory synaptic transmission at cortical GABAergic cells[45-46]. The silence of GABAergic neurons in response to their synaptic inputs makes them to be initiated difficultly and slowly in maintaining the homeostatic balance of the brain.

3.2 The ischemic decrease of GABAergic synaptic transmission

The effect of ischemia on GABA release from inhibitory neurons are examined by measuring the expression of glutamate acid decarboxylase (GAD) that converts glutamate into GABA, the concentration of extracellular GABA and the signal transmission of GABAergic synapses. For instance, the studies with immunohistochemistry and western-blot show that ischemic excitotoxicity is linked with the decreases in the expression of GAD through a NMDAR-mediated process and in the processes of GABAergic neurons. These results indicate that ischemia reduces GABA synthesis and subsequent release[142]. This indication is proved by measuring GABA with micro-dialysis, in which the concentration of extracellular GABA is decreased during ischemia[107,143].

Under the condition of stimulating GABA nerve terminals and recording inhibitory postsynaptic potentials (IPSPs), a brief *in vitro* ischemia invariably causes a marked depression of IPSC amplitude, and this downregulation is fully reversible after the removal of ischemic challenge[94]. A transient cerebral ischemia *in vivo* depresses GABAergic IPSPs on aspiny neurons following ischemia[107]. The associated changes in paired-pulse facilitation indicate presynaptic mechanism, for which endogenous adenosine appears responsible since it is prevented by using adenosine A1 receptor antagonists[94]. In addition, ischemia inhibits GABAergic inhibitory postsynaptic potentials (IPSPs) rapidly on cortical neurons[35]. These results suggest that ischemia leads to an immediate decrease of GABA release from inhibitory neurons.

In accordance with a decrease of GABA release from presynaptic terminals, ischemia appears to decline the expression of postsynaptic GABA receptors. For instance, the study by *in situ* hybridization reveals that the changes in the expression of the $GABA_AR\alpha1/\beta2$ subunit mRNAs appear three phases, a rapid decrease within 1 hour, recovery in 4~12 hours and further decline over next three days[144]. The responses of cortical neurons to GABA appear a considerable rundown with time under anoxic condition through a

process of decreasing ATP synthesis[145]. GABAergic synapses after *in vivo* ischemia appears reduced in their amplitudes of miniature inhibitory postsynaptic currents and GABA-evoked currents at hippocampal pyramidal neurons[146]. This can be explained by a reduced $GABA_AR$ sensitivity or clustering as well as possibly reduced GABA release. It is noteworthy that the expression of $GABA_AR$ mRNA decrease well before pyramidal cell degeneration[144], indicating that the loss of GABAergic neurotransmission may contribute to the development of neuronal degeneration following cerebral ischemia.

3.3 The compensation of GABAergic neurons during ischemia

The ischemic decreases in the active intrinsic property and sensitivity of GABAergic neurons as well as in the signal transmission at GABAergic synapses lead to the imbalance between excitation and inhibition toward the excitotoxicity. On the other hand, this neural excitotoxicity may initiate homeostatic process to enhance inhibitory functions in the brain, a compensatory effect of GABAergic neurons, which is beneficial for the survival of the brain cells after an acute phase of cerebral ischemia. The compensation of inhibitory system in ischemia may include the increases of GABA release and postsynaptic receptors.

The compensatory presynaptic mechanisms are measured by immunohistochemistry to detect the expressions of GAD and synaptic vesicle proteins as well as by electrophysiological recording to analyze a frequency of synaptic events. For instance, cerebral ischemia leads to an increase of GAD67/65-positive neurons, in which some of GAD67-positive neurons are the phenotypic shift of pre-existing somatostatin-containing GABAergic neurons[147-148]. Cerebral ischemia by transient middle cerebral artery occlusion induces a decrease in mRNA expression of vesicular GABA transporters lasting for 3~72 hours, which is detected by immunohistochemistry and western-blot. These increased GABA release and decreased reuptake may leave the relatively high levels of GABA in synaptic cleft to strengthen inhibitory synaptic transmission after cerebral ischemia[149].

The studies in a postsynaptic mechanism demonstrate that cerebral ischemia enhances inhibitory synaptic transmission in the late phase[148]. In addition, ischemia enhances GABAergic synaptic transmission on pyramidal neurons, mainly in the amplitudes of evoked inhibitory postsynaptic current and miniature inhibitory postsynaptic current 12 hours after ischemic procedure. This postsynaptic mechanism needs a tonic activation of adenosine A1 receptors[107,150].

4 The mechanisms underlying ischemic injury of GABAergic neurons

The ischemic impairments of cerebral GABAergic neurons include the apoptosis and necrosis in their morphology as well as the dysfunction of their active intrinsic properties and synaptic transmissions. The mechanisms for the former case may be similar to apoptotic process for neuronal death. Here, we focus on reviewing the mechanisms underlying the functional impairment of GABAergic neurons during ischemia. Neuronal spike encoding and synaptic transmission rely on the membrane potentials[70,106], which are basically controlled by three factors, the gradient of different ions, the functional status of ion channels and the function of ATPase-dependent ionic pumps.

Electrical and chemical gradients for ions in the neurons are maintained by ATPase-related ionic pumps on their membrane and glia cells. The functional status of ion channels is controlled by the kinetics of their channels and the properties of their gates (such as voltage-dependent and ligand-dependent). All of these processes are regulated by intracellular signaling pathways[151-155]. In this regard, the functional impairment of GABAergic neurons may be caused by ischemic changes in their membrane, intracellular signaling and extracellular glia cells (Fig.1).

4.1 The mechanisms mediated by intracellular signals

The functional impairments of GABAergic neurons during cerebral ischemia are characterized as the attenuation in encoding spikes, releasing GABA and responding to their synaptic inputs. These pathophysiological changes are related to the membrane identities, such as ionic channels and ATPase-ion pumps[17,156]. These changes may be due to ischemic intracellular processes since there is no evidence about the direct influences of ischemia on ionic channels and pumps. Cellular pathogenesis during insufficient

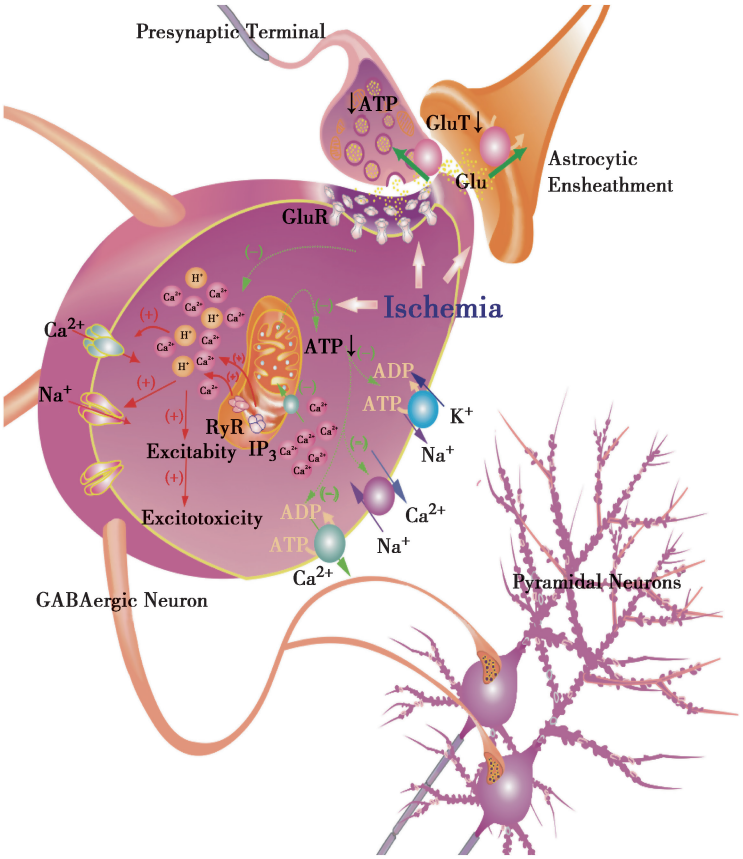

Fig.1　A diagram shows ischemia-induced impairment of cortical GABAergic neurons

The relatively small volume of GABAergic neurons makes them to have a low level of storage in the energy and buffer systems, and their high level of activities raises their energy consume. These factors facilitate GABAergic neurons to be vulnerable to hazard situations, such as ischemia, acid-base imbalance, oxidative stress and toxic environment. Ischemia may lead to the functional impairment of GABAergic neurons through the following steps. Ischemia impairs Glu-T function on astrocytes immediately after ischemia, which may be due to the vulnerability of the astrocytes to lack of energy providers. An accumulation of glutamates in synaptic cleft activates GABAergic neurons through mGluR and NMDAR, which elevates intracellular Ca^{2+} and cellular metabolism to facilitate the vulnerability of GABAergic cells to ischemia. On the other hand, ischemia lowers ATP production in the mitochondria of GABAergic neurons, which in turn impairs molecular transportation related to ATPase-pump, e.g., a reduction of Ca^{2+} pumping back to mitochondria and out of cells. This plus Ca^{2+} release from mitochondria elevate intracellular Ca^{2+} level. Intracellular protons (H^{+}) also increase during the ischemic metabolism. The elevations of Ca^{2+} and H^{+} lead to cellular excitotoxicity and malfunction at cortical GABAergic neurons. The deterioration of inhibitory neurons will shift the balance between excitation and inhibition toward neural overexcitation through disinhibiting excitatory pyramidal neurons.

blood flows includes the lack of glucose/oxygen and an accumulation of metabolic toxic products, such as protons, Ca^{2+} and free radicals, which may activate cytoplasm signaling pathways. Low ATP and high toxics subsequently influence membrane components to impair the functions of GABAergic cells. It is noteworthy that the volume of GABAergic neurons is relatively smaller and the activities of these neurons are higher, compared with pyramidal neurons. The low energy storage, high consumption and low buffer volume on the inside of GABAergic neurons make them being vulnerable to hazard situations, such as ischemia and oxidative stress.

The studies in the mechanism underlying ischemic functional impairment of GABAergic neurons are in an infant stage. The genetically labeling of GABAergic neurons in the central nervous system with green fluorescent protein confers the opportunity to accessing these cells and studying this topic, in which functional cellular imaging and electrophysiological recording plus specific treatments to GFP-labeled GABAergic neurons can be done definitely. Although the theoretical prediction in the mechanisms for the impairment of

GABAergic neurons may be as many as those for other cells[57,102], the evidences are still lack, which we summarize below.

Intracellular Ca^{2+} elevation in cerebral ischemia leads to a functional impairment of GABAergic neurons. The evidences for this conclusion include the investigations by Ca^{2+} imaging, intracellular Ca^{2+} elevation and cheletor. Ca^{2+} imaging in GFP-labeled GABAergic neurons indicate that ischemia induces an immediate increase of intracellular Ca^{2+}, which is associated with the deterioration of neuronal spiking and receptor sensitivity[45-46]. Ischemia-induced malfunction of GABAergic cells is prevented by infusing Ca^{2+} cheletor[105]. Moreover, an elevation of intracellular Ca^{2+} impairs the ability of GABAergic neurons to produce spikes, and this change occludes ischemia-induced changes in the neuronal encoding each other[45,62], indicating Ca^{2+} elevation and ischemia share common pathways to impair GABAergic neurons. Therefore, intracellular Ca^{2+} overload is a toxic factor for ischemia-induced dysfunction of GABAergic neurons.

Ischemic acidosis has been proposed to be a factor of impairing cerebral neurons[157-159]. The smaller volume of GABAergic neurons makes them to contain less acid-base buffers, such that these inhibitory neurons are vulnerable to intracellular acidosis. The study with proton imaging demonstrates that ischemia leads to the immediate increase of intracellular H^+ and the weakness of encoding spikes at cortical GABAergic cells[45]. Moreover, the impairments of GABAergic neuron functions by ischemia and cytoplasmic acidosis occlude each other[45], indicating that cellular acidosis is involved in the functional impairment of GABAergic neurons during ischemia.

In addition, cerebral ischemia evokes an excessive release of presynaptic and astrocytic glutamate[96,112]. The accumulated glutamates in synaptic cleft may activate NMDAR and mGluR on GABAergic neurons. An activation of these receptors raises intracellular Ca^{2+} and an elevated activity of GABAergic neurons strengthens proton production in their metabolism. Cellular Ca^{2+} overload and acidosis may interact each other, e.g., acidification activates acid-sensing ion channels that are highly permeable to Ca^{2+}[158]. Finally, intracellular Ca^{2+} overload and acidosis synergistically impair the function of cortical GABAergic neurons during ischemia[45].

Furthermore, lowering extracellular pH significantly reduces the frequency and the amplitude of spontaneous inhibitory postsynaptic currents mediated by $GABA_AR$. Therefore, extracellular acidosis in cerebral ischemia may impair GABAergic synaptic transmission through presynaptic and postsynaptic mechanisms[160].

4.2 The mechanisms mediated by impairment of glia cells

One of major functions for the astrocytes in the central nervous system is to reuptake presynaptic released glutamates through glutamate transporters that require the sodium gradient established by Na^+/K^+ ATPase pumps[65-66,161]. There is an interaction between the astrocytes and neurons during ischemia[124]. The astrocytes may undergo ischemic dysfunction[79,123,126-127], and have diverse roles in ischemic brain injury through releasing glutamate, D-serine and adenosine[125]. Together these molecules with their attenuated ATP production, the astrocytes are unable to clear glutamates from synaptic cleft via their transporters. The failure of removing glutamates results in glutamate accumulation and subsequent neural excitotoxicity[40]. Despite its possibility, it is still not known whether this mechanism influences the function of GABAergic neurons during ischemia.

We currently observed a time sequence in the dysfunctions of astrocytes and GABAergic neurons. The function of glutamate transporters on the astrocytes appears reduced ahead of the impairments of encoding spikes and transmitting synaptic signals on GABAergic neurons. Moreover, the prevention of astrocytic dysfunction by DHPG (a specific agonist of type Ⅰ/Ⅴ of mGluR) secures the function of GABAergic cells after ischemia[89]. These data indicate that an impairment of astrocytes leads to GABAergic dysfunction. Whether the activation of mGluR-I/V protects the GABAergic neurons directly remains to be studied.

Together the discussions above, we draw a diagram showing a temporal sequence of dysfunctions for glutamate transporters at the astrocytes and functions at GABAergic neurons in Figure 1. The relatively small volume of GABAergic neurons makes them to have a low level of storage in the energy and buffer systems, and their high level of activities raises their energy consume. These factors facilitate GABAergic

neurons to be vulnerable to hazard conditions, such as ischemia, acid-base imbalance, oxidative stress and toxic environment. Ischemia may lead to the functional impairment of GABAergic neurons through the following steps. Ischemia impairs Glu-T function on astrocytes immediately after ischemia, since they are vulnerable to lack of energy providers. An accumulation of glutamates in synaptic cleft activates the GABAergic neurons via mGluR and NMDAR, which elevates intracellular Ca^{2+} and cellular metabolism to facilitate the vulnerability of GABAergic neurons to ischemia. In the meantime, ischemia lowers ATP production in mitochondria of GABAergic cells, which in turn impairs molecular transportation related to ATPase-pump, e.g., a reduction of Ca^{2+} pumping back to mitochondria and out of cells. This process plus Ca^{2+} release from mitochondria elevate intracellular Ca^{2+}. In addition, intracellular protons (H^+) increase in ischemic metabolism. The elevations of Ca^{2+} and H^+ in cortical GABAergic neurons synergistically lead to their ischemic excitotoxicity and malfunction. The deterioration of inhibitory neurons shifts the balance between excitation and inhibition toward neuronal overexcitation through disinhibiting excitatory pyramidal neurons.

5 Pathological consequence of GABAergic neurons' impairment

The major functions of GABAergic inhibitory neurons in the central nervous system are believed to coordinate the activities of excitatory neurons, prevent neuronal over-excitation and increase neuronal sensitivity to their synaptic inputs [48,63,70,129-133,135,162-163]. The functional vulnerability of inhibitory neurons to ischemia causes the neural excitotoxicity and subsequent impairments of other brain cells. In addition to the sequential impairments of cerebral GABAergic neurons and excitatory neurons [35], other evidences for this suggestion comes from the data that securing GABAergic function is able to prevent the ischemic impairment of the brain tissues. The strengthening of GABAergic inhibitory synaptic transmission can be realized by enhancing GABA receptor activation and by elevating GABA concentration in the synaptic cleft (prompting presynaptic GABA release and blocking GABA reuptake).

The enhancers or agonists of GABAR to facilitate inhibitory synaptic transmission protect nerve cells from ischemic injury. For instance, $GABA_AR$ agonist muscimol increases the number of survived nerve cells and delays the process of neuronal death after cerebral ischemia [107,150]. $GABA_BR$ agonists (such as baclofen and saclofen) reduce the effect of ischemia-induced glutamate release on neural damage [164]. The agonists of $GABA_AR$ and $GABA_BR$ result in the neuroprotective effects against ischemia [165]. The enhancers of GABAR benzodiazepines (diazepam and imidazenil) reduce neuronal apoptosis and protect pyramidal cells from the toxic effect of transient cerebral ischemia [110,166]. In addition, the enhancement of GABAR function down-regulates the excessive release of glutamates and the over-activation of GluRs triggered by cerebral ischemia [164].

An increase of GABA concentration in synaptic cleft to facilitate inhibitory synaptic transmission protects nerve cells from ischemic injury. The inhibitors of GABA transporters to block GABA reuptake are used to strengthen inhibitory synaptic transmission. For instance, the inhibitors of GABA transporters (tiagabine and vigabatrin) prevent ischemia-induced neural malfunction [165]. GABA uptake inhibitor No-328 significantly decreases the ischemia-induced loss of cerebral neurons [166].

These procedures for enhancing inhibitory synaptic transmission may shift an ischemic imbalance between neuronal excitation and inhibition toward the inhibitory status of brain functions, which may be beneficial for neuronal tolerance to hazard situations (such as ischemia and oxidative stress) and the brain protection itself [167].

6 Conclusion remark

Cerebral GABAergic neurons appear vulnerable to ischemia, oxidative stress, acidosis and toxic molecules. Their vulnerability may be due to the relatively smaller volume and higher activity, compared with pyramidal neurons. The low storage and high consumption of energy as well as the low volume of intracellular buffer system make GABAergic neurons being vulnerable to the hazard internal environment. Insufficient blood flow initiates ischemic processes in brain cells, such as a lack of glucose/oxygen and an accumulation of metabolic toxic products (proton, Ca^{2+} and free radicals), especially in GABAergic cells

and astrocytes. Such changes activate cellular signaling pathways and influence membrane components in GABAergic neurons. Moreover, an ischemic failure for astrocytes to reuptake glutamates exacerbates the dysfunction of GABAergic neurons. Their dysfunctions in encoding spikes and transmitting synaptic signals may shift neural balance toward excitotoxicity, which leads to the ischemic stroke of nerve cells. Therefore, the study to understand the mechanisms underlying GABAergic neuronal vulnerability to toxic environments should provide the clues for developing therapeutic strategies in the protection of neuronal functions from ischemic injury.

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