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Galanin's implications for post-stroke improvement

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Abstract: Stroke leads to a variety of pathophysiological conditions such as ischemic infarct, cerebral inflammation, neuronal damage, cognitive decline, and depression. Many endeavors have been tried to find the therapeutic solutions to attenuate severe neuropathogenesis after stroke. Several studies have reported that a decrease in the neuropeptide regulator 'galanin' is associated with neuronal loss, learning and memory dysfunctions, and depression following a stroke. The present review summarized recent evidences on the function and the therapeutic potential of galanin in post-ischemic stroke to provide a further understanding of galanin's role. Hence, we suggest that galanin needs to be considered as a therapeutic factor in the alleviation of post-stroke pathologies.

Key words: Galanin, Post-stroke, Depression, Inflammation, Cognitive decline

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Introduction

Stroke represents one of five common causes of death in the world although its incidence and mortality have been decreased last a few decades [1-3]. Stroke causes cerebral dysfunction that leads to irreversible brain injury [4]. Furthermore, post-ischemic inflammation which is an essential response in the pathophysiology of stroke [5], may lead to the clearance of debris caused by necrotic cell death [6] and also aggravate sequential neuropathology after stroke [7, 8]. Post-stroke depression is also a significant long-term issue in stroke patients [9, 10]. According to recent studies, the prevalence of post-stroke depression ranges from 25% to 79% among stroke patients, and depressive symptoms are present in approximately 33% of stroke patients [2, 11]. The cognitive impairment in stroke patients is related to the progression of post-stroke neuro-pathophysiology [12, 13], and the frequency of cognitive impairment is more than four times higher in stroke patients than that in patients who have not suffered from a stroke [14]. The prevalence of post-stroke dementia in the first year after stroke is approximately 7% among the first-time stroke patients [15].

Many therapeutic strategies including glutamate receptor antagonists and calcium channel blockers have been tested to alleviate and prevent brain damage following stroke [16]. The neuropeptide, galanin [17] exerts its effects by binding to galanin receptors throughout the central and peripheral nervous system [18, 19]. Galanin has been reported as a regulator of feeding [20] and a protector of neuronal cells against oxidative stress [21]. Galanin controls the secretion of several stress hormones [22] and may contribute to cognitive dysfunction [23]. Stroke leads to severe pathogenic disorders such as depression [9, 24] and memory dysfunction [25]. In an ischemic stroke model, one study found that middle cerebral artery occlusion (MCAO) injury leads to a decrease in galanin immunoreactivity in the ischemic brain 3 days after a transient MCAO. Moreover, several studies suggest that galanin may

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have a potential to improve the learning and memory decline [26, 27]. In this review, we summarize the recent evidences on galanin's various roles in the brain after stroke. These findings highlight the importance for further research on the role of galanin in post-stroke improvement.

Galanin

Galanin is a neuropeptide composed of 30 amino acids in humans [17, 28]. It is widely distributed throughout the central and peripheral nervous system [18], and localized to brain regions implicated in behavioral function including the locus coeruleus, forebrain, amygdala, and hypothalamus [17, 29]. Galanin is encoded by galanin-like peptide (*GALP*) [30] and exerts its biological action by binding with three G protein-coupled galanin-receptor subtypes (GalR1, GalR2, and GalR3) [31, 32]. These receptor subtypes are expressed in the midbrain and limbic regions, where they mediate stress-related behaviors [20, 33-35]. Cheung et al. [20] shows that injection with galanin may control the feeding in animals. Galanin is negatively regulated by leptin which attenuates food intake and controls body weight [20]. In addition, galanin has a neuroprotective effect on hippocampal neurons by reducing cell death [36] through GalR2 [36], and regulates inflammatory mechanism [37]. Galanin is secreted when neurons were stimulated by behavioral and pharmacological provocation [23]. Moreover, galanin regulates the secretion of glucocorticoids and catecholamines in response to stress in rodents and humans [22, 38], and suppresses the secretion of norepinephrine, serotonin, and dopamine neurons in forebrain regions [39, 40]. Several studies have focused on the relationship between galanin and neurophysiological/neuroendocrine functions [41, 42]. Here in this review, we focused on the relationship between galanin and a variety of neurophysiological/neuroendocrine functions in post-stroke brain conditions.

Galanin and Stroke

MCAO injury is a common method used in the *in vivo* ischemic stroke animal model. Another study using the MCAO model showed that intracerebroventricular administration of a GalR2 or GalR3 agonist leads to a reduction in the ischemic infarct size [43]. Numerous studies using stroke models show the decreases of galanin and GalR gene expression in the brain after ischemic stroke [43, 44]. For example, one study reported that GalR1 mRNA levels were significantly decreased 24 hours after MCAO injury [45]. In another MCAO stroke model without reperfusion, only low levels of galanin were observed 24 hours after injury in infarct regions such as the caudate nucleus [46]. Furthermore, Holm et al. [43] demonstrated that galanin system can be activated in an ischemic brain lesion via a continuous infusion of a galanin agonist for 3 or 7 days. Based on these findings, future studies for the investigation of the galanin system in the post-stroke brain are needed.

Galanin in Post-stroke Depression

Post-stroke depression leads to functional disability [24], poorer rehabilitation outcomes [47], and increased morbidity and mortality [9, 48]. Several studies have revealed that ischemic stroke is one of the leading causes of depression [49, 50]. In a retrospective study, patients with stroke showed rates of recurrence throughout the time course, and 55% of them had an incidence of post-stroke depression over 15 years [51]. Depression symptoms may deteriorate during the chronic phase after stroke [52, 53]. Galanin is considered to be a depression-related peptide [54], and plasma galanin is considered as a biomarker for diagnosing major depressive disorder [33]. Galanin receptors which act via cAMP formation [55] and the cyclic AMP responsive element binding (CREB) signaling pathway [56, 57] modulate brain-derived neurotrophic factor production which is associated with depression [58]. Several studies including animal behavioral [59, 60] and human clinical studies [61] have indicated that galanin plays crucial roles in stress, depression, and anxiety. A change in galanin expression in rat hippocampus alters mild depression, and subsequently leads to changes in depression-related behaviors [54, 62]. Moreover, galanin genes are involved in depression-related phenotypes [63]. Current studies suggest that polymorphisms in the upstream region of the *GAL* gene may affect the expression of galanin in brain regions implicated in depression including the amygdala and hypothalamus [29, 64]. Given this evidence for a relationship between galanin and depression, galanin may be associated with post-stroke depression.

Galanin in Post-stroke Inflammation

Inflammation following ischemic stroke exaggerates vascular dysfunction and leads to neuronal cell death [65]. Post-ischemic inflammation is a common process after ischemic

stroke and significantly associated with post-stroke prognosis [5, 66]. Ischemic stroke triggers cellular damage in the brain via inflammation occurring over hours to days [67]. Many studies have found that stroke is followed by an inflammatory response that includes the secretion of inflammatory cytokines and leukocytes, monocyte infiltration in the brain, and activation of glia cells [68-71]. Leukocyte infiltration in the brain boosts inflammatory activation of various cells such as microglia and astrocytes [72]. Recent studies have explored the ability of neuropeptides with physiological functions such as galanin peptides, to prevent and alleviate post-stroke inflammatory responses [73, 74]. Several studies have demonstrated that upregulation of GalR1 is related to the increased expression of nuclear factor (NF)-κB, which is an inflammatory signaling molecule in inflammatory animal models [75, 76]. The activation of the mitogen-activated protein kinases/extracellular signal-regulated kinase/extracellular signal-regulated protein kinase 1/2 pathway via GalR1 affects the induction of the cell cycle and suppression of cyclin D1 [77]. *In vivo* studies have also suggested that GalR1 is associated with the modulation of CREB [56] and c-fos [78] in the brain. In addition, the regulatory function of GalR2-mediated galanin signaling has been reported in inflammatory, neuropathic, and acute pain models [79]. GalR2-related apoptosis is triggered by the induction of the pro-apoptotic Bcl-2 protein Bim [80]. Several studies have suggested that treatment with galanin may decrease the expression of pro-inflammatory cytokines [81] such as tumor necrosis factor-α and interleukin-1β, and increase anti-inflammatory responses via GalR2 [82]. Consequently, galanin may act as a regulator of inflammation following ischemic stroke by controlling the secretion of inflammatory cytokines.

Galanin in Post-stroke Cognitive Dysfunction

Post-stroke dementia is defined as any dementia that occurs following a stroke [14]. Some studies have reported that up to 70% of stroke patients suffer from cognitive impairments [83, 84]. One clinical study indicated that the pathogenesis of Alzheimer's disease was observed in over one-third of patients with dementia after stroke [85, 86]. Post-stroke depression is a complex psychiatric disorder which causes the delay in functional recovery from rehabilitation and increased cognitive impairment [26, 87]. Galanin and galanin receptors are located in brain areas directly related to cognitive function [88, 89]. The effects of galanin on memory in the brain have been studied [18, 90]. Galanin improves learning and memory via the modulation of the density of muscarinic receptors in hippocampal areas [91]. One *in vitro* study demonstrated that galanin increases the protein expression of M1 muscarin-

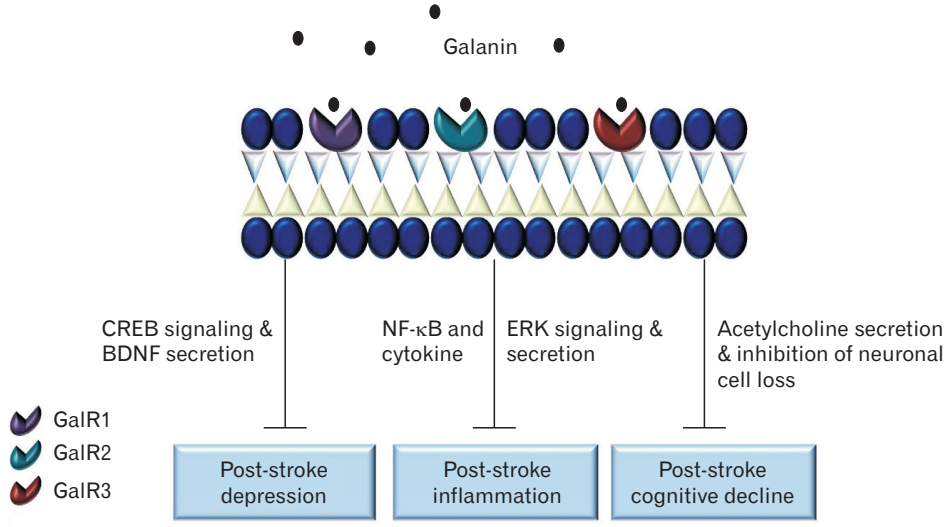

Fig. 1. The schematic image about galanin effect on post-stroke. After stroke, galanin binds galanin receptors such as GalR1, GalR2, and GalR3 and affects several signaling pathways. Galanin regulates CREB signaling and modulates BDNF secretion in neuron, and subsequently contributes to the improvement of post-stroke depression. In addition, galanin induces NF-κB and ERK/MAPK signaling and controls the production of pro- and anti-inflammatory cytokines and subsequently reduces post-stroke inflammation. Finally, galanin ameliorates post-stroke cognitive declines by regulating acetylcholine secretion and inhibiting neuronal cell loss. BDNF, brain-derived neurotrophic factor; CREB, cyclic AMP responsive element binding; NF-κB, nuclear factor κB; ERK/MAPK, mitogen-activated protein kinases/extracellular signal-regulated kinase; GalR, galanin receptor.

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ic acetylcholine receptors in primary cortical neurons [92]. *In vivo* studies show that galanin administered to rat hippocampus improves learning and memory on the Morris water maze test [93] and the administration of galanin improves cognitive function in mice by altering the step-down latency of passive avoidance [94]. In addition, galanin suppresses K^+-stimulated acetylcholine release in the ventral hippocampus and cortical regions [95, 96], but increases the secretion of acetylcholine in the hippocampus when it is infused in Broca's area in rats [90]. Galanin knock-out mice also exhibit a decrease in the secretion of acetylcholine in the hippocampus, and cognitive decline on behavioral tests such as the Morris water maze test [97] and the object-in-place memory task [98]. Furthermore, galanin inhibits neuronal cell loss in regions of the brain related to cognition such as cerebral cortex, basal forebrain, amygdala [99]. In addition, improved cognitive function was associated with higher levels of galanin in the cerebrospinal fluid [100]. Taken together, these findings suggest that galanin could improve cognitive impairment following ischemic stroke.

Conclusions

Inflammation, cognitive impairment, and depression following stroke are crucial issues in the study of post-stroke pathogenesis. To improve the various pathophysiological conditions following a stroke, several studies have investigated fine regulators from neurotransmitters, neuropeptides, hormones, and factors in ion channel pathways that attenuate post-stroke pathogenesis. Galanin is an orexigenic peptide that may control food intake and stress-mediated behaviors such as depression. Here, we focused on the various functions of galanin in post-stroke-related pathophysiologies. Consequently, this review suggests three notable post-stroke roles of galanin: (1) galanin improves depression by promoting the secretion of neurotrophic factors and restricting neuronal cell death under post-stroke oxidative stress; (2) galanin ameliorates the post-stroke inflammation response by attenuating the production of pro-inflammatory cytokines and regulating CREB, c-fos, and NF-κB signaling; and (3) galanin improves cognitive decline by stimulating the activity of cholinergic neurons and attenuating neuronal cell damage (Fig. 1). Although the function of galanin in post-stroke condition is not fully understood, further studies on the function of galanin after an ischemic stroke may reveal the potential for galanin as a therapeutic factor to improve post-stroke pathology.

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