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GHRH and its analogues in central nervous system diseases

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Abstract
Growth hormone-releasing hormone (GHRH) is primarily produced by the hypothalamus and stimulates the release of growth hormone (GH) in the anterior pituitary gland, which subsequently regulates the production of hepatic insulin-like growth factor-1 (IGF-1). GH and IGF-1 have potent effects on promoting cell proliferation, inhibiting cell apoptosis, as well as regulating cell metabolism. In central nerve system (CNS), GHRH/GH/IGF-1 promote brain development and growth, stimulate neuronal proliferation, and regulate neurotransmitter release, thereby participating in the regulation of various CNS physiological activities. In addition to hypothalamus-pituitary gland, GHRH and GHRH receptor (GHRH-R) are also expressed in other brain cells or tissues, such as endogenous neural stem cells (NSCs) and tumor cells. Alternations in GHRH/GH/IGF-1 axis are associated with various CNS diseases, for example, Alzheimer's disease, amyotrophic lateral sclerosis and emotional disorders manifest GHRH, GH or IGF-1 deficiency, and GH or IGF-1 supplementation exerts beneficial therapeutic effects on these diseases. CNS tumors, such as glioma, can express GHRH and GHRH-R, and activating this signaling pathway promotes tumor cell growth. The synthesized GHRH antagonists have shown to inhibit glioma cell growth and may hold promising as an adjuvant therapy for treating glioma. In addition, we have shown that GHRH agonist MR-409 can improve neurological sequelae after ischemic stroke by activating extrapituitary GHRH-R signaling and promoting endogenous NSCs-derived neuronal regeneration. This article reviews the involvement of GHRH/GH/IGF-1 in CNS diseases, and potential roles of GHRH agonists and antagonists in treating CNS diseases.

Keywords Central never system diseases · Growth hormone release hormone/growth hormone/insulin growth factor 1 axis · GHRH analogs · GHRH receptor

1 Introduction

The central nervous system (CNS) diseases include neurodegenerative diseases (NDD), cerebrovascular diseases, psychiatric diseases (mental disorder), dyskinesia, brain tumors, CNS infectious diseases and spinal cord diseases. Among them, NDD, cerebrovascular diseases, psychiatric diseases and brain tumor are the most common CNS diseases. NDD refer to a group of diseases with age-related neurological degenerative changes in the structure and function of the brain and spinal cord, characterized with progressive neuronal cell death and dysfunction [1]. Patients often have cognitive impairment, delayed response, and varying degrees of neurological motor and sensory dysfunction. NDD include Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS) [2].

Most CNS diseases, such as AD, PD and cerebrovascular diseases, are associated with aging and degeneration of

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CNS function, and are difficult to cure. Current therapeutic strategy of these CNS diseases mainly focuses on mitigating neuronal damage through neuroprotective therapies, such as neurotrophic support, anti-inflammatory and antioxidant therapies [3]. Despite some newly developing medications have shown to have promising results in preclinical studies, many therapeutic drugs targeting the nervous system have failed to demonstrate efficacy in clinical trials [4]. Given the close relationship between the nervous system and endocrine system [5], the neurohormones released through the hypothalamus-pituitary gland, such as growth hormone release hormone (GHRH)/growth hormone (GH), play a crucial role in the regulation of systemic endocrine hormone and CNS function [6, 7].

GHRH is a neuropeptide hormone synthesized by neurons in the hypothalamic arcuate nucleus, the synthesized GHRH is transported to the anterior pituitary gland through neuron axons, where it binds to the GHRH receptors (GHRH-R), and promoting the synthesis of GH in anterior pituitary cells and releasing it into the circulating blood [8]. GH stimulates the synthesis of insulin growth factor 1(IGF-1) in the liver and releases it into bloodstream. GH and IGF-1 regulate various physiological activities, such as cell proliferation and metabolism, organ growth and development and form a feedback loop to regulate the synthesis and release of GHRH/GH in the hypothalamus-pituitary gland [9]. In addition to GHRH/GH/IGF-1 axis, GH and IGF-1 receptors are extensively expressed in various neurons and CNS, circulating GH and IGF-1 can act on their receptors in CNS to regulate various neurophysiological function [10]. It has been reported that GHRH and its GHRH-R can be detected in other brain regions and brain tumors [11, 12]. For example, GHRH and its receptor mRNAs are detectable in the cortex of rat, and these cortical GHRH activates local cortical cells to affect electroencephalographic delta wave power state-specifically [11]. These extrapituitary GHRH/GHRH-R act as paracrine manner to regulate CNS function. While the administration of exogenous GHRH analogues (GHRH-As) can directly regulate brain function through stimulating or blocking brain extrapituitary receptors (Fig. 1). When brain level of GHRH, GH or IGF-1 is changed, which may alter CNS function, leading to various CNS diseases. The administration of exogenous GHRH-As, including agonists and antagonists, may help restore the balance of GHRH/GH/IGF-1 axis, thereby providing potential therapeutic beneficial effects to alleviate or treat CNS diseases. This article briefly reviews the role of GHRH/GH/IGF-1 in the development of CNS diseases and GHRH as a potential therapeutic target for treatment of CNS diseases.

2 Involvement of GHRH-GH/IGF-1 axis in CNS disorders

The hypothalamic-pituitary axis is a complex system that integrates neuronal and hormone signals to regulate various biological and physiological activities. The hypothalamus, located in the lower part of the brain, receives and integrates neural signals from different brain regions. The hypothalamus communicates with pituitary gland by the synthesis and storage of neurohormone in the anterior pituitary gland and controls the release of pituitary hormones, which govern essential physiological activities.

GHRH/GH/IGF-1 axis is one of the most important regulatory systems in the hypothalamic-pituitary neuroendocrine system, involving in the regulation of cell proliferation, somatic growth, energy and metabolic homeostasis. In CNS, GHRH/GH/IGF-1 promotes neuronal cell proliferation, brain development and various neural activities. GHRH regulates CNS activities by stimulating GHRH-R on the pituitary gland and extrapituitary brain areas. GHRH-R is a member of class B of the G protein-coupled receptors (GPCRs) superfamily, primarily expressed in somatotropic cells of the pituitary gland [13]. The GHRH-R contains an extracellular domain and a seven-transmembrane helix domain, which activate various intracellular signal transduction pathways.

In the anterior adenohypophysial lobe, GHRH binds to GHRH-R to activate adenylyl cyclase, which increases cyclic adenosine monophosphate (cAMP) and promotes adenohypophysial gland synthesis and release of GH through activating the cAMP/Protein kinase A (PKA) signaling pathway. The activation of PKA allows the translocation and phosphorylation of cAMP response element binding protein (CREB) into nuclear, thereby stimulating the synthesis and release of GH [14]. GH further stimulates the synthesis and secretion of IGF-1 in the liver. GH and IGF-1 enter the brain and bind to GH or IGF-1 receptors in the brain to regulate CNS activities. Moreover, GHRH can also regulate CNS function through GHRH-R in extrapituitary brain tissue and cells, for example, it has been shown that GHRH-R is expressed in human microvascular endothelial cells, GHRH antagonists reduce inflammation and oxidative stress, providing a potential beneficial effect for treatment of blood-brain barrier dysfunction-related CNS diseases [15, 16]. In addition to its neuroendocrine effects, GHRH is endowed with pleiotropic biological effects, including the regulation of cell proliferation, death, survival and differentiation, antioxidant and anti-inflammatory effects [17, 18]. Alternation in the GHRH/GH/IGF-1 axis has been implicated in various CNS disorders, including AD, ischemic stroke (IS), anxiety and depression, HD, sleep disorder, ALS.

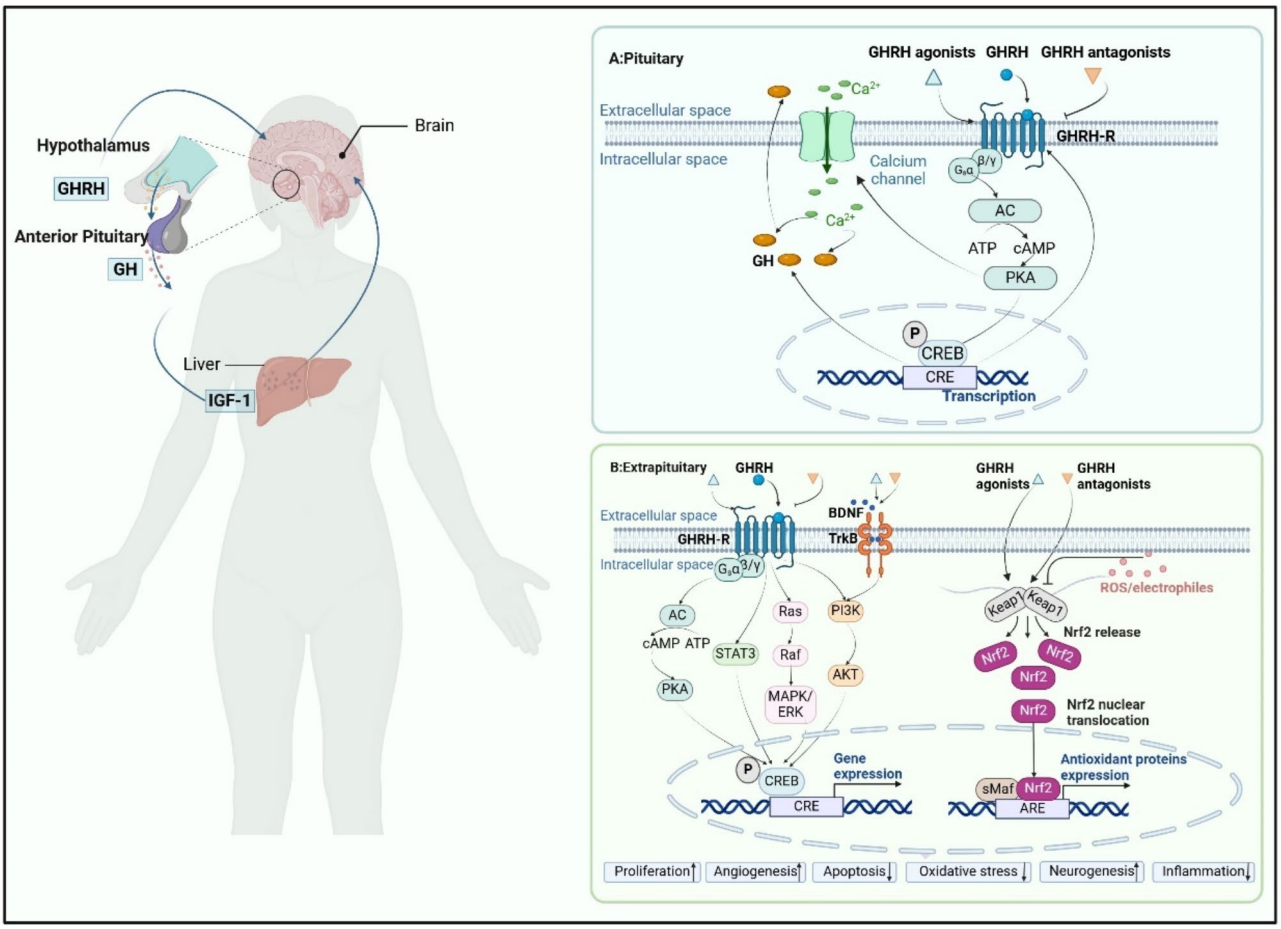

Fig. 1 The molecular signaling mechanisms of endogenous GHRH promoting GH/IGF1 release through activating pituitary GHRH-R and GHRH regulating CNS function through extrapituitary GHRH-R. **A**. In the anterior adenohypophysial lobe, GHRH binds to GHRH-R to activate adenylyl cyclase and increases cAMP, which subsequently activate the PKA/CREB signaling pathway and Ca^{2+} influx to promote the synthesis and release of GH, which further stimulates the synthesis and release of IGF1 in the liver. In addition, GHRH can also activate extrapituitary GHRH receptor-mediated signaling pathways, such as MAPK/ERK1/2, BDNF/TrkB, PI3K/AKT and Keap1/Nrf2, to induce a serious of extrapituitary biological effects, including promoting cell proliferation, neurogenesis, angiogenesis and inhibiting cell apoptosis, oxidative stress and inflammation

2.1 Alzheimer's disease (AD)

AD is characterized by memory loss and progressive cognitive deterioration. Early clinical manifestations of AD encompass cognitive and behavioral alterations, impaired acquisition of new information, as well as language and speech dysfunction. In advanced stages, patients often experience a decline in their ability to manage daily life. Extracellular neurotic plaques and intracellular neurofibrillary tangles are two important pathologic features of AD. Based on the neuropathologic findings, several hypotheses have been proposed to explain the pathogenesis of AD, such as amyloid cascade hypothesis, tau hypothesis, cholinergic hypothesis, and excitotoxicity [19, 20].

Animal and clinical studies suggest that age-related neurophysiological changes, such as cognitive decline, are associated with decreased activity of GHRH/GH/IGF-1 axis. APPswe/PS1ΔE9 (PS1APP) transgenic mouse is an animal model that overexpresses mutant forms of APP and PSEN1 to cause autosomal dominant AD, Liao et al. have reported that intraperitoneal inject of GHRH into the transgenic mice can promote sleep and decrease amyloid b (Ab) in brain interstitial fluid, a pathological marker of AD, which are reversed by treatment with GHRH antagonist [21]. A clinical study has shown that treatment with GHRH (1–29 NH2) for 6 months can partially improve age-related cognitive decline in healthy elderly individuals, mild cognitive impairment and AD patients [22, 23]. Friedman et al. used magnetic resonance spectroscopy to investigate the effects of GHRH on inhibitory and excitatory neurotransmitters in different brain area of patients with mild cognitive impairment. They found that the administration of

tesamorelin, a stabilized analogue of human GHRH, for 20 weeks increased levels of inhibitory transmitters g-aminobutyric acid and N-acetylaspartylglutamate in certain brain regions [24], suggesting that GHRH can ameliorate aging- or disease-related biochemical processes.

GH and IGF-1 are also believed to be involved in regulating brain cognitive and memory functions. It has been shown that plasma levels of GH and IGF-1 gradually decrease with age, GH deficiencies promote aging process, and GH supplementation improves cognitive function [25–29] and enhances neuronal activities, such as synaptic transmission and receptor density in human and animal models of AD [30, 31]. The administration of IGF-1 enhances spatial and reference memory in elderly rats, and prevent age-related decline in spatial memory in the animals after 21 months of administration [32–34]. These results suggest that GHRH/GH/IGF-1 axis is involved in regulating cognitive function and the pathogenesis of AD.

2.2 Ischemic stroke (IS)

IS is one of the most serious and preventable neurological disorders, with a high mortality rate and permanent disability [35, 36]. The sharp decline in cerebral blood flow caused by cerebral ischemia may triggers a series of pathological responses called ischemic cascade, leading to neuronal damage. The ischemic cascade is quite complex, involving various pathophysiological processes, such as excitatory amino acid toxicity, oxidative stress, inflammation, calcium overload, apoptosis and autophagy [37].

Clinical and experimental studies have suggested that there is a close relationship between plasma levels of IGF-1/GH and IS. The patients with severe IS are often accompanied by dysfunction of pituitary endocrine system, with most common change being the coexistence of low IGF-1 level and GH deficiency [38]. Bondanelli et al. found that IS patients with GH deficiency, and decreased plasma concentration of IGF-1 was positively correlated with IS progression [39]. A small clinical study from 85 patients with acute stroke shows that plasma level of IGF-1 is inversely related to clinical outcomes (mainly death events), and that low level of IGF-1 is an index for poor prognosis for IS patients [40]. It has been shown that IGF-1 can promote neuronal cell survival, myelination, and cerebrovascular generation in response to ischemia-induced hypoxia [41, 42]. IGF-1 supplement may have therapeutic beneficial effects on IS. Guan et al. demonstrated that intracerebroventricular administration of IGF-1 significantly reduced cortical infarction and neuronal loss and enhanced neural functional recovery in rats with hypoxic ischemic brain injury. Thus, these results suggest that IS has GH and/or IGF-1 deficiency, and GH or IGF-1 supplement may facilitate neuronal functional recovery following ischemic brain injury [43].

2.3 Anxiety and depression

Anxiety and depression are the two main manifestations of emotional disorders [44]. The pathogenesis of anxiety and depression is complex, including genetic, neurobiological, and psychosocial cultural factors. Changes in monoamine neurotransmitters and their receptors, as well as the overactivation of hypothalamic pituitary adrenal axis are two classic hypotheses to explain the pathogenesis mechanism of depression [45, 46].

Anxiety and depression are often associated with prominent changes in the neuroendocrine system, such as 5-hydroxytryptamine (5-HT), norepinephrine and dopamine [47]. GHRH/GH is also believed to be involved in regulating anxiety and depression-related behaviors, however current evidence suggests that GHRH and GH have opposite effects on anxiety and depression [48–53]. It has been reported that GHRH deficiency increases physical activity and reduces anxiety and depression-related behaviors, the underlying mechanisms may be related to an increase in thyrotropin-releasing hormone and a decrease in norepinephrine in the brain [51, 54]. On the contrary, GH deficiency patients can experience memory dysfunction, atypical depression, abnormal emotional response, social autism, and sleep disturbance, which can be alleviated by GH replacement therapy [55–58]. These results suggest that GHRH can promote depression while GH improves anxiety and depression. Considering the opposite effects of GHRH and GH on anxiety and depression, we speculate that the regulatory effects of GHRH and GH on these emotional disorders may be mediated through different signaling pathways.

2.4 Sleep disorder

Sleep is crucial for brain development, physical and mental health, and maintenance of self-awareness [59]. Insomnia is a pathological condition of sleep disturbances, characterized with difficulty falling sleep, shortened sleep duration, impaired sleep quality, early awakening, and daytime dysfunction [60]. Current medicines used to treat insomnia include benzodiazepine receptor agonists which have drug resistance and side effects [61].

Mounting evidence have shown that GHRH plays a crucial role in regulating sleep, particularly in non-rapid eye movement (NREM) related sleep. The administration of GHRH into various animal species (including rat, rabbit and mouse) promotes NREM sleep response [62–64]. While blocking endogenous GHRH with GHRH antagonist or antibodies can reduce NREM sleep response. Further

mechanistic studies reveal that GHRH is able to increase γ-aminobutyric acid (GABA) levels and activates GABA receptors in the median preoptic nucleus and the ventrolateral preoptic nucleus of the hypothalamus, promoting NREM sleep [65]. In addition, GHRH may exhibit sexual dimorphism in regulating sleep, it has been reported that the administration of GHRH can interfere sleep patterns in healthy young women but enhance slow wave sleep in man [66].

It has been shown that the synthesis and secretion of GH have a circadian rhythm, which is disrupted by poor quality sleep, irregular sleep and sleep disorders [67]. GH secretion occurs in pulses throughout the day, and nighttime sleep period is the main period for GH synthesis and secretion, especially during the deep slow wave sleep period immediately after failing asleep. GH exhibits large bursts of secretion. Sleep deprivation suppresses GH secretion, and large amount of GH releases occur during recovery period of sleep. The administration of recombinant human GH can partially improve poor sleep in patients with GH deficiency, which may be related to the improvement of negative feedback regulation between GHRH/GH [68].

2.5 Amyotrophic lateral sclerosis (ALS)

ALS is a progressive neurodegenerative disorder caused by selective loss of motor neurons in the cerebral cortex, brainstem, and spinal cord, leading to a gradual decline in muscle strength and mass, resulting in dysarthria, dysphagia, respiratory failure and even death. The etiology and pathogenic mechanisms of ALS are still unclear and may be the result of complex interactions between genetic and environmental factors [69]. ALS exhibits a series of pathophysiological changes, including neurotoxicity, mitochondrial dysfunction, oxidative stress, neuroinflammation, RNA metabolism defects, energy metabolism abnormalities, cytoskeleton disruption, and protein homeostasis disturbances [70]. At present ALS lacks effective therapy.

It has been shown that the patients with ASL are often associated with the impairment of GH/IGF-1 secretion. A small-scale clinical study reported that the patients with ASL had lower basal plasma level of GH and a reduced response to GH secretion to the administration of GHRH [71]. It is well known that GH and IGF-1 can promote brain growth, development, and metabolism, as a neurodegenerative disease with GH/IGF deficiency, GH or IGF-1 replacement therapy may be beneficial for ASL. It has been reported that peripheral administration of bovine GH can stimulate the generation of brain cells in female rat [72], and the combination therapy of IGF-1 with appropriate exercise significantly enhances motor function and survival in ALS mice [73]. Kaspar et al. have shown that retrograde viral delivery of IGF-1 enhances survival and delays the progression of ALS symptoms in mice [74]. Despite preclinical studies support the efficacy of GH and IGF-1 in treating ALS, most clinical trials have failed to prove the results. For example, The North American ALS/IGF-1 Study Group has reported that subcutaneous injection of recombinant human IGF-1 into ALS patients does not affect the progression of ALS [75, 76]. A 2-year follow-up clinical trial also reported that subcutaneous IGF-1 is not beneficial on ALS patients [77]. In addition, a clinical study reported that the application of human GH for 12 months cannot improve muscle weakness and reduce mortality in ALS patients [78]. The reasons for the discrepancy between beneficial effects of GH/IGF-1 in animal studies and negative outcomes in clinical trials are still unclear. In addition to species differences in response to GH/IGF-1 therapy between human and animal models, it may also be related to the small sample size and short follow-up period of these clinical trials. Therefore, the efficacy of GH/IGF-1 in treating ALS may need to be verified by large-scale multicenter clinical trials.

2.6 Huntington's disease (HD)

HD is a rare autosomal dominant neurodegenerative disorder caused by excessive amplification of an unstable cytosine-adenine-guanine trinucleotide sequence of the *huntingtin* gene on chromosome 4 [79]. The primary pathological manifestations involve aberrant neurotransmitter transmission, particularly dopamine, GABA, or glutamate [80]. Currently, there are no effective medicines for the treatment of HD; As first-line treatment medicines for HD, tetrabenazine and its deuterium substitute deutetrabenazine can only ameliorate patient symptoms. Apart from neurological impairment, patients with HD have progressive weight loss, abnormal glucose homeostasis and high prevalence of diabetes, which may be related to increased GH secretion. It has been shown that elevated GH levels are associated with a decline in cognitive function [81] and that plasma level of GH and IGF-1 is positively correlated with the severity of motor function impairments in HD patients [82]. Aziz et al. investigated a correlation between 24-hour GH secretion and clinical symptoms in HD patients. They found that GH secretion undergoes dynamic changes in early stages of HD and become more prominent in the late stages of the diseases [83]. In experimental HD model induced by 3-nitropionic acid, intraperitoneal injection of GH deteriorates neurological deficits and increased mortality, underlying mechanisms may involve in disturbing mitochondrial activities [84]. These results suggest that GH exerts adverse effects on HD.

3 Application of GHRH agonists and antagonists for treatment of CNS diseases

GHRH, as an important neuroendocrine hormone in the hypothalamic pituitary system, is widely involved in the physiological and pathological regulation of the CNS. CNS diseases may alter the hypothalamic pituitary GHRH/GH axis or extrapituitary GHRH signaling pathway, which may in turn further promote CNS diseases. Most CNS diseases, such as NDD and IS, are associated with aging and difficult to cure, and regulatory effects of GHRH/GH axis are weakened in the elderly. Therefore, the application of GHRH or GHRH-As may be a potential new strategy for treating age-related CNS diseases. However, as native GHRH can rapidly be degraded by peptidases in bloodstream, and has a short half-life, unstable efficacy and potential side effects, for example, induction of tumor formation. Thus, native GHRH is not suitable for treating human diseases.

Schally's laboratory has synthesized a series of potent GHRH-As including agonists and antagonists [85–88]. These synthesized GHRH-As can resist the hydrolysis of trypsin-like enzymes by modifying the NH_2-terminal of GHRH, thereby enhancing its stability and prolonging its half-life [89, 90]. Antagonists of the Miami (MIA) series are the first to synthesis to suppress tumor growth, and antagonists MIA-602 and MIA-690 are among the most potent antitumor analogs [88]. The MIA series of antagonists as well as antagonist JV-1-36 also display anti-inflammatory activities [91, 92]. By modifying the main chain of GHRH (1–29) NH_2, N-terminal, and C-terminal, as well as substituting Apa30 or Gab^{30} C-terminal groups, a total of approximately 100 agonists within this series have been synthesized, including JI series and MR series [93]. The JI series of GHRH-A, comprising JI-22, JI-34, JI-36, and JI-38 and etc., exhibit a higher affinity towards GHRH-R compared to endogenous GHRH [94]. The MR series of GHRH-A, including MR-356, MR-401, MR-409, and MR-502, have long half-life, more stability, strong affinity with GHRH-R and potent efficacy compared with JI series [93]. It has been shown that these GHRH agonists or antagonists exhibits great beneficial effects on experimental myocardial infarction, heart failure, vascular calcification, type I & II diabetes mellitus [93, 95–97]. In addition, these novel synthesized GHRH-As have shown to have potential therapeutic effects on CNS diseases (Table 1).

3.1 AD

The treatment of AD remains a global challenge in the field of public health. The current medicines for treating AD patients mainly focus on alleviating the symptoms of neurocognitive dysfunction caused by progressive degeneration of brain dysfunction, but it cannot halt the progression of AD [98]. As AD is associated with the dysfunction of neuroendocrine system, some investigators are exploring the possibility of using GHRH-As to treat AD (Fig. 2).

Banks et al. investigated therapeutic effects of GHRH antagonist MZ-5-156 in senescence accelerated mouse prone 8 (SAMP8) mice, a genetic AD model with increased amyloid precursor protein (APP) and Aβ peptide. They found that the administration of MZ-5-156 significantly ameliorated cognitive function and increased the average life expectancy by 8 weeks, the underlying mechanisms may involve in enhanced telomerase activity and attenuated oxidative stress [99]. Telegdy et al. showed that treatment with GHRH antagonist MZ-4-71 can enhance memory consolidation in passive avoidance learning and ameliorate the memory impairment induced by $A\beta_{25-35}$ in mice [100]. The subsequent investigation revealed that MZ-4-71 therapeutic effects may be related to its alteration of neurotransmitter receptor on neurons, such as muscarinic acetylcholine receptor, 5-HT1/5-HT2 serotonergic receptor, and opioid receptors [101]. Jaszberenyi et al. evaluated the anti-AD effect of GHRH antagonist MIA-690 in genetically modified "Alzheimer's" 5XFAD mice. They demonstrated that subcutaneous administration of MIA-690 (2, 5, 10 μg/day) for 6 months significantly improved cognitive and behavioral performance in the Morris water maze while concurrently reducing $A\beta_{1-42}$ levels and Tau filaments. Genomic and proteomic analyses revealed that treatment with MIA-690 downregulated 22 AD-related genes in the brain of 5XFAD mice. MIA-690 treatment increased antioxidant enzyme activity and cell viability of human cortical neuronal (HCN) cells treated by $A\beta_{1-42}$. These results suggest that these GHRH antagonists have potential therapeutic effects on experimental AD [102].

Interestingly, several studies have shown that GHRH agonists also have favorable improvement of cognition. Nair et al. demonstrated that the treatment with GHRH agonist JI-34 but not antagonist MIA-602 attenuated intermittent hypoxia-induced neurocognitive deficits, anxiety and depression in mice, accompanied by reduced oxidative stress and increased IGF-1 expression in hippocampus and cortex [103]. A randomized, double-blind, placebo-controlled clinical trial showed that venous administration of tesamorelin, a stabilized analog of human GHRH, for 20 weeks yielded favorable cognition effects in both adults with mild cognitive impairment and healthy elders [23]. Therefore, current reported data using GHRH-As for treatment of AD or improvement of cognitive impairment has been non-conclusive or sometime even conflicting. The reasons why GHRH agonists and antagonists yield the same therapeutic effects on AD are still unclear, we surmise that these contradictory results may not only be related to the

Table 1 Therapeutic effects of GHRH agonists and antagonists on CNS disorders

	Animal or cell type	GHRH analogue	Type of drug	Dosage	Route	Potential mediators	References
AD	$A\beta_{25-35}$ induced mice	GHRH antagonist	MZ-4-71	0.5、1、2 μg	i.c.v	muscarinic acetylcholine receptor, 5-HT1/5-HT2 serotonergic receptor, opioid receptors	[100, 101]
AD	SAMP8 mice	GHRH antagonist	MZ-5-156	10 μg /d	s.c.	GSH↑, GPx↓, telomerase activity↑	[99]
AD	5XFAD mice	GHRH antagonist	MIA-690	2, 5, 10 μg /d	s.c.	Aβ1–42↓, Tau filaments↓, amyloid precursor proteins, APP-BPs, BACE2, presenilin 1	[102]
AD	$A\beta_{1-42}$ treated HCN2	GHRH antagonist	MIA-690	10nM, 100nM, 1μM	/	ROS↓, GPx↑, BDNF↑	[102]
AD	Mice exposed to intermittent hypoxia during sleep	GHRH agonist	J1-34	50 mg / kg	s.c.	MDA↓, 8-OHDG↓, HIF-1α nuclear binding↑, IGF-1↑、EPO↑	[103]
AD	MCI for adults and healthy older adults	GHRH agonists	tesamorelin	1 mg/d	s.c.	/	[23]
IS	tMCAO-operated mice	GHRH agonist	MR-409	5–10 μg/mouse/d	s.c.	Neurogenesis↑, inflammation↓	[96]
IS	NSCs treated with oxygen and glucose reperfusion	GHRH agonist	MR-409	0.5, 1 μM	/	AKT/CREB↑, BDNF/TrkB↑, STAT3↓	[96]
Anxiety and depression	$A\beta_{25-35}$ induced mice	GHRH antagonist	MZ-4-71	0.5, 1, 2 μg	s.c.	1/2-adrenergic, 5-HT1/5-HT2 serotonergic, GABA-A transmitters, muscarinic acetylcholine receptors	[117, 118]
Anxiety and depression	Mice	GHRH antagonist, GHRH agonist	MIA-690 MR-409	5 μg	s.c.	NE↑, 5-HT↑, NF-kB↓, TNF-α↓, IL-6↓	[123]
Anxiety and depression	Isolated mouse prefrontal cortex treated with lipopolysaccharide	GHRH antagonist GHRH agonist	MIA-690 MR-409	1–5 μM	/	PGE2↓, 8-iso-PGF2α↓, LDH↓, COX-2↓, iNOS↓	[123]
Anxiety and depression	Mice	GHRH antagonist	MIA-602	5 μg	s.c.	Nrf2↑, HO1↑, NQO1↑, BDNF↑, TrkB↑(full length form (140 KDa), PGE2↓, 8-iso-PGF2α↓, COX-2↓, iNOS↓, TNF-α↓	[121]
Anxiety and depression	Isolated mouse prefrontal cortex and hippocampal treated with lipopolysaccharide	GHRH antagonist	MIA-602	1–5 μM	/	PGE2↓, 8-iso-PGF2α↓, COX-2↓, iNOS↓, NF-κB↓	[121]
Anxiety and depression	GHRHKO (-/-) mice	GHRH antagonist	MIA-602	5 μg	s.c.	Nrf2↑, HO1↑, NQO1↑, COX-2↓, iNOS↓, NF-κB↓, P-AKT↑, AKT↑	[122]
Glioma	Thymic nude mice implanted with U-87MG glioblasts	GHRH antagonist	MZ-5-156	20 μg/mouse/d	s.c.	hTRT↓	[126]
Glioma	Thymic nude mice implanted with U-87MG and DBTRG-05 glioblasts	GHRH antagonists	JMR-132 MIA-602	5 μg/d	s.c.	/	[127]
Glioma	U-87MG and DBTRG-05 glioblasts	GHRH antagonists	JMR-132, MIA-602	1 μM	/	p-Akt↓, pp-GSK3b↓, p-ERK 1/2↓, caspase-3↑, PARP↑	[127]
Glioma	Thymic nude mice implanted with U-87MG glioblasts	GHRH antagonists	MIA-604 MIA-690	1, 2, 5 μg	s.c.	/	[128]

Table 1 (continued)

	Animal or cell type	GHRH analogue	Type of drug	Dosage	Route	Potential mediators	References
Glioma	U-87MG glioblasts	GHRH antagonists	MIA-604 MIA-690	10 nM, 100 nM, 1 μM	/	E-cadherin–β-catenin complex↑, integrins↑, FGF↓, PDGFβ↓, TGFβ↓	[128]
Glioma	Thymic nude mice implanted with U-87MG glioblasts	GHRH antagonists	MIA-602 AVR-333 AVR-352	5 μg/d	s.c.	/	[129]

type and dosage of GHRH -As used, but also to the progression of AD, time point to GHRH-As intervention, and animal models.

3.2 Ischemic stroke (IS)

IS is a leading cause of mortality and high permanent disability with limited therapeutic options. IS often causes extensive damage or necrosis of brain neurons associated with deteriorating microenvironment such as hypoxia, inflammation and high reactive oxygen species (ROS) generation. So far, single-drug therapy has been proven to be difficult to prevent brain damage induced by IS. A large amount of neuronal damage can cause neurological dysfunction, which may lead to death. In addition, the inability to repair dead neurons may also cause cognitive and limb motor dysfunction in patients, leading to permanent disability [104, 105].

As a normal neural repair process after IS, quiescent endogenous neural stem cells (NSCs) in the subgrannular zone (SGZ) of the hippocampus and subventricular zone (SVZ) are activated, proliferated and differentiated into progenitor cells and neuroblasts after being stimulated by ischemic injury, and then migrate to damaged brain regions [106]. However, only few NSCs can survive and differentiate into mature neurons in ischemic lesion. Theoretically, the therapies that promote endogenous NSCs proliferation and differentiation into forming new neurons and restore neurological function are considered a promising strategy for treating IS [107, 108]. However, as IS often occurs in elderly patients with a low regenerative ability of neuron cells and faces a disadvantage ischemic microenvironment, which may prevent NSCs from homing and surviving in ischemic lesion. GHRH-As has capability of promoting cell proliferation and inhibiting cell apoptosis as well as suppressing inflammation and antioxidant effects [109–113], these important pharmacological properties of GHRH-As may help improve the cerebral ischemic microenvironment, and promote the proliferation, survival and differentiation of NSCs into mature neurons, repairing neuronal damage caused by cerebral ischemia, and thus improving cerebral ischemic sequelae.

Recently, we used MR-409 to treat mouse model of cerebral ischemia caused by transient middle cerebral artery occlusion (tMCAO). Importantly, we have detected that GHRH-R is expressed in NSCs. As expected, MR-409 significantly increases the proliferation of endogenous NSCs in the SVZ and SGZ of the hippocampus, promotes stem cell-derived neurogenesis and neuroplasticity. Long-term treatment with MR-409 (5–10 μg/mouse/day) by subcutaneous injection significantly reduces the mortality, ischemic insult, and hippocampal atrophy, and improves neurological functional recovery in tMCAO mice. In consistent with these finding in vivo, MR-409 also enhances the proliferation and inhibits apoptosis of NSCs treated with oxygen and glucose deprivation–reperfusion *in vitro*. Further mechanistic studies reveal that MR-409 promotes NSCs proliferation mainly through the activation of protein kinase B (PKB/AKT)/CREB and brain-derived neurotrophic factor (BDNF)/Tropomyosin receptor kinase B (TrkB) pathways [96]. Therefore, despite GHRH may not directly affect neuronal regeneration, GHRH agonist promotes neuronal regeneration after cerebral ischemic injury by promoting the proliferation and differentiation of NSCs into new neurons, repairing neuronal damage and sequelae caused by IS. These results suggest that MR409 may have potential to develop a novel medication that promotes neural regeneration for the treatment of IS sequelae (Fig. 3). Of course, further experimental or clinical studies are needed to confirm our assumption.

3.3 Anxiety and depression

The treatment of depression requires a comprehensive approach, including exercise, psychological counseling, and medication, among them, pharmacological therapy remains the primary modality for treating depression [114]. Current pharmacological therapies for depression include selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine and serotonin reuptake inhibitors (SNRIs), noradrenergic and specific serotonergic antidepressants (NASSAs), 5-HT2A receptor antagonists, and dual-action agents that inhibit both 5-HT reuptake and 5-HT2A receptors. Although these new generation of antidepressants, especially SSRIs, has relatively low incidence of side effects and more efficacy, long-term use of SSRIs and SNRIs may give rise to certain adverse reactions, including gastrointestinal complications,

liver toxicity, hypersensitivity responses, weight gain, sexual dysfunction, and osteoporosis [115, 116].

As mentioned above, GHRH/GH axis is involved in regulating emotional, anxiety, and depressive behaviors, and some synthesized GHRH-As have been shown to have beneficial effects on emotion-related diseases, such as anxiety and depression in preclinical studies. Telegdy et al. reported that the administration of GHRH antagonist MZ-4-71 into the lateral ventricle of mice displayed significant antidepressant and anxiolytic effects [100]. Further, they demonstrated the antidepressant and anxiolytic effects of MZ-4-71may be mediated by altering the release of multiple neurotransmitters, including 1/2-adrenergic, 5-HT1/5-HT2 serotonergic, and GABA-A transmitters, as the blockade of these neurotransmitters by their receptor antagonists prevents antidepressant and anxiolytic effects of MZ-4-71 [117, 118].

Increased evidence has shown that anxiety and depression are associated with the activation of nuclear factor kappa-B (NF*k*b) inflammatory pathway and oxidative stress [119, 120]. It has been shown that GHRH-As exhibit potent anti-inflammatory and antioxidant effects in extapituitary cells and tissues, which may contribute to their antidepressant and anxiolytic effects. A recent study investigated antidepressant and anxiolytic effects of a novel synthetic GHRH antagonist MIA-602, the administration of MIA-602 to mice alleviates the behaviors of depression and anxiety in light-dark box and elevated plus maze test, which are associated with increased expression of antioxidant genes nuclear factor erythroid 2-related factor 2 (Nrf2), heme oxygenase 1 (HO1), and recombinant NADH dehydrogenase, quinone 1(NQO1) and decreased expression of inflammatory genes inducible nitric oxide synthase (iNOS), NF*k*B, and tumor necrosis factor α (TNFa) [121, 122]. Recinella et al. used GHRH-R antagonist MIA-690 to treat mice for 4 weeks, and found that MIA-690 also reduced anxiety-related behaviors in light-dark box and elevated plus maze tests. Interestingly, this article reported that treatment with GHRH agonist MR-409 can also improve depression- and anxiety-related behaviors in mice, which is similar to GHRH antagonist MIA-690, and both MIA-690 and MR-409 reduced NF*k*B activity and expression of inflammatory cytokines TNFa and interleukin-6 (IL6). The only difference is that at the same dose, antagonist MIA-690 has stronger antidepressant and anxiolytic effects than those of the agonist MR-409 [123]. It is particularly important to pointed out that anxiety and depression are not the only diseases in which both GHRH agonists and antagonists have therapeutic effects, it has been reported that both GHRH agonists and antagonists also exhibit therapeutic effects on experimental AD and diabetic retinopathy [97]. Although it is currently unknown why both GHRH agonists and antagonists exhibit the same therapeutic effects, these results suggest that this phenomenon may be relatively common in using GHRH-As therapies. In the previous section, we have introduced that GHRH and GH have opposite pharmacological effects on anxiety and depression. One possible explanation is that the antidepressant effects of MIA-690 may be related to directly blocking GHRH-mediated the biological effects in extrapituitary cells, while MR-409 therapeutic effects may rely more on biological effects of releasing GH. Of course, this is a pure speculation, which needs to be confirmed by further experimental studies.

3.4 Glioma

Glioblastoma are the most prevalent malignant tumor in the CNS, accounts for half of all primary brain malignancies with poor chemotherapy efficacy and high mortality. Although surgery remains the primary therapy for gliomas, due to their high invasiveness, most gliomas are difficult to completely remove through surgery and require a comprehensive therapy including chemotherapy, radiation therapy and hormone therapy [124].

It has been shown that GHRH-R is expressed in various tumor cells. Stimulating these receptors can exacerbate various biological behaviors of malignant tumors, such as tumor cell proliferation, invasion and metastasis, and blockade of this signaling with GHRH antagonists can inhibit tumor growth in experimental breast cancer, small cell lung carcinomas, prostate cancers and colorectal carcinomas [86, 125].

It has been shown that both GHRH and its major splice variant receptors are expressed in human glioblastoma samples, and their expression patterns are associated with a poorer prognosis [12]. It should be pointed out that this pituitary GHRH splice variant receptor has also been detected in many human cancer tissues [86], however, as far, there is no evidence to show the existence of this splice variant receptor in other brain tissues besides the pituitary gland and glioblastoma. Several GHRH antagonists have shown to exert therapeutic beneficial effects on glioblastoma. In U-87MG human glioblastomas, treatment with GHRH antagonist MZ-5-156 inhibits tumor growth and reduces telomerase activity with downregulating the hTRT gene [126]. In human glioblastoma cell lines of DBTRG-05 and U-87MG, treatment with GHRH antagonists JMR-132 or MIA-602 significantly decreases cell viability associated with an increase in apoptosis, and increases the expression p-AKT, phosphorylated glycogen synthase kinase 3β (p-GSK3β), and phosphorylated extracellular regulated protein kinases 1/2 (p-ERK1/2) in the tumor cells. Furthermore, the administration of MIA-602 and JMR-132 significantly inhibits the growth rate of xenografted DBTRG-05 glioblastoma tumors in nude mice [127]. Jaszberenyi et al. investigated

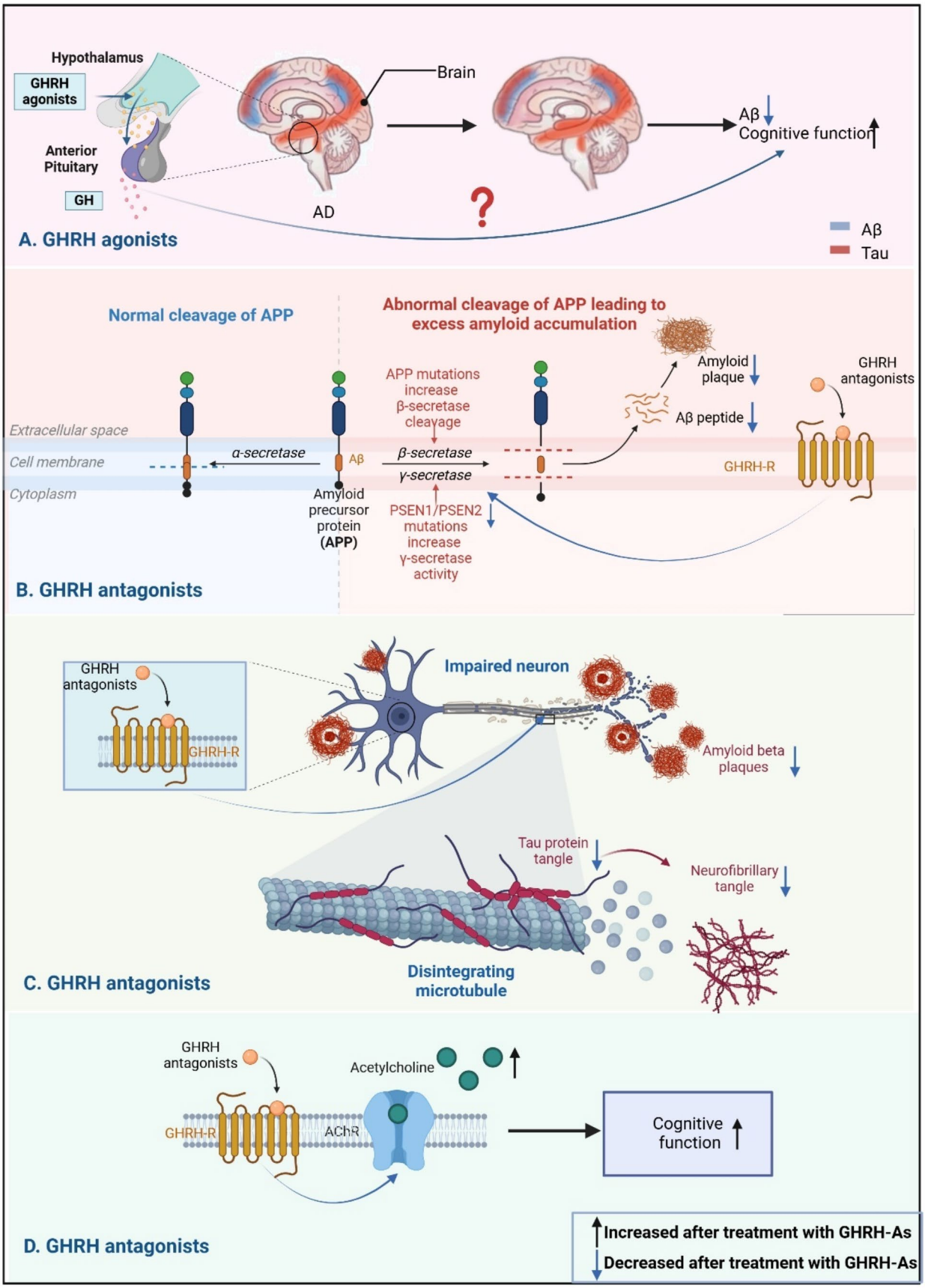
Hypothalamus
GHRH agonists
Anterior Pituitary
GH
Brain
AD
?
Aβ
Cognitive function
A. GHRH agonists
Aβ
Tau
Normal cleavage of APP
Abnormal cleavage of APP leading to excess amyloid accumulation
APP mutations increase β-secretase cleavage
Amyloid plaque
Aβ peptide
GHRH antagonists
Extracellular space
Cell membrane
Cytoplasm
α-secretase
Aβ
β-secretase
γ-secretase
GHRH-R
Amyloid precursor protein (APP)
PSEN1/PSEN2 mutations increase γ-secretase activity
B. GHRH antagonists
GHRH antagonists
GHRH-R
Impaired neuron
Amyloid beta plaques
Tau protein tangle
Neurofibrillary tangle
Disintegrating microtubule
C. GHRH antagonists
GHRH antagonists
Acetylcholine
GHRH-R
AChR
Cognitive function
D. GHRH antagonists
Increased after treatment with GHRH-As
Decreased after treatment with GHRH-As

Fig. 2 Potential therapeutic effects and interfering mediators of GHRH agonists and antagonists in the treatment of Alzheimer's diseases. **A**. Treatment with GHRH agonists improves cognitive function associated with reducing Aβ plaque. **B**-**D**. GHRH antagonists improve cognitive function associated with reducing Aβ plaque, neurofibrillary tangle and increases acetylcholine levels

therapeutic effects of MIA-604 and MIA-609 on U-87 MG glioblastoma multiforme tumors in vivo and *in vitro*. The subcutaneous administration of MIA-604 or MIA-609 dose-dependently suppressed tumor growth in nude mice and inhibited cell proliferation associated with inducing apoptotic and autophagic processes in vitro. Treatment with the two GHRH antagonists promotes contact inhibition by upregulating the expression of the E-cadherin–β-catenin complex and integrins while decreasing the release of humoral regulators such as fibroblast growth factor (FGF), platelet-derived growth factor β (PDGFβ), and transforming growth factor β (TGFβ) that promote glial growth [128]. Recently, Schally's laboratory compared the anticancer effects of GHRH antagonists MIA series and AVR series, they found that AVR series had stronger anti-tumor effects than MIA series in various cancer cell lines, and AVR-352 had stronger inhibitory effects on glioma U-87 cells compared with MIA-602 [129]. Although the mechanisms of GHRH antagonists for treating glioma has not been fully elucidated, both inhibition of GHRH-R signaling in tumor cells and suppression of pituitary-derived GH mediated tumor cell proliferation may be attributed to the anti-tumor effects of these GHRH antagonists. Therefore, these results consistently support that GHRH antagonists may hold a promise as an important adjuvant therapy for the comprehensive treatment of glioblastoma.

4 Conclusion

GHRH, as an important neuroendocrine hormone of hypothalamus-pituitary axis, plays a critical role in brain development, growth and maintenance of CNS homeostasis. GHRH exerts its physiological effects through two pathways: first, GHRH binds to its receptors on the pituitary gland to stimulate GH release and subsequently promote IGF-1 generation in the liver, GH and IGF-1 cross brain-blood barrier to exert regulatory effects on the CNS. Second, GHRH and GHRH-R exist in some extrapituitary brain cells of the CNS, they regulate CNS function through paracrine manner, while the administration of exogenous GHRH affects CNS function through both pituitary and extrapituitary GHRH-R. Some CNS diseases, such as AD, IS, depression and ASL, are associated with aging and decline in GHRH-GH/IGF-1 axis, GH or IGF-1 replacement has been shown to have beneficial effects on these diseases in both animal models and patients who have GH or IGF-1 deficit or secretion deficiency to GHRH stimulation. Other CNS diseases, such as HD, are associated with high level of GH or IGF-1 or increased secretion of GH to GHRH, the administration of GH deteriorates neurological impairment.

Animal studies have suggested potential therapeutic role of synthesized GHRH-As in treatment of CNS diseases, for example, the data on experimental IS supports that GHRH agonist MR-409 has potential therapeutic effects on IS by promoting the proliferation and differentiation of endogenous NSCs into new-regenerated neurons, therefore improving IS-induced neurological impairment and sequelae. However, there are still some limitations to the application of GHRH-As for the treatment of CNS diseases. First, most studies on GHRH-As and CNS diseases focus on therapeutic effects of GHRH-As on CNS diseases and their impact on some biomarkers, lacking in-depth mechanistic studies. The results from current studies are still unable clearly to answer why and how GHRH-As exert beneficial effects on CNS diseases, such as AD and depression. The use of some cutting-edge molecular biotechnologies such as single cell RNA-seq and spatiotemporal transcriptomics combined with CNS disease animal models in vivo and neural cell culture in vitro may help us more accurately to elucidate the molecular and cellular mechanisms and signaling pathways of GHRH-As in treating various CNS diseases. Next, the data on GHRH-As for treatment of AD and depression has been no conclusive, because both GHRH agonists and antagonists have shown to benefit on AD and depression. Third, although some synthesized GHRH-As have been shown to have beneficial effects on CNS diseases, because the GHRH-As are large molecular peptides, most studies do not provide clear scientific evidence to show that these GHRH-As can effectively cross the blood-brain barrier under normal and various CNS pathological conditions, which may require us to further clarify and determine brain concentration of GHRH-As for treating various CSN diseases. Finally, current studies on GHRH-As and CNS diseases are limited to preclinical studies. Future studies may need to further confirm the results in the preclinical studies and translate these fundamental findings into clinical practice.

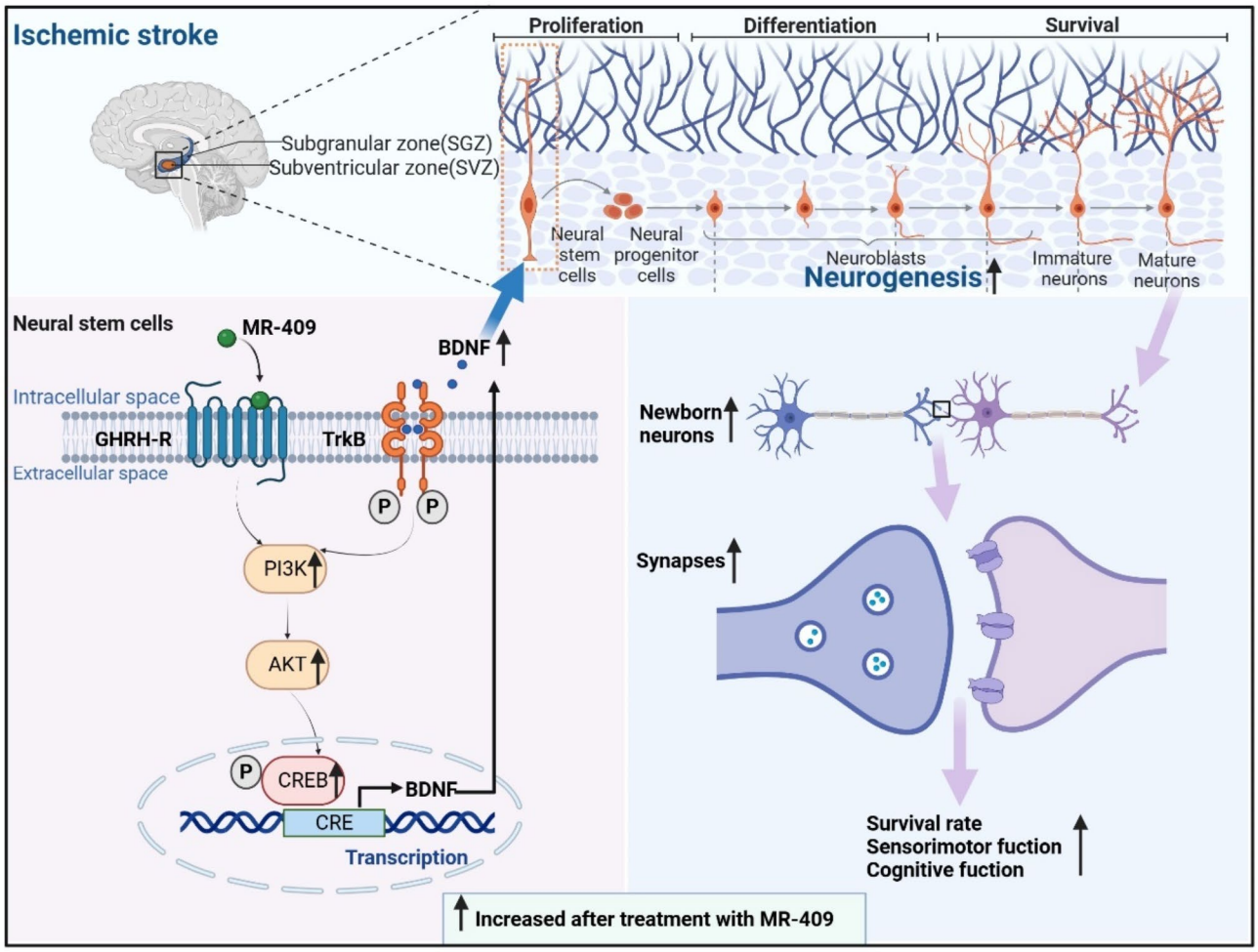

Fig. 3 A schematic diagram showing the potential mechanisms of GHRH agonist MR-409 promoting neuronal regeneration and the neuroprotective effects in ischemic stroke. MR-409 activates multiple signaling pathways, such as AKT/CREB/CREB and BNDF/TrkB in endogenous neural stem cells (NECs) in the SGZ and SVZ of hippocampus, which promote the proliferation, migration, differentiation of NECs into newborn neurons in ischemic lesion. In addition, MR-409 alleviates ischemia-induced NECs environmental niche damage by inhibiting inflammatory response. These effects of MR409 are beneficial on endogenous neurogenesis, the improvement of the synapse plasticity and newborn neuron survival, eventually leading to repairing neurological dysfunction and neurological sequalae caused by ischemia

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Declarations

Conflict of interest The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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