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REVIEW

Effect of intra-hippocampal injection of human recombinant growth hormone on synaptic plasticity in the nucleus basalis magnocellularis-lesioned aged rats

Efeito da injeção intrahipocampal de hormônio do crescimento humano recombinante sobre a plasticidade sináptica em ratos envelhecidos lesados do núcleo basalis magnocellularis

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ABSTRACT

In this study, we proposed that administration of hippocampal growth hormone in ageing animals with growth hormone deficiency can compensate long-term potentiation and synaptic plasticity in nucleus basalis magnocellularis (NBM)-lesioned rats. Aged male Wistar rats were randomly divided into six groups (seven in each) of sham-operated healthy rats (Cont); NBM-lesioned rats (L); NBM-lesioned rats and intrahippocampal injection of growth hormone vehicle (L + Veh); NBM-lesioned and intrahippocampal injection of growth hormone (10, 20 and 40 μg.2 μl-1) (L + GH). *In vivo* electrophysiological recording techniques were used to characterize maintenance of long-term potentiation at distinct times (1, 2, 3, 24 and 48 hours) after high-frequency stimulation. The population spike was enhanced significantly for about 48 hours following tetanic stimulation in rats treated with a dose-dependent growth hormone compared to the vehicle group ($p < 0.05$), possibly through neuronal plasticity and neurogenesis in affected areas.

Keywords: growth hormone; hippocampus; basal nucleus of Meynert; long-term potentiation; Alzheimer disease; cognition disorders.

RESUMO

Neste estudo, propusemos que a administração de hormônio hipocampal do crescimento em animais envelhecidos com deficiência de hormônio do crescimento pode compensar a potencialização em longo prazo e a plasticidade sináptica em ratos lesados do núcleo basalis magnocellularis (NBM). Ratos machos Wistar foram divididos aleatoriamente em seis grupos (sete ratos em cada grupo) de ratos falso-operados saudáveis (Cont); ratos lesados do NBM (L); ratos lesados do NBM e injeção intrahipocampal de veículo de hormônio do crescimento (L + Veh); ratos lesados do NBM e injeção de hormônio do crescimento (10, 20 e 40 μg.2 μl-1) (L + GH). Técnicas de registro eletrofisiológico *in vivo* foram utilizadas para caracterizar a manutenção da potencialização em longo prazo em momentos distintos (1, 2, 3, 24 e 48 horas) após estimulação de alta frequência. O pico populacional aumentou significativamente cerca de 48 horas após a estimulação tetânica em ratos tratados com um hormônio do crescimento dose-dependente, em comparação com o grupo veículo ($p < 0,05$), possivelmente através da plasticidade neuronal e da neogênese nas áreas afetadas.

Palavras-chave: hormônio do crescimento; hipocampo; núcleo basal de Meynert; potenciação de longa duração; doença de Alzheimer; transtornos cognitivos.

Many common age-related problems are due to neuro-endocrine phenomena including memory impairment and Alzheimer's disease (AD)[1]. Alzheimer's disease is a senile neurodegenerative disorder with specific pathological changes in the brain that can cause progressive dementia[2] and is characterized by serious memory problems[3]. The causes and mechanisms of AD are still under intensive investigation[4]. According to the cholinergic hypothesis, high destruction of basal forebrain cholinergic neurons, particularly the nucleus basalis magnocellularis (NBM), have been seen in

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the progression of AD. This nucleus has extensive cholinergic projections containing acetylcholine and choline acetyl transferase to the neocortex and hippocampal areas[5]. There is a relationship between the severity of destruction of cholinergic neurons and memory impairment in AD[6]. The evidence suggests that a functional link may exist between the cholinergic system and growth hormone (GH) secretion. For example, the secretion of GH from the pituitary is enhanced by acetylcholinesterase inhibitor (pyridostigmine)[7] and a primary mediator of growth hormone/insulin-like growth factor-1 (IGF-1) or GH-releasing hormone, which can stimulate secretion of acetylcholine from rat cortical slices and the hippocampus respectively[8,9]. It has recently been shown that age-related reductions in plasma GH, known as somatopause, is associated with increased incidence of cognitive impairment and AD, and can be compensated through GH treatment[10,11]. Various central effects of GH, such as cell genesis, neurogenesis[12] and angiogenesis[13], suggest that GH administration may be effective in preventing the development or progression of AD[9,14,15].

Molecular mechanisms of improved cognitive functions after GH treatment are not known but may be due to the direct impact of the hormone on the brain. Observations have indicated that hormones may cross the blood-brain barrier and have confirmed the existence of GH receptors on neural stem and progenitor cells through immunoreactivity studies of GH and its receptors in the various brain areas (especially regions involved in postnatal neurogenesis such as neurospheres derived from the hippocampus)[16,17,18,19,20,21]. Growth hormone treatment has been shown to promote proliferation, differentiation and survival of these neural stem cells[21].

It seems that GH and IGF-1 affect ultrastructural synaptic and electrophysiological properties[22]. However, in this regard, more studies have been done on IGF-1, but synaptic functions of GH are independent of IGF-1, and the separate effects of GH still need to be evaluated[22]. Previous studies in our laboratory have shown that intrahippocampal and peripheral injection of GH or IGF-1 can attenuate spatial learning deficit in a dose-dependent manner in NBM-lesioned aged rats[15,23]. The purpose of this study was to assess the direct central actions of GH on electrophysiological properties of hippocampal neurons.

METHODS

Animals

Aged male Wistar rats (350–400g, 18-20 months) were housed in a temperature-controlled (22 ± 2°C) and humidity-controlled room (55–60%) with a 12:12 hour light/dark cycle. The animals had *ad libitum* access to food and water throughout the experimental periods. All experimental procedures were in accordance with the local ethics committee for the Care and Use of Laboratory Animals. The animals were divided randomly into six groups (seven in each group): 1) Cont: sham-operated healthy rats (injection of the same volume of distillate water without ibotenic acid into the NBM; 2) L: bilateral NBM-lesioned aged rats with ibotenic acid injection; 3–5) L + GH10, L + GH20, and L + GH40 groups: bilateral NBM-lesioned aged groups and intrahippocampal human recombinant GH treatment (10, 20 and 40 $\mu g.2\ \mu l^{-1}$ respectively, Novo Nordisk, Bagsvaerd, Denmark); and 6) L + Veh: bilateral NBM-lesioned aged rats that received intrahippocampal GH related solvent (benzyl alcohol solution 0.9%) (2 µl) as a vehicle.

Measurement of plasma growth hormone concentrations

Blood samples were taken from the tail vein, immediately centrifuged at 1,000 rpm for 15 minutes at 4°C, plasma was kept frozen at -80°C until GH analysis with enzyme-linked immunosorbent assay method. All blood samples were drawn on the same day and time (8:00 a.m.) to avoid the effects of the circadian rhythm on hormonal concentrations.

Surgery

NBM lesioning: rats were anesthetized with an intraperitoneal injection of ketamine (100 $mg.kg^{-1}$ body weight) and xylazine (10 $mg.kg^{-1}$ body weight)[15]. The animals were placed in a stereotaxic frame, lesions were made by injecting ibotenic acid bilaterally (0.5 $\mu g.0.1\ \mu l^{-1}$ distillate water on each side for 5 min, Sigma-Aldrich Chemical Co., USA) into the NBM according to the rat brain atlas (AP; -1.3, L; ±2.3, V; -6.6)[24]. The injection was made through a 2 µl Hamilton syringe connected to a short piece of polyethylene tube and an injection needle (gage 27). All animals were allowed to recover from surgery for 7–10 days.

Electrophysiology

After recovery, rats were anesthetized with an intraperitoneal injection of ketamine (100 $mg.kg^{-1}$ body weight) and xylazine (10 $mg.kg^{-1}$ body weight); the animals were placed in a stereotaxic frame and small holes were drilled in the skull at the positions for inserting the reference, stimulating and recording electrodes. In addition, a separate hole was drilled in the same side of the skull to insert a stainless steel guide cannula (0.7 mm outer diameter, 10 mm length) for intrahippocampal injection of the drug/vehicle (AP; -2.3, L; -1.2, V; -3.4). Bipolar stimulating electrodes (stainless steel; CFW Company, USA) and bipolar recording electrodes (Tungsten; CFW Company, USA) were placed in the angular bundle of the perforant path (AP; -6.96 , ML; +5 , DV; -3.4) and dentate gyrus (AP; -3.96 , ML; +1.9 , DV; -3.9) respectively, under electrophysiological guidance[24]. Electrodes and cannulas were fixed to the skull by dental cement after insertion. Test stimuli were delivered to the angular bundle of the perforant path every 30 s (0.033Hz) and a maximal field excitatory postsynaptic potential (fEPSP) was recorded with gradual increase of the

intensity of a single stimulus. For further observation in experiments, the amplitude of baseline fEPSP was chosen as 40% of the maximal fEPSP amplitude by adjusting the pulse intensity. Long-term potentiation (LTA) was recorded after induction of single and tetanus stimulating pulses to the perforant path using the high-frequency stimulus protocol (six pulses at 400Hz, repeated six times at 100 msec intervals and a stimulus intensity that evoked an fEPSP of approximately 80% of the maximum response).

Long-term potentiation was measured at separate times by a light anesthesia (one third of the initial dosage of ketamine/xylazine) at 1, 2, 3, 24 and 48-hour post-high-frequency stimulation and expressed as the percentages of amplitude or slope against baseline fEPSPs, which were recorded at the beginning of the high-frequency stimulation and arbitrarily set at 100%.

Intra-hippocamal injection of growth hormone

Different doses of human recombinant GH (10, 20, 40 μg.2 μl^{-1}, over a period of 5 min, twice daily, 9.00 a.m. and 3:00 p.m., for seven days) or GH vehicle (benzyl alcohol solution 0.9%) (2 μl) was infused into the right hippocampus by a 10 μl Hamilton syringe that was connected to an infusion pump (WPI, 101i, USA) through a short piece of polyethylene tube. Injections were made via an internal cannula (0.4mm outer diameter). For all injections, the needle was left in place for a further 3 min to prevent backflow and to allow the infusion.

Histology

At the end of the experiments, animals were sacrificed with an overdose of anesthetic. The brains were removed, fixed in 10% formalin for at least one week and embedded in gelatin. Frozen sections were cut in 40 μm coronal sections for identifying injection sites. Only data from animals with correct locations of lesions and injections were used in the analyses.

Statistical analysis

Data are represented as the mean ± SEM and analyzed using two-factor repeated-measures ANOVA, followed by the Least Significant Difference *post hoc* test (SPSS 15.0). Statistical significance was defined as $p < 0.05$.

RESULTS

Growth hormone plasma levels

The purpose of measuring GH plasma levels was just to show lower levels of GH and the rationale of GH replacement therapy in our experimental aged animals. However, the GH values were not significantly different (Figure 1) but the young group had nearly twice the concentrations (2.18 ± 0.91 ng/ml) of the old group (1.09 ± 0.32ng/ml). The intra-assay and inter-assay variations were 11.4 % and 11% respectively.

Long-term potentiation (LTP)

The percentage of amplitude or slope of LTP against baseline fEPSP, which was arbitrarily set at 100%, is shown in Figure 2. After baseline responses of fEPSP, the high-frequency stimulation was delivered at zero time to the angular bundle of perforant path; then the percentage of LTP against baseline fEPSP was recorded at separate times at 1, 2, 3, 24 and 48 hours later in bilateral NBM-lesioned aged rats with ibotenic acid injection (L); bilateral NBM-lesioned aged rats that received intrahippocampal GH related solvent (L + Veh) compared to sham-operated healthy rats (stereotaxic needle placement into the NBM without injection of ibotenic acid) (Cont). Two-factor repeated-measure ANOVA followed by the Least Significant Difference *post hoc* test revealed that the amplitude of LTP (A) was reduced slowly at 1 hour, 2 hours, 3 hours and 24 hours after LTP induction in NBM-lesioned *versus* control rats and, at 48 hours, showed a significant reduction (45% *vs.* 74%) ($p < 0.05$), which shows long-term memory impairment in NBM-lesioned rats. The slope of the LTP (B) also showed gradual significant decrements over time (at all time points after high-frequency stimulation) compared to the control group ($p < 0.05$).

The effect of intrahippocampal injections of GH (10, 20, 40 μg.2 μl^{-1}) or vehicle (benzyl alcohol solution 0.9%) (2 μl) on the amplitude and slope of LTP showed that GH treatment with 20 μg and 40 μg doses, significantly increased the amplitude of LTP compared with the vehicle-treated group at 24 and 48 hours post-high-frequency stimulation (Figure 3A). Figure 3B illustrates the comparison of the LTP slope (one way ANOVA followed by the Least Significant Difference *post hoc* test). This result showed significant differences between GH and vehicle-treated groups (*$p < 0.05$ and **$p < 0.01$).

Histology

Cannula placement was verified by histological examination of the needle tracks. Histological coronal sections (40 μm) showed the needle was inserted correctly in the NBM of the rat brain (Figure 4A) and within the right hippocampus (Figure 4B).

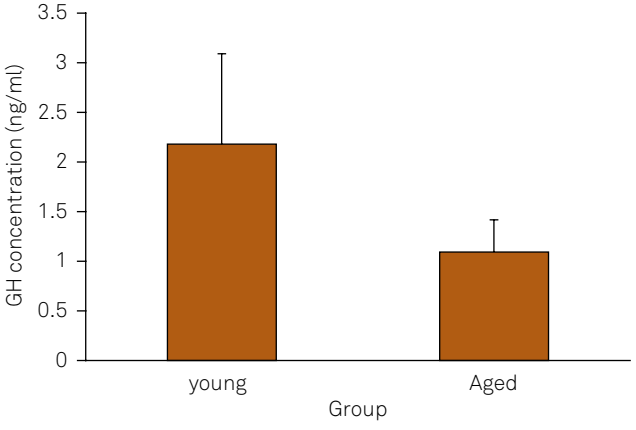
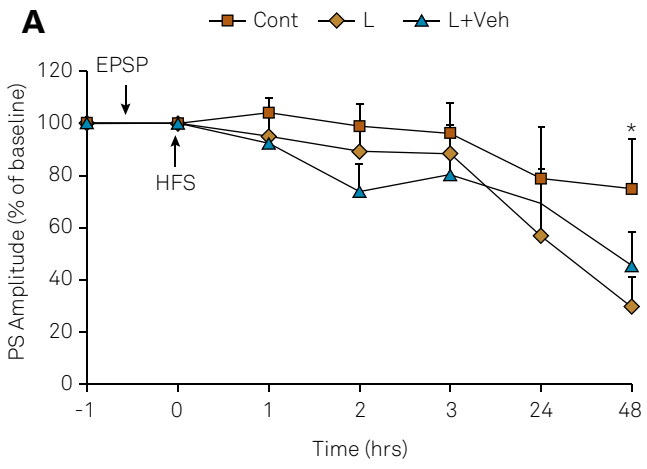
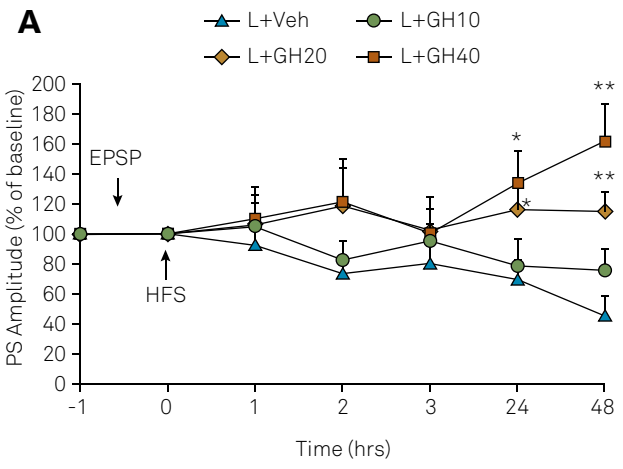
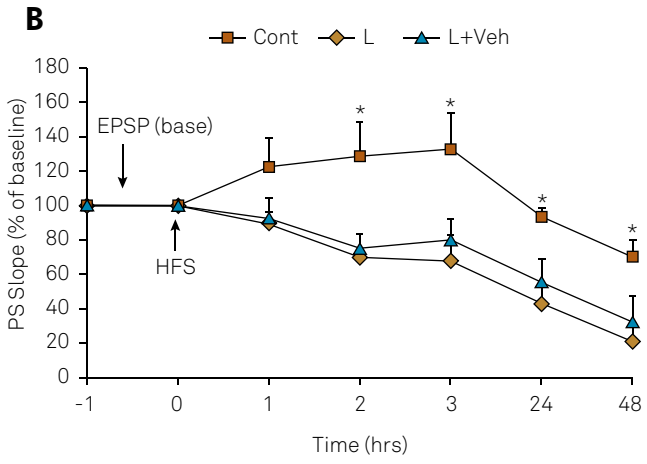
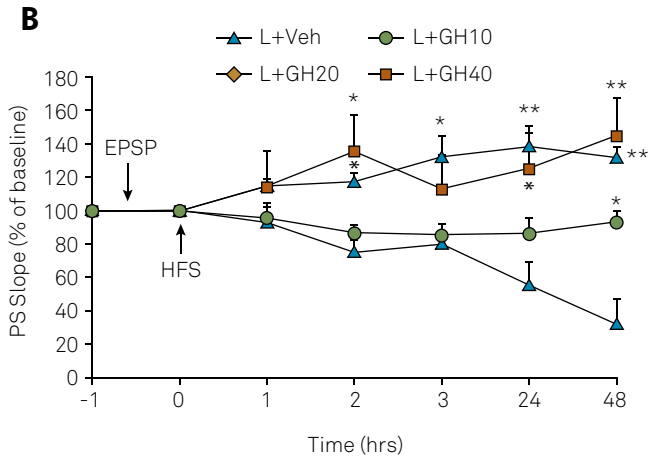


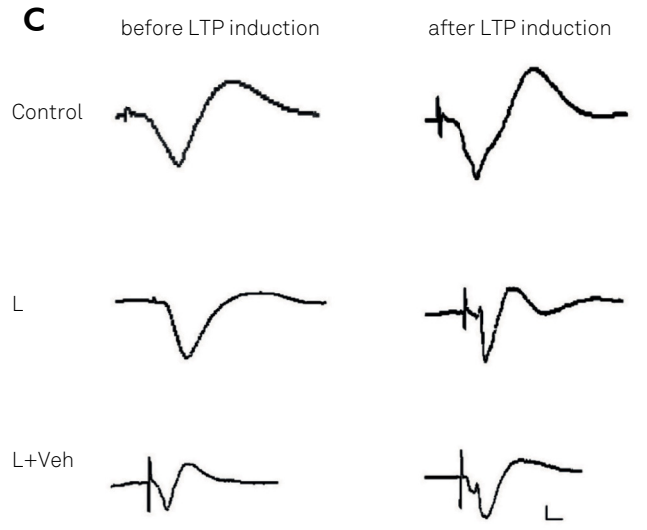
Figure 1. Plasma level of growth hormone in young (3–4-month-old) and aged (18–20-month-old) healthy rats. Data are presented as means ± SEM (n = 6/group).











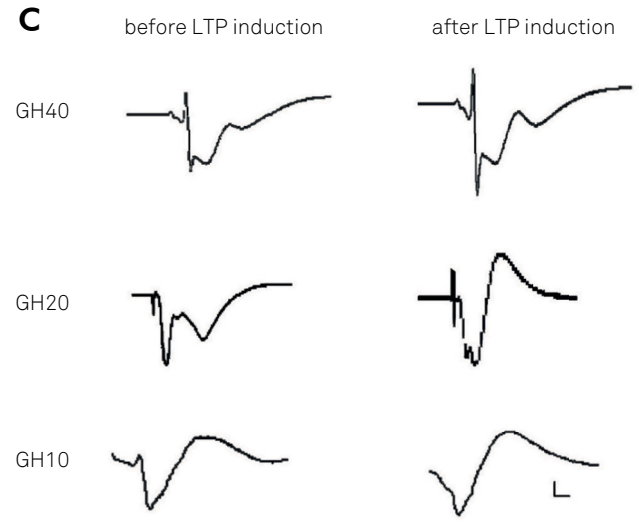


Figure 2. (A) Effects of bilateral nucleus basalis magnocellularis lesion with ibotenic acid injection (L), bilateral nucleus basalis magnocellularis lesion and intrahippocampal growth hormone-related solvent (L + Veh) on amplitude and (B) slope of long-term potentiation (LTP) compared to sham-operated rats (Cont) at separate times after high-frequency stimulation (HFS) (*$p < 0.05$). (C) Single traces recorded before and after induction of LTP in the dentate gyrus of the hippocampus. Horizontal scale bars: 1 mV, vertical scale bars: 5 ms.

Figure 3. (A) The effet of bilateral nucleus basalis magnocellularis lesion and intrahippocampal human recombinant growth hormone treatment on amplitude and (B) slope of long-term potentiation (LTP) *vs.* vehicle-treated rats (*$p < 0.05$, **$p < 0.01$). (C) Single traces recorded before and after induction of LTP in the dentate gyrus of the hippocampus. Horizontal scale bars: 1 mV, vertical scale bars: 5 ms.

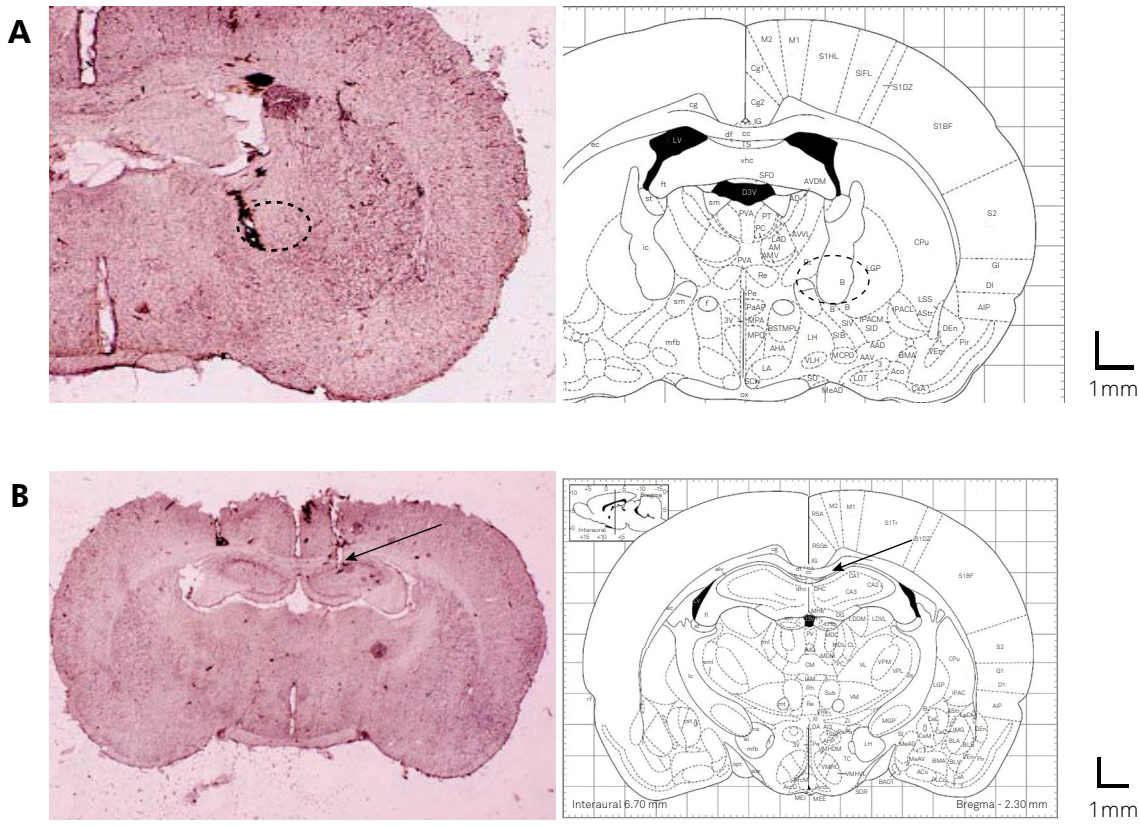


Figure 4. (A) Schematic representation of a rat brain coronal section from Paxinos and Watson and needle track in the nucleus basalis magnocellularis of the rat brain. (B) Schematic drawing of a rat brain coronal section from Paxinos and Watson, showing site of injection within the hippocampus and intrahippocampal growth hormone or vehicle needle track of the rat brain. The arrow shows the injection site of growth hormone or vehicle and circles represent the terminating site of needle.

DISCUSSION

The results of the present study demonstrate, for the first time, that central GH potentiates synaptic plasticity and memory following lesion of NBM in aged rats. The brain cholinergic system is involved in the processing of storage information. It originates extensively from the NBM and projects to the hippocampus and neocortex[25]. Lesioning of the NBM causes degeneration of cholinergic projections, which leads to cognitive deficits similar to Alzheimer's disease[26]. In this study, an NBM lesion resulted in a decreased amplitude and slope of the LTP at separate times after high-frequency stimulation, which represents the survival and sustainability effects of this nucleus in the LTP. It should be noted that our control group was aged rats with GH and memory deficiency. We expected a slight increase in the slope or amplitude of LTP post-high-frequency stimulation in this group. However, there was a decline in LTP over time, especially at 24 hours and 48 hours in this group.

The age-related decline in plasma GH has been shown to be an influencing factor in brain aging, decreased synaptic plasticity and memory[27,28]. Growth hormone-deficient patients have been shown to have short- and long-term memory loss[29]. Because the purpose of our study was the administration of GH to a group that had lower plasma GH levels at the beginning of the experiment, we measured the plasma GH level in young and aged rats to demonstrate the reduced circulating level of GH in our aged study group. As seen in our study, the GH plasma level in aged rats was lower than in the young group (approximately half of the GH plasma concentration in the young). According to this result, and our previous study of impairment in spatial learning and memory in aged compared to young rats[1], we used the aged group for GH replacement therapy and electrophysiological assessment. It should be noted that spot GH serum levels are very uncertain, with high variation, and serum IGF-1 levels are a better option to analyze instead, in future studies.

It has been shown that GH has an effect on the complexity of the neuronal dendritic tree and electrophysiological aspects in the cerebral cortex[22]. It seems that the increased response of GH on amplitude or slope of the LTP in our study (especially after 24 hours and 48 hours post-high-frequency stimulation) demonstrated an effect of the hormone on the synaptic structure, neurogenesis or plasticity.

The cause of instability in the LTP can be related to the separate intervals of recording and GH-induced structural changes. Growth hormone has positive effects on brain cell genesis including neurogenesis, angiogenesis and synaptic

efficacy, therefore it may be used clinically as a pharmacological agent to enhance cell genesis in the central nervous system[22,30]. The age-related decline in neurogenesis following growth factor deficiency can affect dentate gyrus functions[31]. It is now clear that the adult brain contains precursor cells, including endogenous neural stem and progenitor cells that have neurogenic and repair capacity in injury conditions[32]. Stem cell proliferation declines with age and this may contribute to cognitive impairment in the elderly[33]. The presence of GH receptors in neural stem cells suggests the ability of GH to regulate their activities[34]. Blackmore and his colleagues showed that a seven-day intracerebroventricular infusion of GH increases neural stem cell numbers and augments neurogenesis activity *in vitro*[35]. Furthermore, GH treatment promotes the proliferation and survival of hippocampal progenitors[21]. Lynch and his colleagues determined that IGF-1 infusion in the right lateral ventricle for 14 days ameliorates age deficits in local cerebral glucose utilization, a function believed to be correlated with neuronal activity[36] and cerebral blood flow[13,37]. These activities of GH can explain the increase of LTP magnitude after GH treatment, especially at 24 hours and 48 hours after high-frequency stimulation. Interestingly, reversal from long-term depression at 3 hours to LTP at 24 hours and 48 hours post-high-frequency stimulation with a higher dose of hormone (40 μg.2 μl^{-1}) is another reason for this effect of GH. There is some evidence of a negative correlation between age and hippocampal blood flow[38]. Administration of GH in aged rats was found to increase the density of capillaries and blood supply of the brain cortical surface[39]. In the present study, the mechanism by which GH promotes memory and synaptic plasticity remains unclear. Several researchers have proposed mechanisms based on excitatory synaptic transmission in the hippocampus that are mediated by glutamatergic receptors (AMPA) and N-methyl-D-aspartic acid (NMDA). These receptors have been shown to be important for synaptic plasticity and also a common switch for many forms of learning and memory[40]. Ageing is associated with a decline of NMDA receptor subunits in the hippocampus and NMDA receptor-mediated synaptic transmission[41,42,43], whereas GH increases the level of NMDA receptor expression in the hippocampus[44]. Treatment of GH-deficient patients with GH replacement increases aspartate levels, the ligand of the NMDA receptor, in the cerebrospinal fluid[45]. Growth hormone administration reduces oxidative stress in the hippocampus of aged rats by enhancing mitochondrial efficiency, limiting the generation of free radicals or increasing the activity of enzymes that regulate oxidative stress[46].

In conclusion, this study showed, for the first time, that local GH treatment for up to 48 hours ameliorates deterioration in LTP responses caused by a specific NBM-lesion. The positive effects of GH on synaptic plasticity is possibly caused by several mechanisms. The main mechanism may be the role of hormones in the stem cell proliferation and central nervous system neurogenesis to repair the injury areas. This useful possibility needs further in-depth studies.

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Review article must be changed to Original article

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