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Research Paper

Gastrin-releasing peptide facilitates glutamatergic transmission in the hippocampus and effectively prevents vascular dementia induced cognitive and synaptic plasticity deficits

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ABSTRACT

Neuronal gastrin-releasing peptide (GRP) has been proved to be an important neuromodulator in the brain and involved in a variety of neurological diseases. Whether GRP could attenuate cognition impairment induced by vascular dementia (VD) in rats, and the mechanism of synaptic plasticity and GRP's action on synaptic efficiency are still poorly understood. In this study, we first investigated the effects of GRP on glutamatergic transmission with patch-clamp recording. We found that acute application of GRP enhanced the excitatory synaptic transmission in hippocampal CA1 neurons via GRPR in a presynaptic mechanism. Secondly, we examined whether exogenous GRP or its analogue neuromedin B (NMB) could prevent VD-induced cognitive deficits and the mechanism of synaptic plasticity. By using Morris water maze, long-term potentiation (LTP) recording, western blot assay and immunofluorescent staining, we verified for the first time that GRP or NMB substantially improved the spatial learning and memory abilities in VD rats, restored the impaired synaptic plasticity and was able to elevate the expression of synaptic proteins, synaptophysin (SYP) and CaMKII, which play pivotal roles in synaptic plasticity. These results suggest that the facilitatory effects of GRP on glutamate release may contribute to its long-term action on synaptic efficacy which is essential in cognitive function. Our findings present a new entry point for a better understanding of physiological function of GRP and raise the possibility that GRPR agonists might ameliorate cognitive deficits associated with neurological diseases.

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1. Introduction

Gastrin-releasing peptide (GRP) and neuromedin B (NMB) are members of bombesin-like peptides (BLPs). GRP, an endogenous neuropeptide originally isolated from the porcine stomach, is the mammalian counterpart of bombesin. They exhibit a variety of physiological functions through bombesin receptors, including gastrin-releasing peptide receptor (GRPR/BB2) and neuromedin B receptors (NMBR/BB1), which are G-protein-coupled receptors on cell membrane in humans and rodents (Gonzalez et al., 2008). GRP and its receptors are widely distributed in a variety of brain regions including the hippocampus, hypothalamus, amygdala and cortex (Jensen et al., 2008; Kamichi et al., 2005) and participate in food intake, circadian rhythm generation, fear memory, itch sensation, control of smooth muscle contractions and sexual behavior (Ladenheim et al., 2002; Moody and Merali, 2004; Shumyatsky et al., 2002; Sun and Chen, 2007; van den Pol et al., 2009). Dysfunctions in GRP signaling and receptors expression might play a role in a variety of neurological diseases including epilepsy, anxiety, Parkinson's disease, Alzheimer's disease and autism (Andrews et al., 2000; Papalas et al., 2008; Zhang et al., 2014).

A recent study indicated that BLPs remarkably increase GABA release in the entorhinal cortex which contribute to their antiepileptic effects (Zhang et al., 2014). In addition, GRPR occurs on dendrites and cell bodies of neurons in regions including the dorsal hippocampus (Kamichi et al., 2005). This pattern of location suggests that it is specifically involved in regulating synaptic transmission which may contribute to hippocampus-associated cognitive impairment. But there is no definitive electrophysiological evidence demonstrating GRP's direct effects on hippocampal glutamatergic synaptic transmission. Therefore, we first examined the effects of GRP on glutamatergic transmission in the hippocampal CA1 neurons by using whole-cell patch-clamp recording.

Increasing evidences in rodents showed that GRP/BB2-receptor activation was important for memories involving emotional arousal and

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fear. For instance, findings from early pharmacological studies have indicated that systemic administration of GRPR agonists could improve memory retention in rodent models (Flood and Morley, 1988; Mountney et al., 2008; Rashidy-Pour and Razvani, 1998). Later, lines of studies indicated that infusions of a GRPR antagonist into the CA1 hippocampal area or the amygdala impair consolidation of memory for aversive conditioning (Roesler et al., 2003; Roesler and Schwartsmann, 2012), whereas infusion of the GRPR agonist bombesin into the hippocampus enhances consolidation of long-term fear memory and prevents memory deficit produced by intrahippocampal administration of beta-amyloid peptide (25–35) (Roesler et al., 2006). These findings provided preliminary preclinical evidence suggesting that pharmacological stimulation of the GRPR might rescue memory deficits associated with neurodegenerative disorders including Alzheimer's disease (AD) or vascular dementia (VD). In addition, a recent study suggested that GRP expression played a role in directly modulating neurogenesis and neuronal development and contributed to hippocampal circuit function (Walton et al., 2014).

However, a previous study proposed that GRPR deficient mice showed enhanced long-term potentiation (LTP), greater and more persistent long-term amygdala-dependent fear memory. By contrast, these mice formed normally in hippocampus-dependent Morris maze (Shumyatsky et al., 2002). Thus, the role of the GRPR in hippocampal function and memory formation appears to be complex. In spite of the above studies, it is still not clear whether GRP signaling is associated with the spatial learning and memory which is an essential function of the hippocampus especially in some neurodegenerative diseases characterized by varying degrees of cognitive impairment (Gold and Kesner, 2005). Thus for the second purpose, we further examined whether injection of GRP could ameliorate the spatial cognitive and synaptic plasticity impairment induced by VD.

2. Materials and methods

2.1. Patch-clamp recording in hippocampal CA1 neurons

A total of 13 male Wistar rats of postnatal 21–28 day (30–50 g) were killed by decapitation under isofluorane anesthesia. The brain was quickly removed and placed in a 3–5 °C buffered solution that contained (in mM) sucrose 220, KCl 2.5, $CaCl_2$ 1, $MgCl_2$ 6, $NaHCO_3$ 26, NaH_2PO_4 1.23 and D-glucose 10. All solutions were oxygenated by bubbling with a mixture of 95% O_2 and 5% CO_2. Longitudinal brain slices (350 μm thick) containing the hippocampus were cut with a Vibratome (VT1000S, Leica, Germany) and incubated for 1 h at 30 °C in artificial CSF(ACSF) before recording (in mM; NaCl 124, $NaHCO_3$ 26, D-glucose 10, KCl 2.5, NaH_2PO_4 1.23, $CaCl_2$ 2 and $MgCl_2$ 2; pH 7.4).

Hippocampal slices were bath perfused with ACSF (23–25 °C) at a rate of 2–3 ml/min and visualized under a BX51WI upright microscope (Olympus) which equipped with an infrared-differential interference contrast (DIC). Individual hippocampal slice was gently transferred into a glass-bottomed recording chamber (1 ml). Whole-cell membrane currents in voltage-clamp mode were amplified using a HEKA EPC10 amplifier. The data acquisition was controlled by Pulse 8.52 software installed on a computer. All the cells were held at −70 mV by pipettes with 3–7 M resistance after being filled with solution containing (in mM) K-glu 130, $MgCl_2$ 2, HEPES 10, EGTA 3, Na_2-ATP 2, pH 7.3. The pipettes were pulled by using a micropipette puller (PIP5, HEKA, Germany). For measurement of eEPSCs, a bipolar stainless-steel stimulating electrode was placed ventral to the recorded CA1 cell in the Schaffer collateral pathway, and the stimulations were delivered with a Master-8 stimulator (AMPI, Israel) using a stimulus isolator (AMPI, Israel). The stimulus intensity was 0.05–0.09 mA, and the inter-stimulus interval was 20 s. Signals were acquired at a bandwidth of 10 kHz and filtered with a 2 kHz low-pass Bessel filter.

2.2. Animal care and VD model procedure

Adult male 220–250 g Wistar rats (of clean grade) were used in this experiment. Rats were housed in cages in the animal house of Medical School, Nankai University and reared at specific pathogen-free condition under a 12-h light-dark cycle. Food and water were freely available. All animal experiments were approved by the Animal Research Ethics Committee, School of Medicine, Nankai University. All animal experiments were performed in accordance with the Animal Management Rules of the Ministry of Health of the People's Republic of China. In addition, all efforts were made to minimize the number of animals used and their suffering.

40 rats were randomly divided into four groups, including the sham group, VD group, VD + GRP group and VD + NMB group. The VD rat model was established as previously described (Yang et al., 2014). Briefly, before surgery, rats were fasted, but had access to water for 6 h, and then they were anesthetized by 10% chloral hydrate (350 mg/kg i.p.) and laid on their backs. Firstly, a ventral midline incision was made in the neck and the muscle retracted on either side of the trachea to expose both the right and left common carotid arteries, around which loose threads were placed. Secondly, the vessel was fully ligated, and the wound were sutured. During the operation, animals were maintained normal body temperature and respiratory tract. After coming to their senses, all rats were reared in the animal house, and given free access to food and water. The sham group received a surgery without touching the vessel. In the other three groups, 33 animals were subjected to bilateral common carotid artery occlusion (2-VO) described above for 14 days. At 72 h after surgery, the survival rate of the 2-VO surgery was about 82%, thus the rats in the four groups were sham group ($n = 7$), VD group ($n = 8$), VD + GRP group ($n = 9$) and VD + GRP group ($n = 8$) separately. Then, rats were injected intraperitoneally with GRP (4 nmol/kg/day, Sigma-Aldrich, USA) daily for 5 consecutive days in the VD + GRP group 72 h after surgery, and NMB (4 nmol/kg/day, Sigma-Aldrich, USA) daily for 5 days in the VD + NMB group. Rats in the VD group were injected intraperitoneally with saline.

2.3. Behavioral experiments in Morris water maze

On the 15th day of post-surgery, all rats were trained and tested in Morris water maze (MWM, RB-100A type, Beijing, China) to monitor their spatial learning and memory behaviors as described in our previous studies. The tank for MWM test was 150 cm in diameter and 60 cm in height and was filled with water to the depth of 40 cm. There is a platform 1–2 cm under the water. Nontoxic black ink was poured into water to make the platform out of sight. We divided the tank to four quadrants, namely zones 1, 2, 3, 4 and the platform was placed in the center of quadrant 3. The experiment consisted of two consecutive stages: initial training (IT) and space exploring test (SET). Rats were subjected to two sessions (8 h between them) of eight trials per day for five consecutive days in IT stage. In each trial, rats were released into water individually from one of four starting points of the tank (from quadrant 1 to 4) and allowed to swim freely until they reached and stayed on the platform at least 5 s. The time required to find the platform (escape latency) and the swimming speed were recorded. If they failed to find the platform within 60 s, they were placed on it for 10 s and the escape latency was recorded as 60 s. Then in SET stage, the platform was removed from the tank after five training days. The rats were released individually into water from the starting point of quadrant 1 and allowed to swim for 60 s. Quadrant dwell time (the percentage of time spent in quadrant 3) was measured. Only one session tested in this phase.

2.4. In vivo LTP recording from Schaffer collaterals to hippocampal CA1

The next day after MWM experiment, long-term potentiation (LTP) was recorded as previously described on the same rats in MWM test

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