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Effects of the cannabinoid 1 receptor peptide ligands hemopressin, (m)RVD-hemopressin(α) and (m)VD-hemopressin(α) on memory in novel object and object location recognition tasks in normal young and $A\beta_{1-42}$-treated mice

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ABSTRACT

The cannabinoid system plays an important role in memory processes, many studies have indicated that cannabinoid receptor ligands have ability to modulate memory in rodents. A nonapeptide hemopressin (Hp) derived from rat brain, acts as a peptide antagonist or selective inverse peptide agonist of cannabinoid 1 (CB1) receptor. N-terminally extended forms of Hp isolated from mouse brain, (m)RVD-hemopressin(α) (RVD) and (m)VD-hemopressin(α) (VD) also bind CB1 receptor, however, as peptide agonists. Here, we investigated the roles of Hp, RVD, and VD on memory in mice using novel object recognition (NOR) and object location recognition (OLR) tasks.

In normal young mice, intracerebroventricular (i.c.v.) infusion of Hp before training not only improved memory formation, but also prolonged memory retention in the tasks, these effects could be inhibited by RVD or VD at the same dose and intraperitoneal (i.p.) injection of a small molecule agonist of CB1 receptor WIN55, 212-2 15 min before administration of Hp inhibited the memory-improving effect of Hp. In addition, under the same experimental conditions, i.c.v. RVD or VD displayed memory-impairing effects, which could be prevented by Hp (i.c.v.) or AM251 (i.p.), a small molecule antagonist of CB1 receptor.

Infusion of amyloid-β (1–42) ($A\beta_{1-42}$) 14 days before training resulted in impairment of memory in mice which could be used as animal model of Alzheimer's disease (AD). In these mice, RVD or VD (i.c.v.) reversed the memory impairment induced by $A\beta_{1-42}$, and the effects of RVD and VD could be suppressed by Hp (i.c.v.) or AM251 (2 mg/kg, i.p.). Separate administration of Hp had no effect in $A\beta_{1-42}$-treated mice.

The above results suggested that Hp, RVD and VD, as CB1 receptor peptide ligands, may be potential drugs to treatment of the memory deficit-involving disease, just as AD.

1. Introduction

The cannabinoid system is involved in numerous biological processes including appetite (Hao, Avraham, Mechoulam, & Berry, 2000; Williams & Kirkham, 1999), early pregnancy events (Sun & Dey, 2009), analgesia (Sagar, Jhaveri, & Chapman, 2009), stress (Gorzalka & Hill, 2009), and learning and memory (Arain, Khan, Craig, & Nakanishi, 2015; Goodman & Packard, 2015; Herkenham et al., 1991; Matsuda, Bonner, & Lolait, 1993; Tsou, Brown, Sanudo-Pena, Mackie, & Walker, 1998; Wilson & Nicoll, 2002). This system is also related to a number of diseases, including drug addiction (Justinova, Panlilio, & Goldberg, 2009), anxiety and depression (Patel & Hillard, 2009), feeding disorders and obesity

Abbreviations: AD, Alzheimer's disease; CB1, cannabinoid 1; CB2, cannabinoid 2; BLA, basolateral complex of the amygdala; CNS, central nervous system; Hp, hemopressin; RVD, (m)RVD-hemopressin(α); VD, (m)VD-hemopressin(α); NOR, novel object recognition; OLR, object location recognition; i.c.v., intracerebroventricular; $A\beta_{1-42}$, amyloid-β (1–42); TET, total exploration time; DI, discrimination index; Acsf, artificial cerebrospinal fluid; DMSO, dimethyl sulfoxide; LTP, long term synaptic potentiation; 2-AG, 2-arachidonoylglycerol; AEA, anandamide; HFS, high frequency stimulation; SP, senile plaque; NFT, neurofibrillary tangles; ACEA, arachidonyl-2-chloroethylamide.

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(Cervino, Vicennati, Pasquali, & Pagotto, 2009), schizophrenia (Arseneault et al., 2002; Henquet et al., 2005; Volk & Lewis, 2016), Tourette's syndrome (Hemming & Yellowlees, 1993; Sandyk & Awerbuch, 1988), and Alzheimer's disease (AD) (Di Marzo & Petrosino, 2007; Heimann et al., 2007), making it an attractive target for pharmaceutical development (Bomar & Galande, 2013). Some evidence indicated that administration of exogenous or release of endogenous cannabinoids have marked effects on learning and memory (Marsicano & Lafenetre, 2009; Wilson & Nicoll, 2002). The endocannabinoid system includes two cannabinoid receptors, cannabinoid 1 (CB1) and cannabinoid 2 (CB2) receptors. The CB1 receptor is expressed at a high level in central neurons, including neurons located in the hippocampus, cortex, and basolateral complex of the amygdala (BLA), regions that are crucial for learning and memory (Davies, Pertwee, & Riedel, 2002; Ikeda, Ikegami, Kai, & Kamei, 2015; Matsuda, Lolait, Brownstein, Young, & Bonner, 1990; Munro, Thomas, & Abu-Shaar, 1993). The CB2 receptor is primarily present in cells of the immune system, but it also has been identified throughout the central nervous system (CNS), where its expression level is lower than that of the CB1 receptor (Ashton, Friberg, Darlington, & Smith, 2006; Nunez et al., 2004; Onaivi et al., 2008; Stella, 2004; Van Sickle et al., 2005).

Hemopressin (Hp, PVNFKFLSH-OH) is a nonapeptide that was first isolated by Rioli et al. from rat brain in 2003 (Rioli et al., 2003). Hp was later shown to be a peptide antagonist or selective inverse peptide agonist of the CB1 receptor (Heimann et al., 2007). Hp displays significant non-opioid antinociceptive effects in rats (Dale et al., 2005; Heimann et al., 2007) and reduces food intake in a CB1-dependent manner in rats and mice (Dodd, Mancini, Lutz, & Luckman, 2010). Two N-terminally extended forms of Hp, (m)RVD-hemopressin(α) (RVD, RVDPVNFKLLSH-OH) and (m)VD-hemopressin(α) (VD, VDPVNFKLLSH-OH) were identified by Gomes et al. through peptidomics analyses of mouse brain extracts (Gomes et al., 2009). RVD and VD also bind to the CB1 receptor, but in contrast to Hp, these two peptides function as CB1 receptor peptide agonists. A previous study in this laboratory indicated that VD exerts central antinociception through the CB1 receptor and that it suppresses locomotor activity (Han, Fang, et al., 2014). However, little information is available on the central functions of RVD.

There is a growing body of evidence suggesting that cannabinoid play an important role in learning and memory, including both short-term and long-term memory (Campolongo et al., 2013; Marsicano & Lafenetre, 2009; Wilson & Nicoll, 2002). However, the effects of Hp, RVD and VD on memory are still unknown.

Novel object recognition (NOR) and object location recognition (OLR) tasks are animal behavioral models using to evaluate memory-affecting effect of drug, which were non-aversive learning paradigms based on the animals' spontaneous preference for a novel object and the object's novel location, respectively (Han et al., 2013). In present study, we investigated whether Hp, RVD and VD have roles in memory during the performance of NOR and OLR tasks. We found that in normal young mice, administration of Hp led to improvement of memory but that RVD and VD induced impairment of memory in the tasks. By studying the effects of drug combinations of Hp and RVD or VD in the tasks, we found that Hp and the other peptides inhibited the effect of each other. We also used CB1 receptor small molecular ligands, agonist WIN55, 212-2 and antagonist AM251 in this study, we found WIN55, 212-2 inhibited the effect of Hp and AM251 prevented the effects of RVD and VD.

The endocannabinoid system plays a role in AD, and memory impairment is one of the classical symptoms of AD (Di Marzo & Petrosino, 2007; Heimann et al., 2007). Intracerebroventricular (i.c.v.) amyloid-β (1–42) ($A\beta_{1-42}$) impairs cognitive functions in rats and mice and is used as a model of AD (Chacon, Barria, Soto, & Inestrosa, 2004; Dao, Zagaar, Salim, Eriksen, & Alkadhi, 2014; Nitta, Itoh, Hasegawa, & Nabeshima, 1994). We previously reported that i.c.v. $A\beta_{1-42}$ induced impairment of memory in mice NOR and OLR tasks (Han et al., 2013). Here, we investigated whether Hp, RVD and VD could alleviate amnesia induced by $A\beta_{1-42}$. We found Hp had no effect on memory in the AD model mice. In contrast to their effects in normal young mice, RVD and VD showed memory-improving effects on memory in the AD model mice, and these effects could be inhibited by Hp and AM251.

Administration of CB1/CB2 receptor agonists has been reported to affect activity in animals (Chaperon & Thiebot, 1999), exercise could improve memory function and reverse memory impairment in humans and in animals (Dief, Samy, & Dowedar, 2015; Erickson et al., 2011; Kim, Kim, Kim, Kim, & Seo, 2015). In order to investigate whether the effects of CB1 peptide receptor Hp, RVD and VD on memory in mice were through the exercise-influencing effect, we examined it in open field, and we found that none of the three drugs, when administered at doses that affect memory, influenced the locomotor activity of mice.

To sum up, this study indicated that the CB1 receptor peptide ligands Hp, RVD and VD might through inhibiting or activating the receptor activities to influenced memory performance in normal mice and AD model mice, and these memory-affecting effects of Hp, RVD and VD were not related to the locomotor activity of the animals.

2. Materials and methods

2.1. Animals

Male mice (Kunming strain of Swiss) were bought from the Experimental Animal Center of Lanzhou University, China. Animals were housed in cages (6–8 animals/cages) in an animal room at 22 ± 2 °C on a 12-h light/dark cycle with free access to food and tap water. The experimental protocols used in this study were approved by the Ethics Committee of Lanzhou University, China.

2.2. Surgical procedures

Surgical implantation of a cannula into the lateral ventricle was described in our previous report (Zhang et al., 2015). Mouse (20–24 g, 5–6 weeks) was placed in a stereotaxic frame (Leica, Germany) after being anesthetized with sodium pentobarbital (75 mg/kg, Sigma-Aldrich, USA). The skull was exposed, and the incisor bar was regulated to maintain the height of bregma and λ at the same point. In accordance with the atlas of Paxinos and Franklin (Paxinos, Franklin, & Franklin, 2001), 9 mm 26-gauge stainless-steel guide cannulas were implanted over the lateral ventricle (0.5 mm posterior to bregma, 1.0 mm lateral to the midline, and 2.0 mm ventral to skull surface) and fixed with dental cement. The mice placed in warmed cages until they recovered fully from anesthesia. Then, the mice were caged individually and maintained over a period of 5–7 days.

2.3. NOR and OLR tasks

The NOR and OLR tasks have been described in detail by Okamura et al. (2011). Each mouse was tested in its home cage in a dimly lit, silent room. The general procedure included two sessions: a training phase and a test phase, with the test phase conducted 1 day or 3 days after the training phase. All objects were made of plastic or glass and were of similar size (4–5 cm high) but of different colors and shapes; each object had several copies for using interchangeably. The objects were cleaned completely between trials to make sure no olfactory cues were present. Explo-