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Research report

Intrahippocampal injection of Cortistatin-14 impairs recognition memory consolidation in mice through activation of sst_2, ghrelin and $GABA_{A/B}$ receptors

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ABSTRACT

Cortistatin-14 (CST-14), a neuropeptide related to somatostatin, is primarily localized within the cortex and hippocampus. In the hippocampus, CST-14 inhibits CA1 neuronal pyramidal cell firing and co-exists with GABA. However, its role in cognitive is still not clarified. The first aim of our study was to elucidate the role of CST-14 signaling in consolidation and reconsolidation of recognition memory in mice, using novel object recognition task. The results showed that central CST-14 induced in impairment of long-term and short-term recognition memory, indicating memory consolidation impairment effect. Similarly, we found that CST-14 did not impaired long-term and short-term reconsolidation recognition memory. To further investigate the underlying mechanisms of CST-14 in memory process, we used cyclo-somatostatin (c-SOM, a selective sst_{1-5} receptor antagonist), cyanamid154806 (a selective sst_2 receptor antagonist), ODN-8 (a high affinity and selectivity compound for sst_3 receptor), [D-Lys_3]GHRP-6 (a selective ghrelin receptor antagonist), picrotoxin (PTX, a $GABA_A$ receptor antagonist), and sacolfen (a $GABA_B$ receptor antagonist) to research its effects in recognition. Our results firstly indicated that the memory-impairing effects of CST-14 were significantly reversed by c-SOM, cyanamid154806, [D-Lys_3] GHRP-6, PTX and sacolfen, but not ODN-8, suggesting that the blockage of recognition memory consolidation induced by CST-14 involves sst_2, ghrelin and GABA system. The present study provides a potential strategy to regulate memory processes, providing new evidence that reconsolidation is not a simple reiteration of consolidation.

1. Introduction

Cortistatin (CST) is a recently discovered cyclic neuropeptide which is widely distributed in the peripheral tissues and Central Nervous System (CNS), especially in the cortex and hippocampus (de Lecea, 2008). Neuropeptide CST exhibits several biologically active forms, including CST-29, CST-17 and CST-14, and is extremely conserved across multi-species including humans, mice or rat. CST-14, one of the endogenous isoforms, consists of 14 amino acids and the sequence is P-c[CKNFFWKTFSSC]-K (de Lecea, 2008; Gahete et al., 2010). A large number of physiological and pathophysiological roles of CST, including the production or formation of tumors (Cassoni et al., 2002, 2006; Padova et al., 2008), inflammation (Gonzalez-Rey et al., 2006; Morell et al., 2014; Zhang et al., 2015a, 2015b), sleep and memory have been reported (Mendezdiaz, 2004; Rubio et al., 2008; Tallent et al., 2005).

CST-14 shows high structural similarity to somatostatin-14 (SRIF, AG-c[CKNFFWKTFTSC]), which shares 11 of 14 residues with SRIF, including two cysteines that is forming a cyclic peptide and the amino acid sequences (FWKT) that is crucial for SRIF binding to its receptors (Gahete et al., 2010; Markovics et al., 2012). Thus, CST binds to all five cloned SRIF receptors (sst_1–sst_5), and shares many pharmacological and functional properties of the SST, including the depression of neuronal activity and inhibition of cell proliferation (Cassoni et al., 2002, 2006; Spier and de Lecea, 2000). However, CST also has many properties distinct from SRIF, including induction of slow-wave sleep (Mendezdiaz, 2004), reduction of locomotor activity and anti-inflammatory effect (Gonzalez-Rey et al., 2006; Spier and de Lecea, 2000). In addition to $SSTR_{1-5}$, CST can also bind to other receptors, including the growth hormone ghrelin receptor and the MAS-related gene receptor ($MrgX_2$), but not SRIF (Cassoni et al., 2006; Robas et al., 2003).

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SRIF and its receptor have been reported to be involved in regulation of learning and memory processes such as sst_2, sst_3, and sst_4 (Adori et al., 2015; Gahete et al., 2010; Gastambide et al., 2009, 2010). CST-14 is strongly expressed in the learning-and-memory-associated brain regions, including hippocampus and cerebral cortex, suggesting CST-14 may be participated in the regulation of memory processes (Borbely et al., 2013; de Lecea, 2008). This possibility is also supported by the following evidences. First, CST-14 restrained neuronal firing of hippocampal CA1 neurons and blocked acetylcholine induced changes on evoked paired-pulse stimulation of CA1 neurons (Mendez-Diaz et al., 2005; Mendezdiaz, 2004). Second, it also alters the production of cAMP in vitro, which plays an important roles in learning and memory (Mendez-Diaz et al., 2005). Third, Flood et al. consider that CST-14 is co-localized with γ-aminobutyric acid (GABA) in the hippocampus and cortex (Flood et al., 1997). Most recently, the literature reported that CST-14 inhibits neuronal excitability in hippocampal slices or in the hippocampus of anesthetized rats, and CST-14 injected into the hippocampus of rats and mice impairs memory consolidation in a passive avoidance paradigm (Mendez-Diaz et al., 2005; Sanchez-Alavez et al., 2000). According to these reasons, we determined to research the effect of its recognition, especially in object recognition memory.

To further investigate the role of CST in novel object recognition task (NOR) both in short-term memory (STM) and long-term memory (LTM) in mice, which is a non-aversive learning paradigm, avoiding the potential confounds of using differential rewards or punishments, which is based on animals' spontaneous preference for the novel object, and is widely used to evaluate the effects of various drugs in learning and memory processes (Antunes and Biala, 2012). Meanwhile, we observed that what possible receptor(s) are involved in the actions of CST-14. For this purpose, we used cyclosomatostatin (c-SOM, a selective $sst_{1\text{-}5}$ receptor antagonist) (Ionov and Pushinskaya, 2013), cyanamid154806 (a selective sst_2 receptor antagonist), ODN-8 (a high affinity and selectivity compound for the human sst_3 somatostatin receptor subtype transfected in CCL39 cells) (Reubi et al., 2000), [D-Lys_3]GHRP-6 (a selective ghrelin receptor antagonist) (Patel et al., 2012), picrotoxin (PTX, a $GABA_A$ receptor antagonist) (Das et al., 2003), and sacolfen (a $GABA_B$ receptor antagonist) to research the effects of it in recognition (Li et al., 2016).

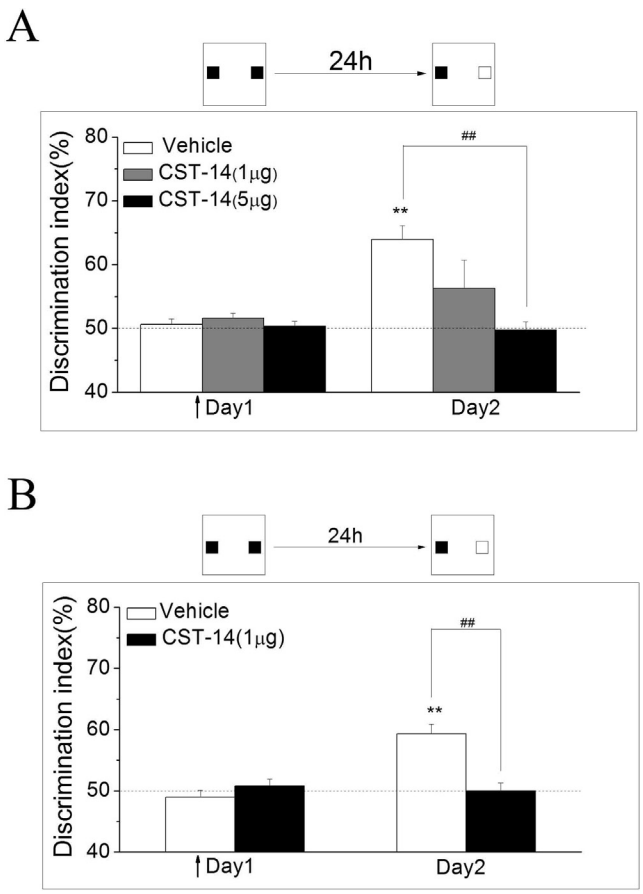

Fig. 1. The effect of CST-14 on long-term memory (LTM) consolidation. (A) CST-14 (1 and 5 μg) injected into the lateral ventricles (i.c.v) immediately when tested 1 day after training dose-dependently blocked LTM consolidation. (B) CST-14 (0.5 μg/side) infused into the bilateral hippocampus immediately when tested 1 day after training also blocked LTM consolidation. The dashed line indicates 50% chance level. $^{\#\#}p < 0.01$ compared with vehicle; $^{**}p < 0.01$ compared with chance level. Vertical lines represent SEM.

2. Results

2.1. The role of CST-14 in LTM

In the training phase, when total exploration time (TET) was 20 s and memory was examined after 24 h, vehicle-treated mice showed good memory performance. While CST-14 (5 μg, i.c.v.)-treated mice failed to make a distinction between the novel object and the familiar one ($p < 0.01$) ($F(2,18) = 5.463$ for vehicle vs CST-14, Fig. 1A), indicating that CST-14 impairs object recognition memory. Likewise, CST-14 (1 μg) infused into the bilateral hippocampus also disrupts object recognition memory ($p < 0.01$) ($F(1,11) = 4.856$ for vehicle vs CST-14, Fig. 1B). No significant difference was detected between treatments in the duration of the training phase, as well as in the duration and TET of the test phase (Table 1).

2.2. The role of CST-14 in STM

When tested 30 min and 60 min, i.c.v. administration of vehicle or CST-14 (5 μg) showed significant preference for the novel objects, as indicated by the discrimination index (DI) of these groups was significantly higher than 50% chance level. And when tested 90 min after training, CST-14 (5 μg, i.c.v.) impairs STM formation ($F(1,11) = 4.914$; $p < 0.01$ for vehicle vs CST-14; Fig. 2A). Similarly, when tested 90 min after training, CST-14 (1 μg) infused into the bilateral hippocampus also impairs object recognition memory ($p < 0.01$ for vehicle vs CST-14, Fig. 2B).

2.3. The role of CST-14 in reconsolidation of recognition memory

In training phase (day 1), the DI of each group was almost identical to 50% (Fig. 3A, B). On day 2, mice were brief reexposed to the familiar objects to reactivate the memory trace. During the retrieval phase, both vehicle- and CST-14-treated mice showed no preference for the two familiar objects (Fig. 3A, B). Whereas, in STM, 1.5 h after reactivation (day 2, 1.5 h), the DI of vehicle- and CST-14-treated mice was similar and significantly higher than the chance level (Fig. 3A). In LTM, the training phase and retrieval phase were similar with STM, whereas, 24 h after reactivation (day 3), both vehicle- and CST-14-treated mice showed a significantly higher DI (Fig. 3B). Taken together, these data indicate that CST-14 did not block long-term and short-term recognition memory after retrieval, suggesting CST-14 did not disrupt the reconsolidation of recognition memory (Johansen et al., 2011).

Throughout the experiment, there was no significant difference in the total exploration time between vehicle- and CST-14-treated mice (Table 2).