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Original Article

Kisspeptin-13 ameliorates memory impairment induced by streptozotocin in male rats via cholinergic system

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Abstract

Introduction: Kisspeptin-13 (KP-13) is a novel endogenous factor, increases synaptic transmission and is involved in several behavioral functions such as anxiety, locomotion, epilepsy and avoidance learning. However, the role of this peptide on cognition has not been well clarified yet. Here we studied the effect of kisspeptin-13 pretreatment on spatial learning and also interaction with cholinergic and adrenergic systems.

Methods: Eighty adult male Wistar rats were divided into 10 groups: saline + saline; saline + STZ; KP-13 + STZ; propranolol + STZ; prazosin + STZ; atropine + STZ; saline + KP-13 + STZ; propranolol + KP-13 + STZ; prazosin + KP-13 + STZ; atropine + KP-13+ STZ. Streptozotocin (STZ) (3mg/Kg) was administrated intracerebroventricularly (i.c.v), kisspeptin-13 was infused (1µg/2µl, i.c.v) 30 minutes before STZ and antagonists were infused (i.p) 30 minutes before kisspeptin-13. Memory performance was measured 14 days after STZ injection using Morris Water Maze (MWM) consisting of 4 blocks and one probe tests.

Results: Pretreatment with kisspeptin-13 ameliorated acquisition ($p = 0.001$) and retrieval of memory impaired by STZ ($P = 0.011$). Moreover, we found that injection of atropine, but not propranolol or prazocin was able to reverse the memory enhancement caused by kisspeptin-13 ($P = 0.037$).

Conclusion: Our findings indicate that facilitatory action of kisspeptin-13 on the spatial learning and memory in STZ-induced Alzheimer's is mediated, at least in part, through cholinergic systems.

Keywords:
kisspeptin;
Spatial memory;
Adrenergic system;
Cholinergic system;
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Introduction

Alzheimer's disease (AD) is a human neurodegenerative disorder associated with a progressive loss of neuronal synapse and cognition (Selkoe, 2001) with high incidence worldwide (Qiu et al., 2009). Considering the growing incidence of AD, finding new therapeutic strategies to combat cognitive deficits in AD is of great importance.

Kisspeptin-13 (KP-13) is a neuropeptide encoded by KISS1 gene (Lee et al., 1996), playing diverse roles in brain functions such as: puberty (Shahab et al., 2005), locomotor activity (Csabafi et al., 2013), feeding (Kim et al., 2010) and anxiety (Csabafi et al., 2013). KP-13, distinct from other peptides, is dynamically regulated by neuronal activity and

increases synaptic transmission over a long time (Arai, 2009). Receptor for KP-13, GPR54 (G- protein coupled receptor-54), is widely expressed in the brain regions related to the learning and memory, including hippocampus and amygdala (Arai and Orwig, 2008), but there is yet little information about the function of this neuropeptide in these areas. Interestingly, it is shown that kisspeptin enhances excitatory synaptic transmission in the dentate gyrus of the hippocampus and that neuronal activity leads to up regulation of *KISS1* expression in order to sustain basal levels of Brain derived neurotrophic factor (BDNF) (Arai and Orwig, 2008; Binder, 2007). Telegdy and his colleagues have reported for a first time that i.c.v. injection of KP-13 could facilitate avoidance learning in a passive avoidance paradigm (Telegdy and Adamik, 2013). In addition, KP-13 has been shown to prevent Amyloid-ß (Aß) peptide neurotoxicity in vitro (Milton et al., 2012).

On the other hand, it has been well known that different neurotransmitters play different roles in learning and memory. For example, injection of noradrenaline into the hippocampus and entorhinal cortex enhances memory formation (Izquierdo et al., 2000). The adrenergic receptors of α1, α2, and β-receptors (each with three subtypes have distinct roles in learning and memory formation (Bylund et al., 1992). The α1 receptors are mainly postsynaptic, activate phospholipase c and Ca^{2+} signaling pathways and play important role in learning and memory (Stuchlik et al., 2009; Birnbaum et al., 2004). On the other hand, propranolol infusion in basolateral amygdala revealed that β adrenergic receptors are also important in memory storage (Liang et al., 1986). In addition, cholinergic transmission in target areas of the brain, is connected with impairments of learning and memory (Schliebs and Arendt, 2011; McNamara and Skelton, 1993; D'Hooge and De Deyn, 2001; Tinsley et al., 2011). In the forebrain, the m1, m2, and m4 receptors are the most abundant subtypes of cholinergic receptors (Flynn et al, 1995) and, m2 is the predominant subtype in the basal forebrain which is involved in learning and memory process (Levey, 1996).

Considering the expression of kisspeptin and its receptor in the regions involved in the learning and memory formation, and also evidences indicating the role of kisspeptin on behavioral regulations, we hypothesized that this neuropeptide might have positive interactions with brain adrenergic and cholinergic systems in regulation of memory engram. Therefore, the purpose of the present study was to examine the effects of KP-13 on spatial memory and also interactive effect of this neuropeptide with adrenergic and cholinergic systems in an AD model of rats. In order to approach this, AD model was induced by intracerebroventricular (i.c.v) infusion of streptozotocin which has been wildly used as a model of sporadic dementia of AD (Sharma and Gupta, 2001; Salkovic et al., 2006; Salkovic et al., 2011; Lester-Coll et al., 2006; Agrawal et al., 2011; Lannert and Hoyer, 1998). Kisspeptin was administered as pretreatment with respect to various mechanisms of memory impairment induced by STZ.

Materials and methods

Animals

Eighty adult male wistar rats weighing 200–240 g were kept in a room with 12/12 h light/dark cycle (lights on 7:00 h) and temperature of 22 ± 2 $^{\circ C}$. The following groups were included in the study (8 animals per each group): saline + saline; saline + STZ; KP-13 + STZ; propranolol + STZ; prazosin + STZ; atropine + STZ; saline + KP-13 + STZ; propranolol + KP-13 + STZ; prazosin + KP-13 + STZ; atropine + KP-13+ STZ. The study was approved by the ethical committee of Guilan University of Medical Sciences.

Surgery

After deep anesthesia with (75 mg/ kg of ketamine and 5 mg/kg of xylazine), animals were placed in stereotaxic apparatus (Stoelting, USA) and were bilaterally implanted with 22- gauge guide steel cannula into the ventricle according to the coordination's: AP: − 0.8; ML: ± 1.5; and DV: -3.4. (Paxinos and Watson, 2007).

Drugs & treatments

One week after the recovery period, STZ (3 mg/kg) dissolved in 0.9% saline was injected in a volume of 5µl into each lateral cerebral ventricle using Hamilton micro syringe pump for 3 consecutive days. KP-13 (1 µg/2 µl) was dissolved in saline and then administered i.c.v. 30 minutes prior to STZ for 3 days. Propranolol (10 mg/kg), prazosin (2 mg/kg) and

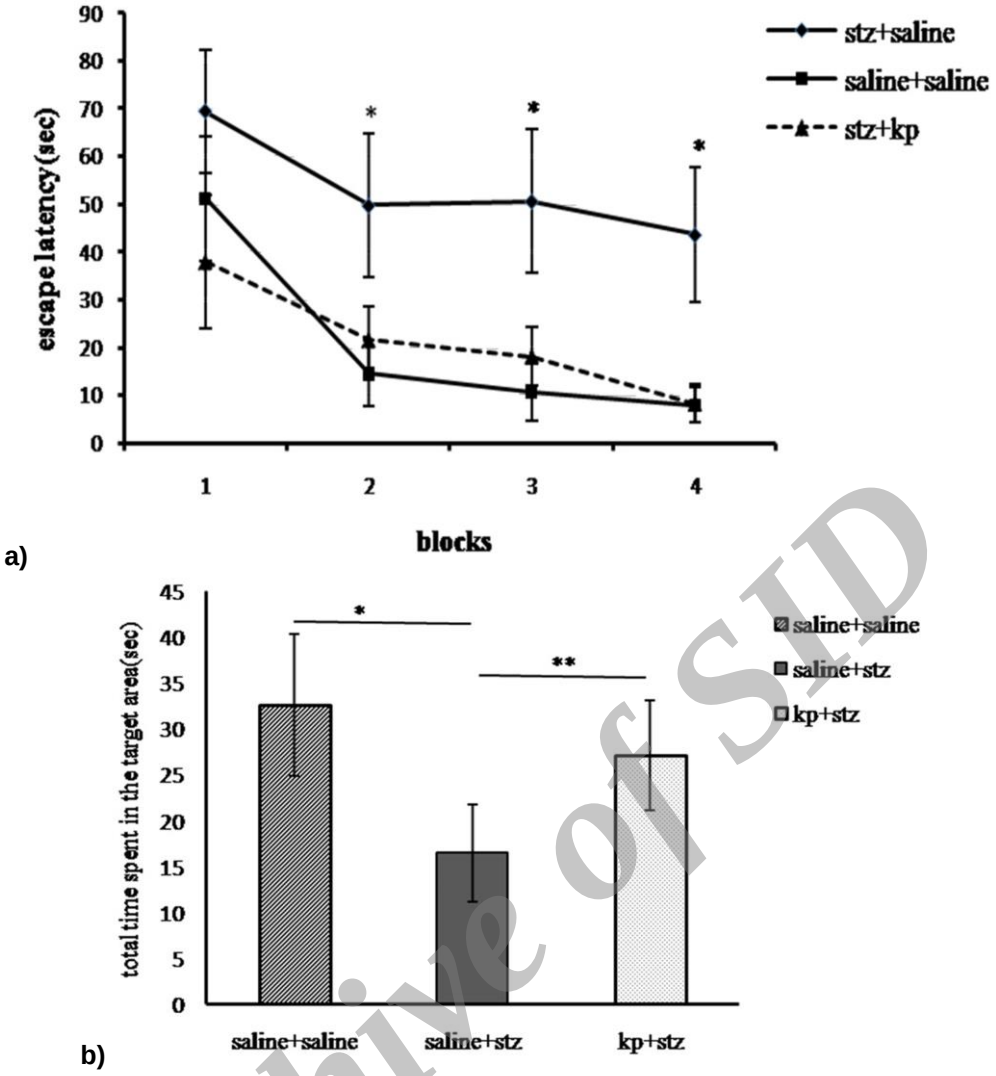


Fig.1. (a) The effect of STZ, KP and saline on acquisition of spatial memory in MWM. Data are expressed as means ± SD. Escape latency time in the 2nd, 3rd and 4th days in the control group were significantly lower than STZ group ($P < 0.0001$). STZ+ KP rats learned to find the platform more rapidly than STZ (* $P = 0.001$),
(n=8 per each group). (b) Total time spent in the target quadrant was longer in the KP receiving group than STZ ones. Data are expressed as means ± SD (* $P < 0.001$), ** $p< 0.01$). Asterisks indicates significance difference in each group compared with STZ group. (n=8 per each group)

atropine (2 mg/kg), were dissolved in distilled water and were administered intraperitoneally (i.p.) 30 minutes before KP-13. The antagonists doses used in the present study were not effective per se on memory and were chosen according to the previous studies (Puumala et al, 1998; Decker et al, 1990; Telegdy and Adamik 2002).

Behavioral test

After 2 weeks of surgery, spatial learning and memory of animals were assessed using Morris water maze (Morris, 1981). The apparatus was consisted of a circular water tank (146 cm in diameter and 60 cm high) with a rectangular platform (10 cm) at a fixed position in the target quadrant, 2 cm below the water level .The water temperature maintained at 26°C. At the start of the experiment, rats were individually placed on the platform for 20 s in order to explore the environment and to find the cues placed on the walls. The procedure was consisted of 4-day acquisition and one day of probe memory test performed on day 5, each trial having a cutoff time of 90 s. Also visible test was carried out after the probe test to examine the animal's vision. The time spent searching for the platform (which had been previously removed) within the target quadrant, and velocity of swimming were recorded using camera and Ethovision tracking system (Noldus, Netherland).

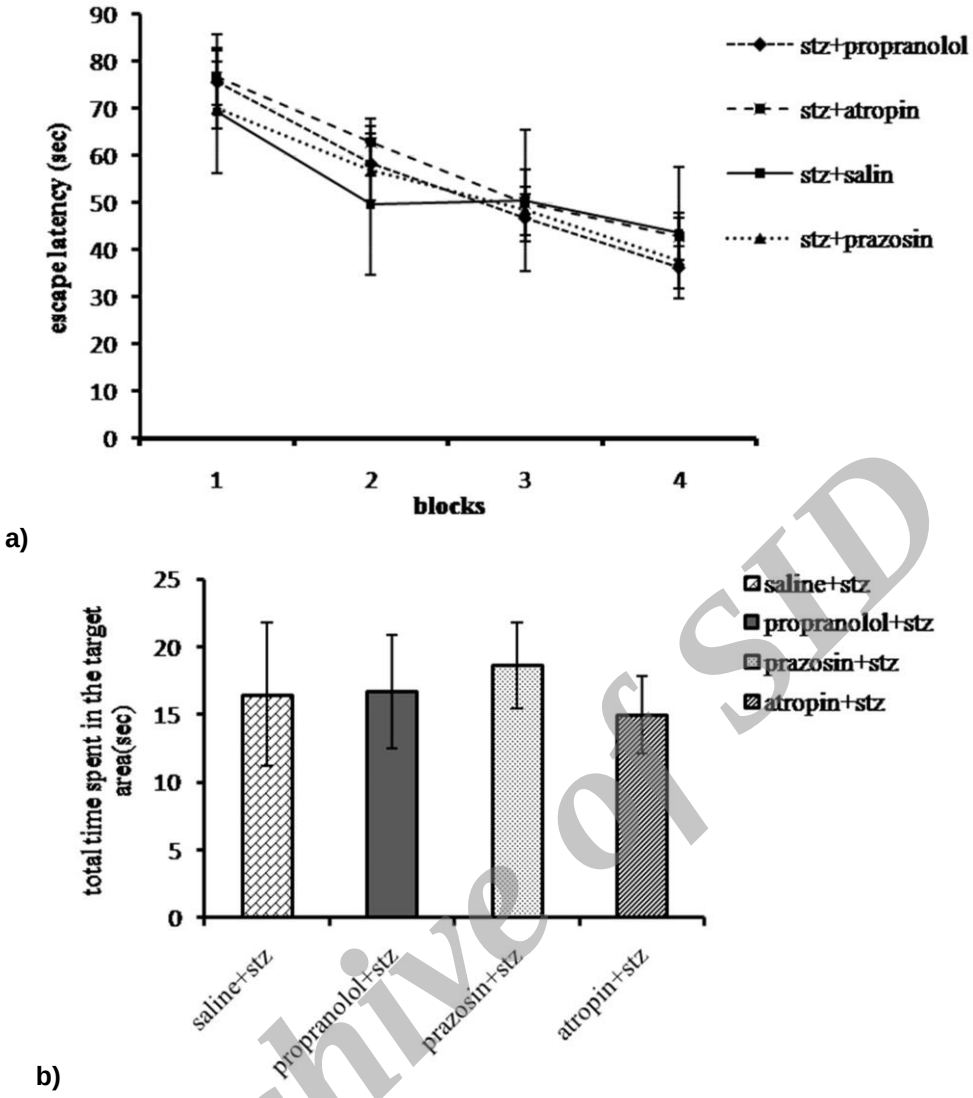


Fig.2. (a). The effect of propranolol, prazosin and atropine, on escape latency time during acquisition in STZ-induced memory deficits. Neither of antagonists showed significant change in acquisition measured by escape latency, (n=8 per each group). (b). The effect of propranolol, prazosin and atropine, on total time spent in the target area in STZ-induced memory deficits. Data are expressed as means ± SD. Neither of antagonists showed significant change in retrieval of memory measured by TTS (n=8 per each group).

Statistical analysis

Repeated measure and one-way ANOVA with Tukey's posttest were used for comparing between group differences and level of significance was P<0.05 in all statistical evaluations. Data were analyzed in SPSS version 19, and expressed as means ± SD.

Results

During the training sessions all groups showed significant trial effects in the learning procedure F (5, 768) = 33.46, P < 0.001. Escape latency time (ELT) in the 2nd, 3rd and 4th day in the STZ + saline group was significantly increased, but total time spent in the target quadrant was decreased compared with control group P< 0.001 (Fig.1a, Fig.1b, Fig.4b). Since there were no significant difference in swimming speed (F (5, 768) = 0.68; p = 0.723), the time latency to find the platform and total time spent in the target quadrant (TTS) were used as indicators of learning performance. STZ + KP rats learned to find the platform more rapidly than STZ + saline (F = 36.799, P = 0.001), (Fig 1a, Fig. 4b). There was significant difference in the total time spent in target quadrant between STZ + KP and STZ + saline groups (27 ±

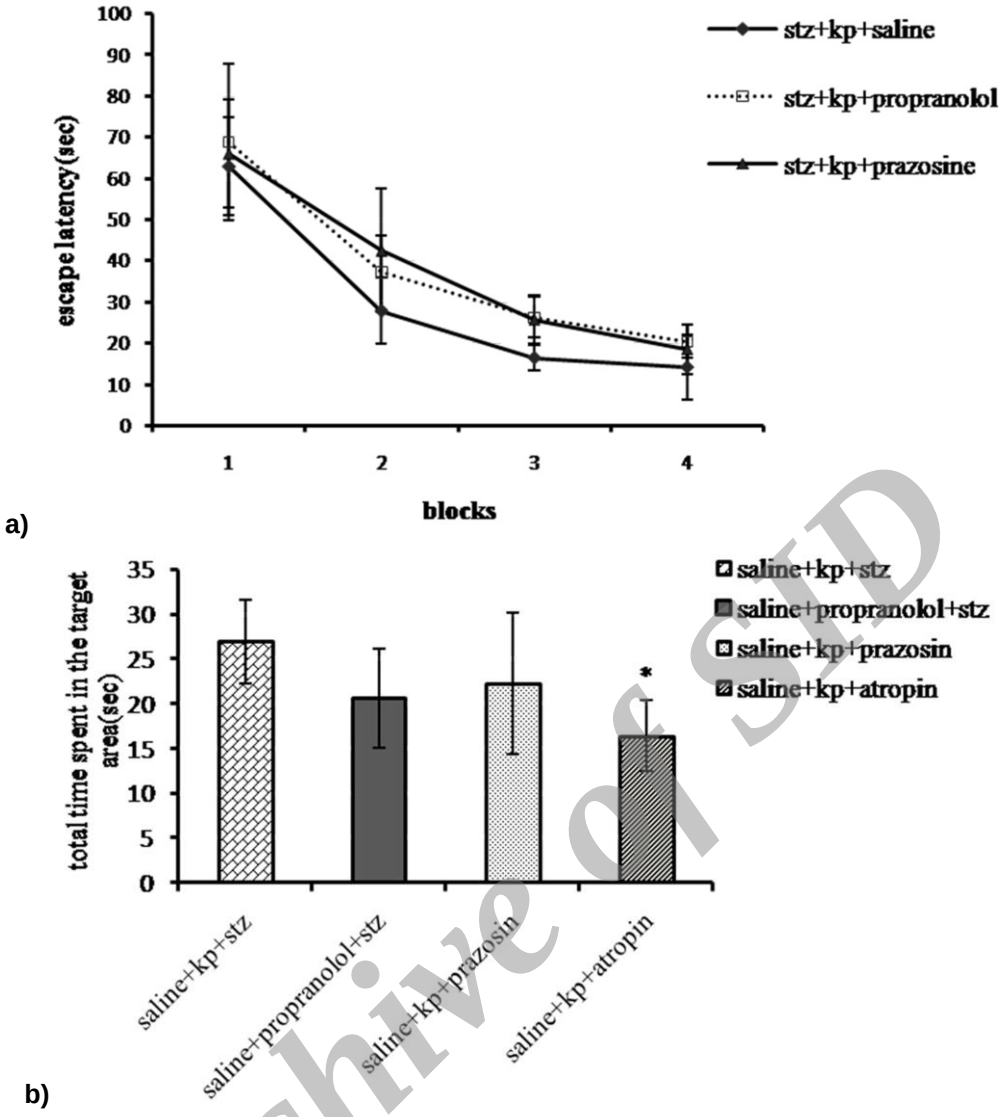


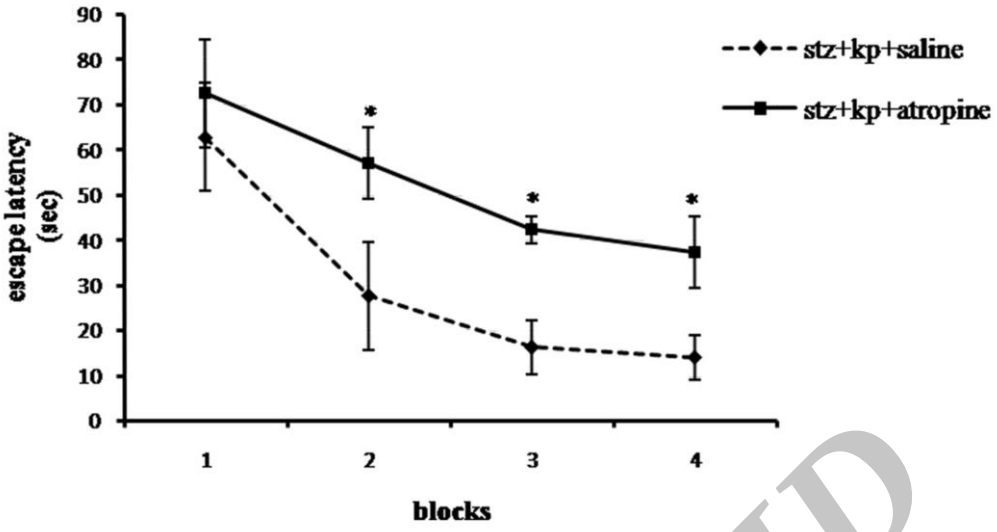
Fig.3. (a). The effect of propranolol, prazosin and atropine, on escape latency time during acquisition in STZ-induced memory deficits. Neither of antagonists showed significant change in acquisition measured by escape latency, (n=8 per each group). (b). The effect of propranolol, prazosin and atropine, on total time spent in the target area in STZ-induced memory deficits. Data are expressed as means ± SD. Neither of antagonists showed significant change in retrieval of memory measured by TTS (n=8 per each group).

6.01 versus 16 ± 5.2 s, P < 0.001), (Fig.1b).

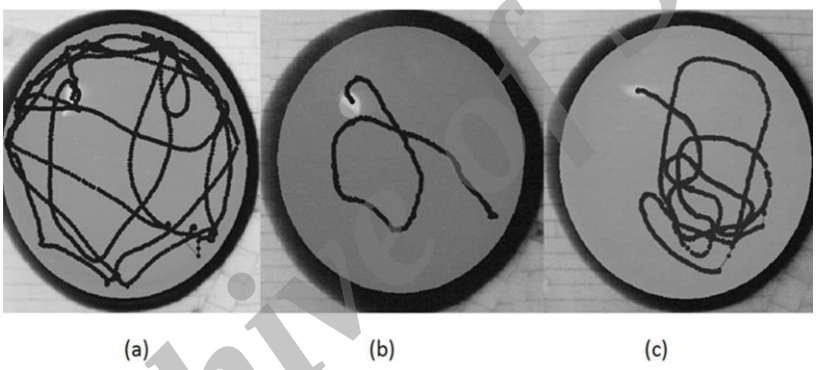
Tukey's post hoc test showed that the pretreatment with atropin prior to KP administration significantly decreased total time spent in the target quadrant compared with saline group (16.4 ± 3.94 versus, 26.9 ± 4.68 s, P = 0.037). Infusion of propranolol, prazosin and atropine in appropriate doses, 30 minutes before STZ, did not cause any significant effect per se either on acquisition or retrieval of memory compared with STZ + saline (Fig. 2a, .2b). Although adrenergic antagonists, propranolol and prazosin slightly reduced the memory improvement by kisspeptin, it was not statistically significant P> 0.05 (Fig. 3a). As Fig 4a shows, only atropine significantly prevented the positive effect of kisspeptin on acquisition (p=0.001, Fig.4a) and retrieval of memory (p=0.037, Fig. 4b).

Discussion

Our study shows that i.c.v. injection of STZ, significantly impaired acquisition and retrieval of spatial memory which is in line with the previous studies (Yazdani et al, 2015; Sharma and Gupta, 2001; Salkovic et al., 2006; Salkovic et al., 2011; Lester-Coll et al., 2006; Agrawal et al., 2011). STZ induces memory impairment via different mechanisms such as: malfunction in brain glucose



a)



b)

Fig.4. (a). The pretreatment effect of atropine on the acquisition process of spatial memory in MWM before kisspeptin administration. Data are expressed as means ± SD. Atropine significantly prevented the positive effect of kisspeptin on the acquisition measured by ELT (*P < 0.001, n=8 per each group). (b). Example of Ethovision tracking from probe trial (90s). (a): saline + STZ; (b): Kisspeptine + STZ, (c) Atropin+kisspeptine+STZ

metabolism (Lannert and Hoyer, 1998; Labak et al., 2010), elevation of oxidative stress (Sharma and Gupta, 2001, Ishrat et al., 2009) and disruption of cholinergic transmission (Ishrat et al., 2009; Ishrat et al., 2006).

The main finding of this study is that KP-13 infusion 30 minutes before STZ successfully ameliorated the cognitive deficits, and this effect was reversed by pretreatment of atropine. It has been previously reported that KP-13 plays a modulatory role in various physiological processes such as reproduction (D'Anglemont de Tassigny et al., 2010), feeding (Kim et al., 2010), depression (Tanaka et al., 2013) and epilepsy (Arai, 2009). Facilitatory effect of KP-13 on learning and memory in our study is in line with the previous studies (Yazdani et al, 2015; Telegdy and Adamik, 2013). Telegdy and Adamik have reported that, the effects of KP-13 on passive avoidance learning and consolidation are mediated through interactions of the a_2-adrenergic, 5-HT2 serotonergic, beta-adrenergic, cholinergic and GABA-A receptors (Telegdy and Adamik, 2013). Our results in the present study contradict their findings on the adrenergic, but are in agreement with the involvement of cholinergic system.

There is no doubt about major role of acetylcholine (Ach) in the regulation of cognitive functions (Blokland, 1995). Disturbances in cholinergic transmission in the prefrontal cortex, hippocampus, striatum or amygdala, are connected with

impairments of learning and memory (Schliebs and Arendt, 2011).

To explain how KP-13 could significantly prevent the STZ –impaired memory, and this effect was reversed by atropine as well, we can postulate that, kisspeptin might enhance the Ach responses to compensate for reduction in the Ach level induced by STZ (Ishrat et al., 2006; Khan et al., 2 012b; Tota et al., 2011; Grunblatt et al., 2007). It has been demonstrated that i.c.v injection of STZ disturbs glucose energy metabolism by inhibiting the insulin receptor system (Lannert and Hoyer, 1998) and decreasing the activity of ChAT in the hippocampus (Blokland and Jolles, 1993). Previous studies suggest that a period of 7 days is enough to increase acetyl cholinesterase level (AChE) upon i.c.v STZ administration (Tota et al., 2010; 2011). Therefore cognition deficit tested in our study, 14 days following STZ injection, could be partially related to cholinergic disturbances. In addition, the impairment in insulin signaling following STZ, reduces cholineacetyltransferase (ChAT) and increases oxidative stress as well (Lester-Coll et al., 2006).

In the present study, KP-13 effects were abolished by muscarinic antagonist atropine. Regarding the fact that the M1, and to a lesser extent M2 cholinergic receptors are considered as the most highly expressed muscarinic receptors in the hippocampus (Kruk et al., 2011; Binder, 2007), it is assumed that KP-13 might upregulate M1, and increases Ca^{2+} signaling (D'Anglemont de Tassigny et al., 2010), or down regulate M2 to prevent K^{+} efflux as reported in the hypothalamus before (D'Anglemont de Tassigny et al., 2010) to induce excitatory synaptic activity. However, we cannot rule out the direct effect of kisspeptin via its own receptor to induce an additive effect with cholinergic system through crosstalk in signaling pathways. As Ji,ang, et al., 2015 suggested that kisspeptin binds to its receptor GPR54, and activates different signaling cascades, such as phospholipase C, intracellular Ca^{2+}, protein kinase C, mitogen activated protein kinases (MAPK) and ERK (Hetherington et al., 1994; Illario et al., 2003). Elevations in ERKs signaling have direct effects on neuronal function via phosphorylating proteins such as potassium channels, synapsin and NMDA receptors (Adams et al., 2000; Lewis et al., 1998; Matsubara et al., 1996; Slack et al., 2004). On the other hand, hippocampal kisspeptin/GPR54 system has unusual and complex properties, in a way that, it utilizes signaling systems that are usually coupled with trophic factors such as BDNF in a positive feedback pattern, to potentiate each other. Elevation in super oxide dismutase and catalase; two antioxidant defense systems could be valuable per se, to reduce oxidative damage induced by STZ (Khan et al., 2012a; D'Anglemont de Tassigny et al., 2010).

Therefore, KP-13 improves learning and memory deficits may be through enhancing cholinergic responses, or reducing oxidative damages by increasing the level of antioxidant defense system of the brain. Taken together, these findings are in complete agreement with the literatures suggesting that kisspeptin may play a more general role in behavioral regulation. However, whether or not kisspeptin and acetylcholine are colocalized in the hippocampus and which subgroups of muscarinic receptors exactly mediate the kisspeptine synaptic transmission remain to be elucidated.

Conclusion

In conclusion, our study indicates that centrally injected KP-13 facilitates spatial learning and memory in STZ-induced Alzheimer's at least in part through cholinergic receptor systems. From clinical point of view, KP-13 as a novel endogenous neuropeptide has physiological role in ameliorating cognitive deficit and might be considered as a therapeutic peptide in Alzheimer's disease.

Acknowledgment

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Conflict of Interest

The authors declare no conflict of interest in this study.

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