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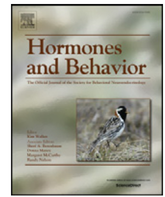

Steroid sulfatase inhibitor DU-14 protects spatial memory and synaptic plasticity from disruption by amyloid β protein in male rats

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ABSTRACT

Alzheimer's disease (AD) is an age-related mental disorder characterized by progressive loss of memory and multiple cognitive impairments. The overproduction and aggregation of Amyloid β protein (Aβ) in the brain, especially in the hippocampus, are closely involved in the memory loss in the patients with AD. Accumulating evidence indicates that the Aβ-induced imbalance of dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEAS) in the brain plays an important role in the AD pathogenesis and progression. The level of DHEA is elevated, while DHEAS is dramatically decreased in the AD brain. The present study tried to restore the balance between DHEA and DHEAS by using a non-steroidal sulfatase inhibitor DU-14, which increases endogenous DHEAS through preventing DHEAS converted back into DHEA. We found that: (1) DU-14 effectively attenuated the $A\beta_{1-42}$-induced cognitive deficits in spatial learning and memory of rats in Morris water maze test; (2) DU-14 prevented $A\beta_{1-42}$-induced decrease in the cholinergic theta rhythm of hippocampal local field potential (LFP) in the CA1 region; (3) DU-14 protected hippocampal synaptic plasticity against $A\beta_{1-42}$-induced suppression of long term potentiation (LTP). These results provide evidence for the neuroprotective action of DU-14 against neurotoxic Aβ, suggesting that u*p*-regulation of endogenous DHEAS by DU-14 could be beneficial to the alleviation of Aβ-induced impairments in spatial memory and synaptic plasticity.

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Introduction

Alzheimer's disease (AD), the most common form of dementia, is characterized by memory loss and multiple cognitive impairments (Uzun et al., 2011). The estimated number of AD patients is approximately 35.6 million worldwide by the end of 2010, which is still rising with the world population aging (Wimo and Prince, 2010). It is frustrating that the precise etiology of AD is not completely clarified and nearly no therapy can stop or reverse the inexorable neurodegenerative process (Hölscher, 2014). According to the amyloid hypothesis, the overproduction and aggregation of amyloid β protein (Aβ) in the brain, especially in the hippocampus and cortex, are closely involved in the memory loss of AD patients (Hardy and Selkoe, 2002). The neurotoxicity of Aβ has been thought to be a major pathological mechanism underlying AD (Epelbaum et al., 2015; Yankner and Lu, 2009), which causes disruption of Ca^{2+} homeostasis (Lazzari et al., 2014; Mattson et al., 1993), cholinergic abnormalities (Leon and Marco-Contelles, 2011; Pakaski and Kalman, 2008), and dysfunction of learning and memory.

Neuroactive steroids refer to steroids which, regardless of their origin, are capable of regulating neural activities. Neuroactive steroids, either synthesized *de novo* in the nervous tissue or in the peripheral endocrine glands or as synthetic steroids, have exhibited multiple important modulatory effects on brain functions and diseases (Zheng, 2009). It is reported that the declining of some neuroactive steroids, such as dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEAS) are closely associated with the increased risk of AD and reduced neuroprotection (El Bitar et al., 2014; Taylor et al., 2014; Wojtal et al., 2006). Some studies indicated that the administration of either DHEA or DHEAS could enhance memory, but further studies confirmed that DHEAS is the actual active agent for memory enhancement (Johnson et al., 2000). DHEAS has many effects including enhancing ACh release in the brain (Rhodes et al., 1997), inhibiting Aβ-induced $[Ca^{2+}]_i$ elevation (Kato-Negishi and Kawahara, 2008) and protecting hippocampal neurons against glutamate-induced neuronal toxicity (Kaasik et al., 2001). Several recent clinical studies have shown that DHEAS are significantly decreased in the brains and serum of AD patients (Bonomo et al., 2009; Cho et al., 2006; Kim et al., 2003). Some research even found that DHEAS concentrations were negatively correlated with Aβ levels in some brain regions, such as striatum and cerebellum (Weill-Engerer et al., 2002). Different from the dramatical decrease in the DHEAS level, DHEA is significantly higher in the AD brains than age-matched controls, especially in the region of hippocampus

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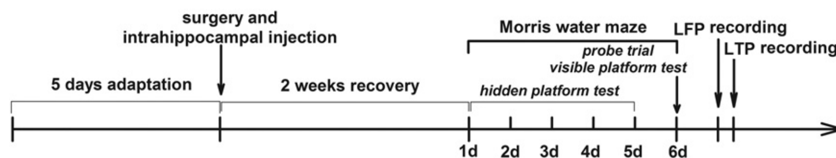

Fig. 1. Experimental timeline for intrahippocampal injection, Morris water maze test and *in vivo* electrophysiological recording. After 5 days of acclimatization, rats were subjected to intrahippocampal Aβ_{1-42} or/and DU-14 injection. Two weeks later, Morris water maze test and *in vivo* electrophysiological recording (*in vivo* hippocampal LFP and LTP recording) were performed.

(Brown et al., 2003; Naylor et al., 2008). DHEA produced in the brain does not help to protect brain from AD onset and progression (Kim et al., 2003). Some studies showed that high concentrations of DHEA is ineffective (Bologa et al., 1987) or even neurotoxic (Kimonides et al., 1999).

It seems that the imbalance of DHEA and DHEAS during their mutual transformation may play an important role in the AD pathological process (Luchetti et al., 2011). Steroid sulfatase, an enzyme involved in steroid metabolism, catalyzes the hydrolysis of steroid sulfates (*e.g.* DHEAS) into their unconjugated forms (*e.g.* DHEA) (Reed et al., 2005). Steroid sulfatase inhibitor can alter the metabolism of neuroactive steroids and prevent sulfated steroids from being converted back into their unsulfated forms (Maltais and Poirier, 2011). According to Rhodesr's study, a single acute administration of p-O-(sulfamoyl)-*N*-tetradecanoyl tyramine (DU-14), a non-steroidal steroid sulfatase inhibitor, produced a significant inhibition of steroid sulfatase activity in brain after 24 h (Li et al., 1997). As well as elevating brain DHEAS levels, DU-14 can also enhance brain acetylcholine levels and reverse scopolamine-induced amnesia (Johnson et al., 2000; Li et al., 1997; Rhodes et al., 1997). However, none of these studies provide any evident that DU-14 can protect cognitive function and synaptic plasticity from AD-related or Aβ-induced disruption. Therefore, the present study was designed to investigate the probable neuroprotective roles of DU-14 against Aβ_{1-42}-induced impairments in spatial memory, neuronal cooperative activity and hippocampal synaptic plasticity.

Materials and methods

Animals and drugs preparation

Adult male Sprague-Dawley rats (Research Animal Center of Shanxi Medical University, Taiyuan, China) weighing 180–200 g at the time of surgery served as subjects. Rats were kept in a standard animal room (25 ± 2 °C, 50 ± 5% humidity, 12 h light-dark cycle) individually with food and water available *ad libitum*. Animal handling and experimental procedures were performed according to the guidelines of the Shanxi Animal Research Ethics Committee. Efforts were made to minimize the number of animals used and their suffering. DU-14 (LKT Laboratory, USA) was dissolved in DMSO (50 μg/μl). Aβ_{1-42} (Abcam, USA) solution was prepared according to the procedure described by Tan Tao et al. (23 °C for 36 h, 5 μg/μl) (Tan et al., 2011). The stock solutions were stored at −80 °C before using. After 5 days of acclimation, rats were randomly divided into four groups: vehicle (0.045% DMSO solution) + saline, DU-14 + saline, vehicle + Aβ_{1-42}, and DU-14 + Aβ_{1-42}. DU-14 and/or Aβ_{1-42} were injected into bilateral hippocampi. Two weeks after injection, Morris water maze test and *in vivo* electrophysiological recording were performed. Fig. 1 shows the experimental timeline (Fig. 1). After finishing all experiments, the animals were painlessly killed with an overdose of urethane.

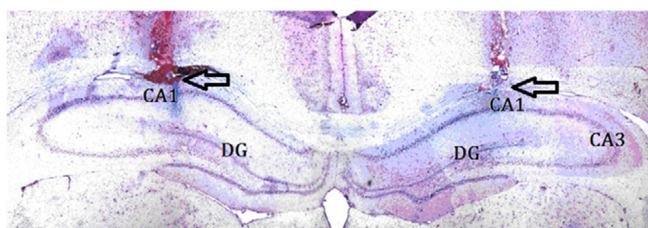

Fig. 2. A photomicrograph showing the injection sites in the hippocampus of rats. Two arrows in the figure indicated the injection sites in bilateral hippocampi, just the top of CA1 regions. The coordinates of drug delivery sites are: anterior posterior (AP), −3.0 mm; medial lateral (ML), ±2.2 mm; dorsoventral (DV), −3.0 mm from bregma.

Bilateral intrahippocampal injection

The surgical operation for bilateral intrahippocampal injection was performed as previously described (Han et al., 2013). In brief, SD rats were anesthetized with chloral hydrate (0.3 g/kg, i.p.) and placed onto a stereotaxic apparatus (RWD, Shenzhen, China). The hair covering the skull surface was removed and an incision was made to expose the dorsal skull. Two small holes (0.4 mm) were drilled bilaterally in the skull for intrahippocampal injection. Dissolved drug (50 μg DU-14 and/or 10 μg Aβ_{1-42}) solution (totally 3 μl) was injected into the CA1 region of dorsal hippocampus with an injection rate of 0.15 μl/min under the control of micropump (KDS310 Plus, KD Scientific Inc., USA). The coordinates of drug delivery site are: anterior posterior (AP), −3.0 mm; medial lateral (ML), ±2.2 mm; dorsoventral (DV), −3.0 mm from bregma (Paxinos and Watson, 2006). Fig. 2 shows a typical photomicrograph with two injection needle tracks. Two arrows in the figure indicated the injection sites in the brain slice, located at just the top of CA1 regions. The needle of micropump (D = 0.4 mm) was kept in the hippocampus for an additional 5 min in order to facilitate the diffusion of the drugs. In co-application group, Aβ_{1-42} was injected at least 20 min after DU-14 injection. After completion of the intrahippocampal injections, the burr holes were sealed with bone wax and skin was closed using silk surgical suture. Rats were monitored closely and kept warm until they fully recovered from anesthesia.

Morris water maze test

Morris water maze (MWM) test was designed and performed to evaluate the hippocampal-dependent spatial learning and memory ability of rats (Inostroza et al., 2011). After 3 day acclimatization, the rats were submitted to the Morris water maze as described before (Morris, 1984). The maze was a circular stainless steel pool with a diameter of 150 cm. The interior surface of the pool was painted flat black. The pool was filled with clear tap water at 23 ± 2 °C to avoid hypothermia, and was surrounded by curtains containing various prominent visual cues. The black escape platform (diameter, 14 cm) was positioned in the center of target quadrant and submerged 1.0 ~ 2.0 cm beneath the water surface.

Hidden platform test

The hidden platform test consisted of 5 consecutive training days and 4 trials per day with a 15 s intertrial interval. On each training day, a trial was started by introducing each rat to the water facing the pool wall and allowing it to swim freely to the escape platform. If the rat did not reach the platform within a period of 120 s, it will be guided to the platform gently. The rat was allowed to stay on the platform for 15 s. The swimming track of rat was monitored *via* a camera mounted overhead and the path distance and escape latency were analyzed by

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