Exogenous DHEAS reverses the dendritic changes of the central neurons in aging male rats

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Abstract

Sex hormones are known to help maintaining the cognitive ability in male and female rats. Hypogonadism results in the reduction of the dendritic spines of central neurons and are believed to underline memory and cognition and cause fatigue and poor concentration. Ongoing in our lab show that castration caused the reduction of dendritic spines of rat cortical neurons. Interestingly administration of dehydroepiandrosterone sulfate (DHEAS), a steroid produces by the adrenal gland that can be converted into androgen or estrogen and is known to be reduced in aging animals, restored the loss of dendritic spines in these neurons. Here we explored whether exogenous DHEAS is effective in restoring the central neuronal dendritic changes of aging male rats. Neuronal dendritic arbors were revealed with intracellular dye injection and reconstructed 3-dimensionally. Our results show that DHEAS appeared to improve the behavioral performance and increased the length of the dendrites as well as the densities of dendritic spine on these neurons simultaneously. Our results suggest that DHEAS works at the central neuronal level to effectively ameliorate aging symptoms.

Introduction

Dendrites are dynamic structures and their arbors and spines alter in response to environmental changes. Gonadal hormones have recently been reported to alter the dendritic structures of hippocampal, prefrontal and primary sensorimotor cortical pyramidal neurons. Hypogonadism, commonly associated with aging, has been implied to affect memory and impair cognition. Dehydroepiandrosterone (DHEA) is a precursor of sex hormone secreted by the adrenal gland, used clinically to treat hypogonadalism and menopause syndromes. In the blood, most DHEA is found as DHEAS (Dehydroisoandrosterone sulfate) with levels that are about 300 times higher than those of free DHEA. In this study, we explored whether aging down-regulates the densities of dendritic spines on primary cortical and hippocampal pyramidal neurons in the male and whether exogenous DHEAS reverses these changes.

Materials and methods

Five young adult and ten aged male SD rats (CD® IGS, BioLasco, Ilan, Taiwan) were studied. Half of the aged rats received intraperitoneal DHEAS injection (4mg/kg, Sigma, n = 5) and the other receiving the vehicle, sesame oil (n = 5) injection daily starting five days before being sacrificed. The dendritic structures of interested neurons were shown with intracellular dye injection. After injection, slices were postfixed in 4% paraformaldehyde in 0.1 M PB and then cryoprotected and sectioned into 70-μm-thick serial sections. Sections were processed with biotinylated rabbit anti-LY (Molecular Probes) and then with standard ABC-HRP reagent and DAB as chromagen. Injected neuron was reconstructed 3-dimensionally with Neur olucida (MicroBrightField) and analyzed. For layer III pyramidal neurons, proximal and distal basal dendrites were defined as the segments 25–75 μm (around the first to second branch) and 100–150 μm (around the last one or two branches) from the soma, respectively. For layer V pyramidal neurons, proximal and distal basal dendrites were defined as the segments 25–75 μm (around the first to second branch) and 150–200 μm (around the last one or two branches) from where they originate from the soma, respectively. On the other hand, proximal apical dendrites were the first or second branch of the apical tree and distal apical dendrites were the last branch of the apical tree (around the last one or two branches) from which the apical dendrites originate from the soma, respectively. To measure blood gonadal hormone, 1.5 ml blood was sampled via heart perforation, centrifuged (3000g, 15 minutes, 4 °C) and the plasma stored at -20 °C. Level of testosterone was assayed with an automated chemiluminescence system on an ACS: 190 analyser (Chiron Diagnostics, East Walpole, MA, USA) with Chiron Diagnostics kits commissioned by a clinical laboratory.

Conclusion

Like female counterpart, aging in the male reduced blood testosterone and at the same time altered brain structures. Aging rats performed poorer in Morris water maze and all pyramidal neurons of their primary cortical and hippocampal pyramidal neurons had reduced dendritic arbors and spine densities. Densities of the dendritic spines all over the dendritic arbor were reduced by 50%. Exogenous DHEAS rectified the behavioral deficits and at the same time restored the dendritic spines on these neurons. Our results show that DHEAS appeared to work on CNS neurons to maintain their excitatory synaptic connection for effectively alleviating aging-related behavioral deficit.

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