Behavioural Brain Research 321 (2017) 137–147

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Research report

Dehydroepiandrosterone increases the number and dendrite maturation of doublecortin cells in the dentate gyrus of middle age male Wistar rats exposed to chronic mild stress

J.J. Herrera-Pérez[a], L. Martínez-Mota[a,***], G. Jiménez-Rubio[a], L. Ortiz-López[b], E.A. Cabrera-Muñoz[b], N. Galindo-Sevilla[c], E. Zambrano[d], F. Hernández-Luis[e], G.B. Ramírez-Rodríguez[b,**], M. Flores-Ramos[f,g,*]

[a] *Farmacología Conductual, Dirección de Investigaciones en Neurociencias, Instituto Nacional de Psiquiatría "Ramón de la Fuente Muñiz", Calzada México-Xochimilco 101, Col. San Lorenzo Huipulco, Tlalpan, C.P. 14370, México City, Mexico*

[b] *Laboratorio de Neurogenesis, Subdirección de Investigaciones Clínicas, Instituto Nacional de Psiquiatría "Ramón de la Fuente Muñiz", Calzada México-Xochimilco 101, Col. San Lorenzo Huipulco, Tlalpan, C.P. 14370, México City, Mexico*

[c] *Departamento de Infectología e Inmunología, Instituto Nacional de Perinatología, Montes Urales 800, Colonia Lomas de Virreyes, C.P. 11000, México City, Mexico*

[d] *Departamento de Nutrición Animal, Instituto Nacional de Ciencias Médicas y Nutrición "Salvador Zubirán", Avenida Vasco de Quiroga No. 15, Col. Belisario Domínguez Sección XVI, Tlalpan, C.P. 14080, México City, Mexico*

[e] *Departamento de Farmacia, Facultad de Química, Universidad Nacional Autónoma de México, Circuito Exterior S/N, Coyoacán, Cd. Universitaria, C.P. 04510, México City, Mexico*

[f] *Catedrática del Consejo Nacional de Ciencia y Tecnología, Av. Insurgentes Sur 1582, Col. Crédito Constructor, Del. Benito Juárez, C.P. 03940, México City, Mexico*

[g] *Clínica de Trastornos Afectivos, Instituto Nacional de Psiquiatría "Ramón de la Fuente Muñiz". Calzada México-Xochimilco 101, Col. San Lorenzo Huipulco, Tlalpan, C.P. 14370, México City, Mexico*

HIGHLIGHTS

- Neuroplastic changes induced by dehydroepiandrosterone in middle age male rats.
- Dehydroepiandrosterone increases DCX-cells.
- Dehydroepiandrosterone promotes dendrite complexity of DCX-cells.

ARTICLE INFO

Article history:
Received 21 September 2016
Received in revised form
30 December 2016
Accepted 2 January 2017
Available online 4 January 2017

Keywords:
Dehydroepiandrosterone
Adult neurogenesis
Chronic mild stress
Middle age
Aging
Doublecortin

ABSTRACT

Aging increases the vulnerability to stress and risk of developing depression. These changes have been related to a reduction of dehydroepiandrosterone (DHEA) levels, an adrenal steroid with anti-stress effects. Also, adult hippocampal neurogenesis decreases during aging and its alteration or impaired is related to the development of depression. Besides, it has been hypothesized that DHEA increases the formation of new neurons. However, it is unknown whether treatment with DHEA in aging may stimulate the dendrite maturation of newborn neurons and reversing depressive-like signs evoked by chronic stress exposure. Here aged male rats (14 months old) were subjected to a scheme of chronic mild stress (CMS) during six weeks, received a treatment with DHEA from the third week of CMS. Changes in body weight and sucrose preference (SP) were measured once a week.

* Corresponding author at: Clínica de Trastornos Afectivos, Instituto Nacional de Psiquiatría "Ramón de la Fuente Muñiz", Calzada México-Xochimilco 101, Col. San Lorenzo Huipulco, Tlalpan, C.P. 14370, México City, Mexico.

** Corresponding author at: Laboratorio de Neurogenesis, División de Investigaciones Clínicas, Instituto Nacional de Psiquiatría "Ramón de la Fuente Muñiz", Calzada México-Xochimilco 101, Col. San Lorenzo Huipulco, Tlalpan, C.P. 14370, México City, Mexico.

*** Corresponding author at: Farmacología Conductual, Dirección de Investigaciones en Neurociencias, Instituto Nacional de Psiquiatría "Ramón de la Fuente Muñiz", Calzada México-Xochimilco 101, Col. San Lorenzo Huipulco, Tlalpan, C.P. 14370. México City, Mexico.

E-mail addresses: lucia@imp.edu.mx (L. Martínez-Mota), gbernabe@imp.edu.mx (G.B. Ramírez-Rodríguez), monica.flores@imp.edu.mx, flores_ramos@hotmail.com (M. Flores-Ramos).

http://dx.doi.org/10.1016/j.bbr.2017.01.007

DHEA levels were measured in serum, identification of doublecortin-(DCX)-, BrdU- and BrdU/NeuN-labeled cells was done in the dentate gyrus of the hippocampus. CMS produced a gradual reduction in the body weight, but no changes in the SP were observed. Treatment enhanced levels of DHEA, but lack of recovery on body weight of stressed rats. Aging reduced the number of DCX-, BrdU- and BrdU/NeuN- cells but DHEA just significantly increased the number of DCX-cells in rats under CMS and controls, reaching levels of young non-stressed rats (used here as a reference of an optimal status of health). In rats under CMS, DHEA facilitated dendritic maturation of immature new neurons. Our results reveal that DHEA improves neural plasticity even in conditions of CMS in middle age rats. Thus, this hormone reverted the decrement of DCX-cells caused during normal aging.

1. Introduction

Hippocampal neurogenesis is the process observed across species that give rise to new functional neurons [1,2]. This process is regulated by diverse factors such as exercise, enriched environment, stress and exogenous glucocorticoid or some other pharmacological agent's administration [3,4]. Notably, alterations in the neurogenic process are implicated in the pathophysiology of mood and anxiety disorders [4]; that maybe mediated by the presence of stress, which has been extensively studied as an important factor involved in the origin of psychopathology [5–10]. Animal models have shown that stress plays a role as a neurogenesis inhibitor in adult rats. However, some differences may be observed depending on the stressor type and duration [11]. It has been observed that brief and chronic unpredictable stress suppresses hippocampal cell proliferation [12], while prolonged mild stress exposure inhibits the survival of newborn cells [4]. In addition to cellular proliferation and survival, dendrite complexity could be regulated by prolonged exposure to stress depending on the brain area. Thus, changes in the hippocampal dendritic morphology were demonstrated by exposure to excess glucocorticoids, particularly in the CA3 pyramidal cells [13] as well as a decrease in the number of branch points and total dendritic length in the same cells after exposure to chronic social stress [14].

The possibility to revert the stress effects on the generation of new cells in the hippocampus might have clinical implications as well, such as prevention and/or treatment of affective and anxiety disorders [4,15,16], cognitive impairment [17], and other neuropsychiatric disorders [18,19]. Evidence show that to revert the effects of stress on neurogenesis, it could be possible to use some antidepressant drugs [20–22] but also by physical exercise [23], environmental enrichment [24,25] and steroid hormones [26,27] [12,28]. In this line, neurosteroids are compounds associated with neuronal survival, neurite outgrowth and neurogenesis, all which diminish with age and during stressful conditions [29]. Thus, neurosteroids could participate as a link between aging, stress and neurogenesis.

During aging, neurogenesis progressively declines in the dentate gyrus of the hippocampus in rats from 4 to 12 months old [30] and diverse mechanisms have been proposed to be associated with this process [31]. It has been observed that the number of radial glia-like stem cells, progenitor cell proliferation, and the generation of new neurons in the hippocampus decrease in middle-aged rats (10 months) and remains very low in the aged hippocampus. However, fractions of newly formed cells that exhibit appropriate migration and prolonged survival could differentiate into neurons [31].

It is proposed that steroid hormones could restore brain functions that have been impaired by aging. Among these steroids, DHEA is considered the "youth hormone" because of its levels in humans peak around 30 years old (in coincidence with optimal health) and decline in maturity. DHEA is an endogenous neurosteroid, which is synthesized *de novo* by cells in the central nervous system (CNS) in rats [32]. DHEA and its sulfated metabolite (DHEAS) are neuroactive steroids with multiple effects in the CNS, among them a neuroprotective one, and have different actions on neurite growth, promotion of hippocampal neurogenesis and neuronal survival. In addition, DHEA and DHEAS have shown antioxidant effects as well as an antagonistic effect on glucocorticoids [33]. Previous studies report that DHEA interferes with actions of stress hormones (glucocorticoids) [33,34], which has been associated with behavioral deficits in rodents. Moreover, it has been reported that DHEA stimulates neurogenesis and enhances survival of new neurons in the hippocampus of adult rats. In addition DHEA counteracts the effects of corticosterone on neurogenesis [34,35]. However the impact of this neurosteroid on the number of DCX-expressing cells and dendrite maturation of immature neurons in the hippocampus of middle age male Wistar rats exposed to chronic mild stress is not known.

Chronic mild stress (CMS) is an animal model that simulates anhedonia, a core sign of depressive disorders. In this paradigm, constant exposure of the animal to several stressors of moderate intensity during several weeks leads to a reduction of the consumption of a palatable sucrose solution, indicating an anhedonic state that is reversible by treatment with antidepressant drugs [36]. Recently it has been recognized that CMS produces other signs of depression such as changes in feeding and body weight, alterations in corticosterone levels, impairment of social and sexual behaviors, and increase in anxiety-like behaviors in different paradigms [37,38], which give strength the validity of CMS for the study the neurobiology of depression.

DCX is a microtubule-associated protein involved in cell migration and neuritogenesis. This protein is distributed throughout the dendritic cytoplasm [39]. Thus, this marker makes possible to study changes at the level of dendrite maturation of newborn neurons [40]. In this study we analyzed the effect of DHEA supplementation and the age on the number and morphology of DCX-labeled cells in the dentate gyrus of male Wistar rats exposed to chronic mild stress.

2. Materials and methods

2.1. Animals

Middle-aged (14 months) male Wistar rats were obtained from vivarium of *Instituto Nacional de Perinatología*. Animals were individually housed in cages measuring 27 × 16 × 23 cm and kept in an inverted 12 h dark-light cycle (light was turned off at 10:00 h), under controlled temperature and humidity. The animals had free access to water and food, except for the periods required by the CMS procedure. Animal management was done according to the general principles of laboratory animal care (National Research Council Committee, 2011). All experimental procedures were performed in accordance with the Mexican official norm for animal care and handling (NOM-062-ZOO-1999) and approved by the Ethical Com-