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Original Article

Physiology Section

Dehydroepiandrosterone and Acute Stress Attenuation: An Interventional Rodent Study

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ABSTRACT

Introduction: Stress activates hypothalamo-pituitary-adrenal axis leading to the release of glucocorticoid that mediates the stress response. This adaptive response is self-limited but if persistent for prolonged periods can lead to disease states. Nature has endowed the body with efficient buffer systems to attenuate the stress effects and Dehydroepiandrosterone (DHEA), a steroid hormone with neuromodulatory functions is implicated as an efficient candidate to buffer stress.

Aim: To assess the effect of prophylactic administration of DHEA in the attenuation of acute stress in male Wistar rats.

Materials and Methods: This interventional study was carried out at centre for Toxicology and Developmental Research, Sri Ramachandra Institute of Higher Education and Research, Chennai, between June 2021 and August 2021, in compliance with the animal welfare guidelines of CPCSEA, and in accordance to the protocol approved by Institutional Animal Ethics Committee. The 18 male Wistar rats approved for the study were segregated into 3 groups with 6 animals in control (no stress) group, 6 in stress group and 6 in intervention group that received DHEA prophylactically 30 min before stress procedure. Animals in stress and intervention groups were subjected to one hour immobilisation stress. Blood samples were collected from all animals after the stress period and serum corticosterone, the stress marker, was estimated. The data were expressed as mean±standard error of mean (mean±SEM) and Mann-Whitney U test was used to test the significant difference between the: (i) control and stress groups; (ii) stress and study groups; and (iii) control and study groups. The p-value <0.05 was considered significant. The analysis was done using SPSS version 23.0.

Results: The values of corticosterone in control, stress and intervention groups were 26.6±4.4 ng/mL, 51.6±3.9 ng/mL and 23.4±3.6 ng/mL, respectively. Significant difference in the mean serum corticosterone levels with p-value 0.013 between control and stress groups and with p-value 0.008 between stress and DHEA groups were observed.

Conclusion: It could be observed from the findings that prophylactic DHEA administration attenuated acute stress efficiently in male Wistar rats as reflected by the significant decrease in serum corticosterone levels in the group that received DHEA intervention, thus inferring the efficiency of DHEA in stress buffering.

Keywords: Adrenal androgen, Anxiety, Immobilisation, Psychological stress, Serum corticosterone

INTRODUCTION

The maintenance of internal balance (homeostasis) at times of real or perceived stress is made possible by the evolution of stress response that brings about adaptive changes through the activation of autoregulated neural and hormonal systems. Of the two mechanisms, the hormonal mechanism serves as the key regulator in mediating the Hypothalamic-Pituitary-Adrenal (HPA) axis. By the activation of HPA axis glucocorticoid is ultimately released from adrenal cortex and mediates the adaptive response to stress [1]. Glucocorticoids are primarily concerned with ensuring energy availability by mobilisation and distribution of energy to various organ systems in appropriation to demands, both at basal and stressed states thus rendering adaptive response at times of stress an efficient mechanism to meet the demands of the dire moments [2]. Glucocorticoids exert action via both non genomic and genomic mechanisms and its effects could be observed almost on all tissues in the body as its receptors are widely distributed in all body systems [3,4].

These neuroendocrine mediated metabolic, physiological and behavioural adaptations that ensures improved survival in the face of temporary stressors by establishing stability through changes, is referred as allostasis [5,6]. Such adaptations if persistent for prolonged periods or repeated can often lead to physiologic dysregulation with poor health outcomes like increased susceptibility to infections, cardiovascular disease, metabolic syndrome, obesity, cancer, and mental health disorders that constitutes the allostatic load [1].

Stress affects mental health and on the long-term impairs the quality of life. Therefore, in the recent past many research endeavours in the field of mental health have revealed various endogenous biomolecules to possess efficient stress buffering capacity. In this vein, DHEA and its sulphated derivative DHEA-Sulfate (DHEAS) which were previously considered to serve only as a precursor of potent androgen and oestrogens on peripheral conversion, were recently found to have a plethora of beneficial effects that includes stress attenuation as it has antiglucocorticoid properties [7]. DHEA is observed to modulate endothelial function, improve insulin sensitivity, reduce inflammation, improve blood flow, regulate body composition, bone metabolism, sexual function, enhance neuroprotection, improve cognition and memory as well counteract the immunosuppressive actions of corticosteroid [8,9]. Age related metabolic derangement, cognitive decline, neurodegenerative disorders as well as the aetiopathology of many psychiatric illness lie with derangement in endogenous DHEA levels [10-12].

The DHEA, as an antistress agent, is observed to prevent the stress induced inhibition in body weight gain, increase in adrenal weight, and concentration of glucocorticoid receptor levels in liver, thymus, and spleen when administered to stress male Sprague-Dawley rats and it also reduces the lipid peroxidation levels in the liver and heart [13]. Similarly, DHEA is also observed to inhibit the stress induced corticosterone mediated inhibition of testosterone in experimentally stressed adult Sprague-Dawley rats [14]. Previous research reported a contradictory observation where the administration of sulphated form of DHEA in high-anxiety rats induced anxiolysis while it induced

anxiogenesis in low-anxiety rats which infers a stress modulatory effect of DHEA [15].

Though the above mentioned observations have highlighted the efficiency of DHEA in stress buffering, there is paucity of experimental evidence to establish the beneficial effect of prophylactic DHEA administration in attenuation of acute stress. As rodents share physiologic and genetic similarities with human and the stress response could be better studied with appropriate stress paradigm in regulated and controlled conditions from stress induction to interventional outcomes in animal model [16], this study was planned as a preclinical study to assess the beneficial effect of prophylactic DHEA administration in the attenuation of acute stress in Wistar male rats.

MATERIALS AND METHODS

This interventional study was carried out at Centre for Toxicology and Developmental Research, Sri Ramachandra Institute of Higher Education and Research, Chennai, Tamil Nadu, India between July and September 2021. The study was performed in compliance with the animal welfare guidelines published by CPCSEA [17], Government of India and standard operating procedures of CEFTE in accordance to the Protocol approved by Institutional Animal Ethics Committee (IAEC number: IAEC59/SRIHER/659/2019).

Study Procedure

Animal procurement, acclimatisation and housing: Eighteen adult male Wistar rats, as sanctioned by IAEC, were procured from in-vivo Bioscience, Hyderabad. The animals were 60-70 days of age with 200-250 g bodyweight and were acclimatised under laboratory conditions for about 14 days. The animals were housed in rooms maintained at 19-23ºC temperature and humidity of 30-70%, with air exchange in the range of 12-15 air changes per hour, respectively. The animals were provided with photoperiod of 12 hour artificial light and 12 hour darkness and were segregated into three groups by simple randomisation technique, viz., six animals in control (non stressed) group, six animals in stress group and six animals in intervention group that received DHEA prophylactically 30 minutes before immobilisation stress. Animals were segregated by the random number generated using Microsoft excel. The animals were housed in groups in polypropylene cags covered with stainless steel grid. Dedusted and autoclaved paddy husk was used as bedding material which was changed on alternate days. The animals were habituated to handling during the acclimatisation period and the same personnel handled the animals on all days and even for the experimental procedures. Animals were provided with standard rodent pelleted feed (Krishna Valley Agrotech LLP, Maharashtra) and portable UV treated water was provided ad libitum in autoclaved bottles.

Treatment: The experiment commenced on the fourth day following the completion of acclimatisation period. The intervention group was administered with intraperitoneal DHEA-at a dose of 25 mg/kg diluted in 2-3 drops of Dimethyl Sulfoxide (DMSO) and then with physiological saline, 30 minutes before the stress procedure [18]. DHEA was procured from Avanti Polar Lipids, Alabaster, Alabama.

Acute immobilisation stress: Acute immobilisation stress was inculcated to the stress and intervention groups by immobilisation of the animal in a restrainer (25×7 cm plastic) and adjusting it with plaster tape on the outside so that animal was unable to move. For breathing, 1 cm hole at one end was provided [19]. The stress was carried out for a period of one hour between 10 and 11 am. During immobilisation, the rats were not provided with feed and water.

Sample collection and storage: At the end of one hour of immobilisation, blood samples were collected from all three groups: controls (non stressed), stressed, and intervention (stressed 30 min after prophylactic administration of DHEA) groups. Blood samples were collected through retro-orbital plexus under sterile aseptic precautions and allowed to clot in non heparinised tubes. The sera were collected from the samples by centrifugation at 3000 rpm for 15 minutes at room temperature. The serum thus separated was stored in ID tagged eppendorf at -80ºC until hormone analysis was performed.

Animal rehabilitation: After sample collection, the animals were returned to animal facility for reuse.

Serum corticosterone estimation: The hormone concentrations were determined as per the instructions provided in 96-well Enzyme Linked Immunosorbent Assay (ELISA) kit for rat corticosterone, procured from Elabscience. The standards were diluted as per the instruction provided in the kit 0-25 ng/mL. The samples were diluted at a ratio of 1:2 and then at 1:4, in duplicates, as the former dilution yielded the response beyond the standard range. Standard and samples were taken in the respective wells and incubated with biotinylated detection antibody followed by HRP conjugate working solution at 37ºC for specific period and washed. Plates were treated with substrate and the reaction was terminated using stop solution. The plate absorbance was detected at 450 nm using a microplate reader. Hormone assay was performed by a third party completely blinded from the experiment, as per the kit insert. All data received were included in the results. However, no blinding was done during result assessment.

STATISTICAL ANALYSIS

The data were expressed as mean±standard error of mean (mean±SEM) and Mann Whitney U test was used to test the significant difference between the: (i) control and stress groups; (ii) stress and intervention groups; and (iii) control and intervention groups. Comparison between the three groups was done using Kruskal Wallis test. The p-value <0.05 was considered significant. The analysis was done using SPSS version 23.0.

RESULTS

A total of 18 adult male Wistar rats were included in the study. Six animals were in control group (unstressed), 6 in stress group and 6 in intervention group where animals received DHEA prophylactically 30 minutes before immobilisation stress procedure.

Comparison of the body weight of the animals in the 3 groups showed no significant difference (p=0.271) [Table/Fig-1].

Comparison of serum corticosterone levels between the three groups as calculated by Kruskal Wallis test revealed a significant mean difference existing between the three groups with a p-value 0.007* [Table/Fig-2].

Serum corticosterone level was significantly elevated in stress group when compared to control with p-value 0.013* and the same was attenuated significantly in intervention group with a p-value 0.008* when compared to stress group. No significant difference was observed in the comparison between control and intervention groups [Table/Fig-3].

Body weight (gm)	Control group (n=6)	Stress group (n=6)	Intervention group (n=6)	p-value#
	281.5±14.9	271.8±17.7	284.7±18.6	0.271

[Table/Fig-1]: Comparison of body weight of Wistar rats between control, stress and intervention groups.
#Kruskal Wallis test

Serum corticosterone (ng/mL)	Control group (n=6)	Stress group (n=6)	Intervention group (n=6)	p-value#
	26.6±4.4	51.6±3.9	23.4±3.6	0.007*

[Table/Fig-2]: Intergroup comparison of serum corticosterone levels between control, stress and intervention groups.
#Kruskal Wallis test *statistically significant (p<0.05)

Groups compared	p-value#
Control vs. Stress group	0.013*
Stress vs. Intervention group	0.008*
Control vs. Intervention group	0.689

[Table/Fig-3]: Comparison of serum corticosterone levels between control, stress and intervention groups.
#Mann-Whitney U test
*Statistically significant ($p<0.05$)

DISCUSSION

Stress begins as an acute event inducing an adaptive response in the biological system by the release of glucocorticoid into circulation that helps tackle the demands of the moment of crisis. This acute adaptive phenomenon is beneficial and has autoregulatory self-limiting mechanisms. But the persistence of this response for longer periods renders the autoregulatory processes ineffective and ends in disease states. Moreover, stress outcomes are determined by the individual's vulnerability and the sequels of morbidity are more pronounced among the stress susceptible traits [20]. As personality influences anticipatory stress vulnerability and effectiveness of coping interventions, prophylactic measures to attenuate the stress response in this vulnerable population can promise them with a better quality of life. Hence, this study was designed as a preclinical research to evaluate the efficiency of prophylactic DHEA administration in the attenuation of acute stress.

In the present study, it was observed that one hour immobilisation induced stress significantly in the stress group animals which is evident from the significant elevation of serum corticosterone levels in them with a p-value 0.013* when compared to the control group. With prophylactic administration of DHEA the reduction in the stress marker was significant as observed from the comparison between the stress and intervention (stressed with prophylactic administration of DHEA) groups with a p-value 0.008*. On comparing control group values with intervention group, no significant difference was observed reflecting the prophylactic administration of DHEA had significantly reduced serum corticosterone comparable to that of control values observed in non stressed control group. Significance was observed with intergroup difference (p-value 0.007*).

During stress, at the stimulation of Adrenocorticotropic Hormone (ACTH), the biosynthesis of adrenal DHEA begins with the rate-limiting step of importing cholesterol from cytosol to the inner mitochondrial membrane by steroidogenic acute regulatory protein, StAR, which is then converted to pregnenolone by the mitochondrial cholesterol side-chain cleavage enzyme, cytochrome P450scc. Pregnenolone by the action of 17-alpha hydroxylase gets converted to 17OH-pregnenolone (17OH-Preg) and then to DHEA subsequently by the action of 17,20-lyase [21].

Though it was reported that the rodent's adrenal CYP17A1 lack 17,20-lyase activity, thus rendering the adrenal cortex of adult rodents with compromised capacity to synthesise adrenal androgens, the diurnal rhythm of DHEA and corticosterone metabolites are found to follow a similar temporal pattern in them thus inferring the common source of both steroids from adrenal gland [22,23]. It was also reported that DHEA that circulates in lower concentrations in rodent blood (around 1-3 nM or less) is synthesised from non adrenal steroidogenic source such as gonads, and placenta as well by the nervous system, as evident from the observations of their levels in the blood of adrenalectomised and castrated rats [24].

The DHEA thus formed, is reversibly converted to its sulfate ester-DHEA-S by the enzyme sulfotransferase (SULT2A1) in which form it is predominately found in circulation (about 300 times higher than that of free DHEA, in human). Diurnal variation is exhibited by DHEA but not by DHEA-S, with former having a short terminal half-life while DHEA-S has a much longer half-life thus making the inference that DHEA-S primarily serves as a reservoir of DHEA with a lesser role in physiological functions [25].

The DHEA thus circulating is found to exert its effect on a wide range of tissues like liver, kidney, adipose tissue, reproductive tissues, and central nervous system as well on various neural structures. The hormone DHEA and its sulphated form, DHEA-S, exert their physiological effects either by its direct actions on DHEA-specific plasma membrane receptors coupled via G-protein or through various neuroreceptors like N-Methyl-D-Aspartate (NMDA), aminobutyric-acid-type A, and sigma-1 (S1R) receptors; or by binding to androgen and oestrogen receptors (ARs, ERα, or ERβ) either directly or by their more potent steroid metabolites-testosterone, dihydrotestosterone, and estradiol [26]. But further exploration is needed to establish the exact mechanism.

DHEA being a potent antistress hormone is found to exert an inhibitory modulation on stress axis. Budziszewska B et al., in their in-vitro study with Neuro-2A cells observed that neither DHEA nor DHEA-S is found to modify CRH gene promoter activity, implying that DHEA has no modulatory effect on the activation of HPA axis [27]. But Taguchi T et al., observed that at supraphysiological doses the hormone is observed to inhibit POMC transcription in-vitro in ACTH secreting cell line AtT-20 and thus decrease the expression of ACTH [28].

Chang LL et al., reported that DHEA attenuated ACTH induced corticosterone release in in-vitro study with rat zona glomerulosa fasciculate cell cultures not only by decreasing the activities of the enzymes involved in the keysteps of corticosterone biosynthesis viz., P450scc, 3β-HSD, 21-hydroxylase and 11β-hydroxylase but also the prime step of ACTH induced cAMP formation. It is observed that the incubation of rat adrenal cells with the substrates of the steroidogenic enzymes viz 25-OH-cholesterol, pregnenolone, progesterone and deoxycorticosterone, respectively corticosterone release was enhanced. But the same was attenuated significantly when incubated in presence of DHEA thus making the inference that DHEA appears to decrease the activities of 3β-HSD, 21-hydroxylase and 11β-hydroxylase. No significant attenuation of actions was observed with P450scc as the binding of 25-OH-cholesterol and P450scc is not affected by DHEA, while only the quantity of P450scc involved in the process is reduced. DHEA inhibits 11β-hydroxylase activity by the mechanism of competitive inhibition and interferes with the formation of the binding complex of 11β-hydroxylase and deoxycorticosterone. DHEA is also observed to decrease the expression of StAR protein that transfers cholesterol from cytoplasmic pool to the inner mitochondrial membrane, by decreasing the translation of its protein [29].

Apostolova G et al., observed that DHEA exerted its antiglucocorticoid effect either by downregulating 11β-HSD1-dependent glucocorticoid regeneration from 11 dehydrocorticosterone, the inactive metabolite, or by enhancing 11β-HSD2-dependent glucocorticoid inactivation into the inactive metabolite in the peripheral tissues. In 2005, they reported that DHEA induced the downregulation of 11β-HSD1-dependent glucocorticoid regeneration in liver, adipose tissue, and kidneys of C57BL/6J mice [30]. The same team in 2008 reported their observation that DHEA induced the activity of 11β-HSD2 in a rat cortical collecting duct cell line and in kidneys of C57BL/6J mice and Sprague-Dawley rats whereby the corticosterone was converted to dehydrocorticosterone. DHEA is also reported to attenuate ischaemia/reperfusion-induced oxidative stress in rodent kidney [31].

From the observations of the above mentioned in-vitro studies (Taguchi T et al., 2006, Chang LL et al., 2003, Apostolova G et al., 2005, Apostolova G et al., 2008) it could be inferred that DHEA exerts its antistress effects by inhibiting the transcription of ACTH as well the enzymes involved in adrenal glucocorticoid synthesis [28-30]. It is also observed to enhance the reduction in the plasma concentration of corticosterone by upregulating 11β-HSD2 dependent glucocorticoid inactivation in the kidney and downregulating 11β-HSD1 dependent glucocorticoid regeneration

in liver, adipose tissue, and kidneys [28-31]. In accord with these observations, it was observed in the present study that intervention with prophylactic administration of DHEA, 30 min prior to immobilisation stress led to a significant decrease in serum corticosterone levels in the intervention group when compared to the stress group. The attenuation in the glucocorticoid levels was comparable with control values. This observation could be interpreted as the prophylactically administered DHEA had exerted a significant attenuating effect on stress axis and thus the stress response could have been decreased by the above mentioned mechanisms and the corticosterone levels in intervention group was comparable with that of control values, reflecting the efficient role of prophylactically administered DHEA in the attenuation of acute stress.

Limitation(s)

The observations of the present study have made a significant inference on the stress-attenuating potency of DHEA though the molecular mechanism of the stress attenuation by DHEA was not explored. With further molecular research endeavours the exact mechanism of DHEA in stress attenuation could be established.

CONCLUSION(S)

DHEA, the antistress adrenocorticoid, when administered prophylactically in Wistar rats, is found to significantly attenuate stress at supraphysiological doses. Hence, it could be concluded that DHEA is an efficient antiglucocorticoid and is found to be an effective attenuator of stress in animal model. Further research efforts are recommended to establish its clinical utility.

REFERENCES

[1] Russell G, Lightman S. The human stress response. Nat Rev Endocrinol. 2019;15(9):525-34.
[2] Herman JP, McKlveen JM, Ghosal S, Kopp B, Wulsin A, Makinson R, et al. Regulation of the hypothalamic-pituitary-adrenocortical stress response. Compr Physiol. 2016;6(2):603-21.
[3] Panettieri RA, Schaafsma D, Amrani Y, Koziol-White C, Ostrom R, Tliba O. Non-genomic effects of glucocorticoids: An updated view. Trends Pharmacol Sci. 2019;40(1):38-49.
[4] Thau L, Jayashree G, Sharma S. *Physiology, Cortisol*. Treasure Island, FL: StatPearls Publishing (2020). Available online at:https://www.ncbi.nlm.nih.gov/books/NBK538239/. (Accessed June 12, 2020).
[5] Takayanagi Y, Onaka T. Roles of oxytocin in stress responses, allostasis and resilience. Int J Mol Sci. 2022;23(1):150.
[6] Edes AN, Wolfe BA, Crews DE. Evaluating allostatic load: A new approach to measuring long-term stress in wildlife. J Zoo Wildl Med. 2018;49(2):272-82.
[7] Quinn TA, Robinson SR, Walker D. Ehydroepiandrosterone (DHEA) and DHEA sulfate: Roles in brain function and disease. In: Drevenšek G. editor. Sex Hormones in Neurodegenerative Processes and Diseases. London: IntechOpen; (2017).
[8] Traish AM, Kang HP, Saad F, Guay AT. Dehydroepiandrosterone (DHEA)-a precursor steroid or an active hormone in human physiology (CME). J Sex Med. 2011;8(11):2960-82.
[9] Prall SP, Muehlenbein MP. DHEA modulates immune function: A review of evidence. Vitam Horm. 2018;108:125-44.
[10] Yanase T, Muta K, Nawata H. DHEA: Effects on oxidative and glycative stress and glucose metabolism. Glycative Stress Research. 2020;7(1):42-49.
[11] Sorwell KG, Urbanski HF. Dehydroepiandrosterone and age-related cognitive decline. Age. 2010;32(1):61-67.
[12] Maninger N, Wolkowitz OM, Reus VI, Epel ES, Mellon SH. Neurobiological and neuropsychiatric effects of dehydroepiandrosterone (DHEA) and DHEA sulfate (DHEAS). Front Neuroendocrinol. 2009;30(1):65-91.
[13] Hu Y, Cardounel A, Gursoy E, Anderson P, Kalimi M. Anti-stress effects of dehydroepiandrosterone: Protection of rats against repeated immobilisation stress-induced weight loss, glucocorticoid receptor production, and lipid peroxidation. Biochem Pharmacol. 2000;59(7):753-62.
[14] Zhu Q, Ge F, Li X, Deng HS, Xu M, Bu T, et al. Dehydroepiandrosterone antagonizes pain stress-induced suppression of testosterone production in male rats. Front Pharmacol. 2018;9:322.
[15] Semenova OG, Rakitskaia VV, Pivina SG, Ordian NE. The effect of dehydroepiandrosterone-sulphate on stress behavior in high-and low-anxiety rats. Rossiiskii Fiziologicheskii Zhurnal Imeni IM Sechenova. 2012;98(7):862-70.
[16] Bryda EC. The mighty mouse: The impact of rodents on advances in biomedical research. Mo Med. 2013;110(3):207.
[17] Ministry of Environment and Forests and Climate Change Government of India: Compendium of CPCSEA 2018. Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), New Delhi, 2018. http://cpcsea.nic.in/WriteReadData/userfiles/file/Compendium%20of%20CPCSEA.pdf.
[18] Cecconello AL, Torres IL, Oliveira C, Zanini P, Niches G, Ribeiro MF. DHEA administration modulates stress-induced analgesia in rats. Physiol Behav. 2016;157:231-36.
[19] Torres RL, Torres IL, Gamaro GD, Fontella FU, Silveira PP, Moreira JS, et al. Lipid peroxidation and total radical-trapping potential of the lungs of rats submitted to chronic and sub-chronic stress. Brazilian Journal of Medical and Biological Research. 2004;37:185-92.
[20] Ebner K, Singewald N. Individual differences in stress susceptibility and stress inhibitory mechanisms. Current Opinion in Behavioral Sciences. 2017;14:54-64.
[21] Miller WL. Mechanisms in endocrinology: Rare defects in adrenal steroidogenesis. Eur J Endocrinol. 2018;179(3):R125-41.
[22] Ilhan R, Üner G, Yilmaz S, Sahar EA, Cayli S, Erzurumlu Y, et al. Novel regulation mechanism of adrenal cortisol and DHEA biosynthesis via the endogen ERAD inhibitor small VCP-interacting protein. Sci Rep. 2022;12(1):01-09.
[23] Bardi M, Hampton JE, Lambert KG. Fecal dehydroepiandrosterone (DHEA) immunoreactivity as a noninvasive index of circulating DHEA activity in young male laboratory rats. Comp Med. 2010;60(6):455-60.
[24] Gabai G, Mongillo P, Giaretta E, Marinelli L. Do dehydroepiandrosterone (DHEA) and its sulfate (DHEAS) play a role in the stress response in domestic animals? Frontiers in Veterinary Science. 2020;7:588835.
[25] Chimote BN, Chimote NM. Dehydroepiandrosterone (DHEA) and its sulfate (DHEA-S) in Mammalian reproduction: Known roles and novel paradigms. Vitam Horm. 2018;108:223-50.
[26] Clark BJ, Prough RA, Klinge CM. Mechanisms of action of dehydroepiandrosterone. Vitam Horm. 2018;108:29-73.
[27] Budziszewska B, Zając A, Basta-Kaim A, Leśkiewicz M, Steczkowska M, Lasoń W, et al., Effects of neurosteroids on the human corticotropin-releasing hormone gene. Pharmacol Rep. 2010;62(6):1030-40.
[28] Taguchi T, Takao T, Iwasaki Y, Nishiyama M, Asaba K, Hashimoto K. Suppressive effects of dehydroepiandrosterone and the nuclear factor-κB inhibitor parthenolide on corticotrophtumor cell growth and function in-vitro and in vivo. J Endocrinol. 2006;188(2):321-31.
[29] Chang LL, Wun WS, Ho L, Wang PS. Effects of dehydroepiandrosterone on corticosterone release in rat zonafasciculata-reticularis cells. Naunyn Schmiedebergs Arch Pharmacol. 2003;368(6):487-95.
[30] Apostolova G, Schweizer RA, Balazs Z, Kostadinova RM, Odermatt A. Dehydroepiandrosterone inhibits the amplification of glucocorticoid action in adipose tissue. Am J Physiol Endocrinol Metab. 2005;288(5):E957-64.
[31] Balazs Z, Schweizer RA, Frey FJ, Rohner-Jeanrenaud F, Odermatt A. DHEA induces 11β-HSD2 by acting on CCAAT/enhancer-binding proteins. J Am Soc Nephrol. 2008;19(1):92-101.

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