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What physiological role of DHEA in non-primate mammals?

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Abstract

Dehydroepiandrosterone (DHEA) and its sulphate metabolite (DHEAS) are generally considered as androgenic steroid precursors, whose prominent function is their role as prohormones used by several non-endocrine peripheral tissues for the synthesis of androgens and estrogens. In primates, the adrenal glands are the main source of these steroids, while in non-primate mammals the picture is more complex, and the gonads and placenta seem its main. In humans, DHEA(S) is related to aging. Its concentrations peak around puberty and then decrease through the subject's life. A little age effect on DHEA concentrations can be observed in dogs, while no data is available for ungulates. Besides their role as prohormones, DHEA and DHEAS are believed to possess several putative pleiotropic effects: modulation of endothelial function, reduction of inflammation, improvement of insulin sensitivity, blood flow, cellular immunity, body composition, bone metabolism, sexual function, and physical strength, neuroprotective properties, improvement of cognitive functions and memory. Interestingly, DHEA(S) may have antagonistic effects on glucocorticoids and mitigate the stress response. However, available research suggests that the biological properties observed in one animal taxa cannot be straightforward translated to another, and more research is needed to elucidate the role of DHEA in domestic mammals.

Key words: anti-aging; anti-stress; biological functions; DHEA(S); pro-hormones

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DHEA synthesis and metabolism

Dehydroepiandrosterone (DHEA) and its sulphate metabolite (DHEAS) are androgenic steroid precursors, whose prominent function is their role as prohormones used by several non-endocrine peripheral tissues for the synthesis of sex hormones (androgens and oestrogens). Most information about DHEA and DHEAS biosynthesis and secretion in mammals have been obtained from studies performed in humans and laboratory animals. However, differences do exist between primates and rodents, and care should be taken when translating findings obtained in rodents to human or other mammals physiology [1].

Transformation of DHEA into androgens and/or oestrogens occurs in peripheral target tissues and depends upon the levels of expression of steroidogenic and metabolizing enzymes in those tissues. DHEA is synthesized in steroidogenic tissues (adrenals, gonads, and placenta) and in the nervous system from pregnenolone through the delta-5 pathway, thanks to the activity of the enzyme cytochrome P450c17 (CYP17A). It is present in the circulation of primate mammals in large amounts (20–60 nM), while lower amounts (around 1–3 nM or less) of this steroid can be found in the blood of rodents and domestic animals, such as rabbits, dogs, pigs, cattle, sheep, and horses [1].

Our interest about DHEA/DHEAS physiology is long lasting. Originally, we were interested in the overall steroidogenic capabilities of the bovine mammary gland, and investigated how this organ can metabolise C21 (e.g.: pregnenolone) and C19 (e.g.: DHEA) steroid precursors. Overall, we observed a limited steroidogenic capability, even though the bovine mammary gland synthesised 5-androstene-3β,17β-diol (AED), an androgen with a low affinity for the oestrogen receptors [2]. In a subsequent experiment, we measured the variations of DHEA, AED, and 17β-oestradiol (E2) in plasma from the peripheral circulation and plasma drained from the mammary circulation in dairy animals during pregnancy, and the affinity of AED for bovine cytosolic oestrogen receptors. Our results suggested that the plasma DHEA increase observed during pregnancy in dairy cattle reflects the volume and secretory activity increase of foetal-placental tissues, and that the possible estrogenic role of AED in cattle was very modest, as AED is a very weak competitor of the oestrogen receptors [3].

Age and sex effects on DHEA concentrations

In primates, DHEA and DHEAS are primarily produced by the adrenals and are the most represented circulating steroids. In humans, circulating DHEA(S) is higher in men than in women, and its concentrations peak around puberty and then decrease through the subject's life. Indeed, the interest for DHEA resides in its putative anti-aging effect. Conversely, no age-related DHEA decrease has been documented in rodents, and DHEA originates primarily from the gonads. The rat adrenal does not express the CYP17A enzyme and, therefore, does not produce androgen precursors, and corticosterone is the major glucocorticoid in this species. In addition, the tissue expression of sulfotransferase enzymes responsible for DHEAS production is different between rodents and humans [1]. In mice, we observed that DHEA was higher in isolated individuals and this was related to testosterone increase, suggesting a greater reactivity of the Hypothalamic–Pituitary–Gonadal axis following social isolation [4].

Limited data exist on age-related physiological variations in plasma concentrations of DHEA in dogs, despite their potential role in the pathophysiology of ageing. We examined plasma cortisol and DHEA concentrations and cortisol/DHEA ratio variations, according to age and sex in dogs, aged from two months to 16 years. Before adulthood, DHEA concentrations were higher in peripubertal males. During adulthood, cortisol and DHEA were higher in males than females. Among females, DHEA was lower in older dogs, but the decrease was observed at an older age in intact than ovariectomized females. Results suggested that testicles are an important source of DHEA in males, and that DHEA is mainly secreted by the adrenal glands in females, while the ovarian contribution to circulating DHEA appears limited [5, 6]. We could measure DHEA and DHEAS concentrations in the cerebrospinal fluid of dogs diagnosed with several neurologic and

non-neurologic diseases, and we could not observe differences among different diagnoses. However, we could observe that both steroids were higher in males than in females and DHEAS decreased with increasing age [7].

Can be identified a biological role for DHEA?

Besides their role as prohormones, DHEA and DHEAS are believed to possess a wide range of biological actions in different biological systems. Studies in humans and in laboratory rodents, involving DHEA supplementation, suggested that DHEA displays putative pleiotropic effects: it modulates endothelial function, reduces inflammation, improves insulin sensitivity, blood flow, cellular immunity, body composition, bone metabolism, sexual function, and physical strength, and provides neuroprotection, improves cognitive function, and memory enhancement. Interestingly, available data suggest that DHEA(S) have antagonistic effects on glucocorticoids and, at least in humans, their secretion is affected by stressors of different nature (inflammatory, physical, or social), intensity and duration. These observations lead to an increased interest toward the potential role of DHEA(S) as important players in the stress response and potential biomarkers of stress in domestic animals. Indeed, studies on humans and laboratory animals reported that these steroids show effects that compensate for or oppose those of cortisol and are implicated in the short- and long-term stress response [1, 8].

The negative effects of stress are often associated to chronic or repeated elevation of glucocorticoid hormones in the blood and, therefore, the definition of stress has mostly relied on glucocorticoids measurement. Nevertheless, glucocorticoids represent one stress-response system, the hypothalamus-pituitary-adrenocortical (HPA) axis, which is also related to metabolic regulation and it is activated in non-stressful situations (pleasure, excitement, and arousal). Therefore, analysing glucocorticoid levels alone may give only a partial picture of animal welfare and stress response. In this context, the use of DHEA(S) in conjunction with cortisol to improve the definition of the stress phenotype in farmed animals can be seen as an important tool, providing that the extra-adrenal contribution to circulating DHEA can be controlled [8].

In fact, different animal species can display specific features in the synthesis, regulation and biological role of these steroids to satisfy their own physiological requirements. Differences in adrenal androgen synthesis have been observed across species. In humans and other primates, adrenal androgen secretion is responsive to ACTH and stressors. In domestic mammals, adrenal secretion of DHEA in response to ACTH is well-documented “in vitro”. Nevertheless, published “in vivo” studies that have explored DHEA and DHEAS release in response to the administration of exogenous ACTH or stressors produced contradictory results in cattle and dogs [1]. The outcome of a series of experiments performed in the cow suggested that ACTH is not an

important DHEA secretagogue, and the adrenal contribution to plasma DHEA is scarce and, likely, the placenta is the most important source of DHEA, and the lactating mammary gland can affect circulating DHEA levels [9].

Then, other factors than ACTH can affect DHEA(S) synthesis and release. Even though these factors seem quite conserved among animal taxa, nevertheless, similar does not mean equal, and the biological properties observed in one animal taxa cannot be straightforward translated to another. Often, scientific works exploring DHEA(S) release in domestic mammals did not carefully consider the other factors that could affect this phenomenon, such as inflammatory and reproductive status, and the time-interval (chronicity) of exposure to stressors. Having in mind the scientific definition of "biomarkers", which are biological molecules used to understand a physiological process or diagnose an abnormal process or a disease [8], we try to understand whether DHEA(S) can be used as an ancillary biomarker of the stress phenotype in all animal species [1]. The measurement of DHEA in different biological matrices may be used to assess the stress response in animal of veterinary interest. For example, hair steroids (cortisol and DHEA) could be used to assess chronic stress in horses [10] and salivary DHEA is affected in response to physical and thermal stress in young bulls [11]. However, the use of this steroid as a specific stress biomarker is still debated.

Conflicts of Interest The Author declares no conflict of interest

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