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Is DHEA replacement beneficial in chronic adrenal failure?

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Although dehydroepiandrosterone (DHEA) and its sulphate ester dehydroepiandrosterone sulphate (DHEAS) are the most abundant steroid hormones in the human circulation, its exact physiological role is not yet fully understood. In patients with adrenal insufficiency, secretion of DHEA is impaired, leading to decreased circulating DHEA and DHEAS levels, and to androgen deficiency in women. Replacement of DHEA in patients with adrenal insufficiency positively influence mood, sexuality and subjective health status. These effects are generally moderate and show high inter-individual variability. Limited evidence exists for immunomodulatory effects of DHEA. Although an increase of IGF-I levels has been documented, relevant effects on body composition, metabolic or cardiovascular parameters has not been observed in patients with adrenal insufficiency receiving DHEA. Larger-scale phase III studies are still lacking; therefore, initiation of DHEA replacement is decided on an individual basis, focussing on those patients with impaired well-being associated with signs and symptoms of androgen deficiency.

Introduction

Dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulphate (DHEAS) are the most abundant steroids in humans. They are secreted from the adrenocortical zona reticularis. At birth,

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DHEA levels are high but drop thereafter, until they increase again during the adrenarche, shortly before the onset of puberty. Peak levels are achieved around the end of the third decade followed by a continuous decrease thereafter [1–3]. Secretion of DHEA is dependent on adrenocorticotropic hormone and varies diurnally, whereas DHEAS levels are more stable.

Both mechanisms of action and physiological effects of DHEA are not yet completely understood. DHEA is often referred to as adrenal androgen; however, its direct activity at the androgen receptor is negligible. The action of DHEA may more precisely be differentiated into direct and indirect effects (Fig. 1). Indirect effects result from conversion to androgens and oestrogens in the adrenal glands, the gonads and particularly in peripheral target cells. The enzymes 3β-hydroxysteroid-dehydrogenase, 17β-hydroxysteroid-dehydrogenase, 5α-reductase and P450 aromatase, which are necessary for the conversion of DHEA to active androgens and oestrogens, are expressed in almost every cell [4]. Thus, intracellular synthesis and metabolic inactivation may be performed according to the specific need of the cell without relevant changes of serum concentrations of the active steroids. This intracellular conversion and metabolic inactivation represents the classical example for the concept of intracrinology. Although DHEA may be converted to DHEAS by the DHEA sulfotransferase SULT2A1, no relevant amounts of DHEA result from conversion of DHEAS [5]. Therefore, DHEAS levels, which are measured in the routine clinical work up, may not always reflect the amount of available DHEA. In women, exogenous DHEA is mainly converted to androgens. In contrast, conversion to oestrogens is observed in men with normal endogenous DHEA levels, whereas an increase in serum androgens is observed in men with low androgen levels [6–8].

Several examples of direct DHEA effects exist, strengthening the concept of DHEA effects that are independent from its conversion to androgens or oestrogens. Evidence for a significant role of DHEA as a neurosteroid exerting neuroprotective, neurotrophic and anti-inflammatory effects within the brain is mounting [9,10]. High DHEA concentrations in human brains and cerebrospinal fluid have been found [11,12]. The central nervous system expresses P450c17 and other cytochrome P450 enzymes relevant for de-novo synthesis of DHEA, androgens and oestrogens within the brain [13,14]. DHEA and DHEAS show post-synaptic activity by modulating the actions of several cerebral neurotransmitter receptors. Both antagonistic and agonistic action at the GABAA-receptor has been demonstrated [15,16]; furthermore, modulation of the NMDA receptor and agonistic effects on the sigma 1-receptor involved in synaptic plasticity and cognitive function have been observed [17]. Presynaptic effects on neurotransmitter release include modulation of release of glutamate and acetylcholine and increased release of dopamine [9].

Manifold extracerebral direct DHEA/DHEAS effects have additionally been documented, although no DHEA receptor could so far be characterized in detail. Direct cellular effects could be observed that

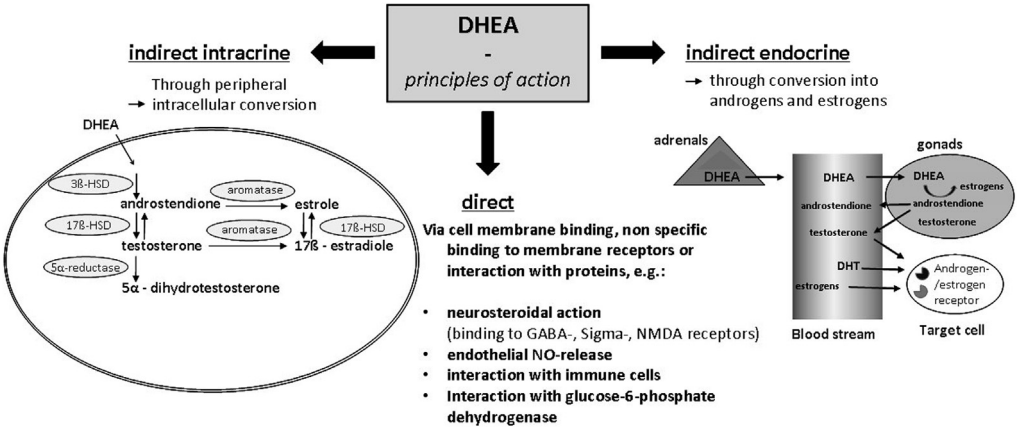

Fig. 1. DHEA principles of action.