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Review Article

Could dehydroepiandrosterone (DHEA) be a novel target for depression?

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Introduction

Steroid hormones are major players in organism development, organisation, and on the ability to respond to environmental challenges. They are produced by the adrenal cortex and may be divided into two categories: corticosteroids and androgens/sex steroids. Corticosteroids have been deeply studied in neurodegenerative disorders, but the interest in androgens for a long time has been related to their role as precursors of sex steroids. Dehydroepiandrosterone (DHEA), along with its sulphated form DHEA(S), account for the most abundant circulating steroid hormones (Baulieu, 1996). Studies point to DHEA and/or DHEA (S) as regulators of neurotransmission, with opposite effects to glucocorticoids. Herein, we provide a state-of-the-art review exploring the relationship between depression and DHEA and/or DHEA(S). We have searched and comprised the main information from cross-sectional and longitudinal studies, clinical trials and other interventional studies (i.e. interplay with antidepressant treatment), and meta-analysis. Moreover, in order to provide a better understanding of the field, we investigated and described elements of DHEA biology, from its genetics, synthesis and metabolism, to possible mechanisms of action by which DHEA may affect depression (e.g. counter effects to cortisol; interplay with neurotransmission; immune modulatory effect). Finally, we indicate gaps that remain open in the field, which could be a target for further research. This could enlighten and deepen the knowledge concerning the role of DHEA and/or DHEA(S) in depression aetiology.

Methods

We conducted a narrative review aiming to investigate the role of DHEA in depression. Study design, search criteria, identification and critical evaluation of results, manuscript preparation and final review by the authors occurred December/2018 to January/2021. The search was carried out in English, on the basis of title, abstract and/or keywords in the following databases: Pubmed, Science Direct, Scholar Google, Web of Science, Springerlink, Wiley online, and Elsevier. The list of keywords contained a combination of terms as the following: "DHEA biology", "DHEA synthesis", "DHEA genetics", "DHEA RNA", "DHEA central nervous system", DHEA steroidogenesis", "DHEA depression", "DHEA major depression", "DHEA major depressive disorder", "DHEA depressive symptoms", "DHEA cortisol", "DHEA/cortisol ratio", "DHEA cohort study", "DHEA cross-sectional", "DHEA longitudinal studies", "DHEA, "DHEA meta-analysis", "DHEA antidepressants", "DHEA neurotransmitters", "DHEA serotonin", "DHEA sigma receptors", "DHEA GABA receptors", "DHEA NMDA receptors", "DHEA inflammation", "DHEA immune system" and "DHEA inflammatory biomarkers" with or without Boolean terms. We excluded all the book chapters, conference abstracts, editorials, and short comments. Due to the methodological diversity and scope of the studies, it was not possible to use standardised selection based on the methodology of each article. However, the final selection of studies ranged from 1973 to 2020 and was critically evaluated by the first author. Our findings were structured and presented in 4 major sections: "DHEA biology", "DHEA and depression – Observational studies", "DHEA and depression – Interventional studies", "DHEA and depression – Potential mechanisms of action". A critical discussion is further proposed regarding the results.

DHEA biology

DHEA synthesis

DHEA is a major adrenal androgen derived from cholesterol. Its synthesis is classically understood to be restricted highest order of primates (Baulieu, 1996; Cutler et al., 1978; Quinn et al., 2016), thus, representing a recent evolutionary development. In humans, steroidogenic production starts from 6 to 8 weeks of gestation according to the embryonic development. At this stage, the production of DHEA derives from the adrenal foetal zone and is high (Mesiano and Jaffe, 1997); afterbirth, the adrenal foetal zone undergoes involution leading to a significant drop in DHEA levels. DHEA and/or DHEA(S) levels will increase once again during adrenarche. DHEA, now produced by the adrenal reticularis zone, is one of the signals that denotes the pubertal increase in adrenal androgens and occurs prior to the onset of increased

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gonadotropin secretion (Dhom, 1973; Gell et al., 1998; Mesiano and Jaffe, 1997; Maninger et al., 2009). Adrenal androgens are relatively weak androgens that are converted to more potent ones such as testosterone, dihydrotestosterone or to oestrogens via aromatization. Plasma DHEA levels have a diurnal rhythm similar to that of cortisol, but plasma levels of DHEA(S) show less variation and are a useful biochemical marker of adrenarche (Loomba-Albrecht and Styne, 2019).

In older age, by 70 to 90 years old, DHEA and DHEA(S) levels are approximately 70–80% lower than their peak levels on men and women (Labrie et al., 1997). It is therefore possible that DHEA plays a particular role in the development of old-age depression. Indeed, lower levels of DHEA and/or DHEA(S) in relation to their age-expectancy levels is associated with increased disease development and mortality (Phillips et al., 2010; Rendina et al., 2017; Tivesten et al., 2014).

DHEA synthesis is dependant on the action of CYP11A1, also known as CYP450scc (derivative from side chain cleavage). This enzyme plays a double step of hydroxylation on carbon bonds (Burstein et al., 1975; Mast et al., 2011; Strushkevich et al., 2011). As a result, there will be the formation of pregnenolone. This molecule is the precursor of all steroidogenic hormones, and its specifically conversion into DHEA involves the enzyme CYP17. This enzyme hydroxylates pregnenolone leading to the formation of 17-OH-pregnenolone, and further production of DHEA (Soucy and Luu-The, 2000).

DHEA to DHEA(S) conversion

DHEA(S) is a derivative from DHEA by the action of the sulfotransferase enzyme sulfotransferase 2A1 (SULT2A1), mainly in the adrenal glands and the liver. The majority of the circulating DHEA levels is on its sulphated form DHEA(S). This catalysis is mediated by the SULT2A1. Albeit an interconversion from DHEA(S) to DHEA might be possible by the action of steroid sulfatase, this reaction is unlikely to be relevant for the circulating levels of the hormones. Adrenal androgens are relatively weak androgens that are converted to more potent ones such as testosterone and dihydrotestosterone or to oestrogens via aromatization. Plasma DHEA levels have a diurnal rhythm similar to that of cortisol, but plasma levels of DHEA(S) show less variation and are a useful biochemical marker of adrenarche. In studies of depression both have been investigated interchangeably and this may add to the variability of the findings to some extent. There is initial evidence showing that the administration of DHEA indeed increases DHEA(S) levels, but the opposite was not observed (Hammer et al., 2005).

Genetic regulation of DHEA and DHEA(S) levels

The regulation of DHEA and/or DHEA(S) levels have been investigated, and genetic variants were identified that encode relevant proteins potentially associated with the regulation of hormone levels. A single nucleotide polymorphism (SNP; rs6162) associated to CYP17A1, which encodes the enzyme involved in the last step of DHEA formation, leads to a variation of up to 20% in DHEA(S) levels (Lévesque et al., 2013).

The widest genome-wide study (GWAS) to date ($n = 14{,}846$) found 8 SNPs associated to DHEA levels. Genes were ZKSCAN5 (rs11761528), ARPC1A (rs740160), CYP2C9 (rs2185570), TRIM4 (rs17277546), BMF (rs7181230), HHEX (rs2497306), BCL2L11 (rs6738028) and SULT2A1 (rs2637125) (Zhai et al., 2011). Of notice, at least two GWAS in an adult general population showed that the SNP rs2637125 on gene SULT2A1 was associated with low circulating DHEA(S) levels (Zhai et al., 2011), but the functional relevance of this finding is still unclear as the presence of this polymorphism did not impact on the actual DHEA/DHEA(S) ratio (Haring et al., 2013). The previously mentioned role of DHEA(S) in ageing may also have a genetic contribution since levels of DHEA(S) are also associated to BCL2 apoptosis regulator and the BCL2 modifying factor with genome-wide significance (Zhai et al., 2011).

A polymorphism (CYP3A7×1C) in CYP3A7 gene was associated to reduced DHEA(S) levels (Ruth et al., 2016) in up to 50% (Smit et al., 2005). This gene codifies the enzyme CYP3A7, which is expressed in the foetal liver, and it is involved in DHEA and/or DHEA(S) metabolism and clearance (Hakkola et al., 1994; Miller et al., 2004; Stevens et al., 2003).

A shunt or an increase on DHEA levels may also occur depending on the expression of 3β-hydroxysteroid-dehydrogenase (3βHSD1). Gene encoding this enzyme may present an adrenal-restrictive allele or an adrenal-permissive allele, which, respectively, limits conversion of DHEA towards other androgens or enhances DHEA metabolism by conferring resistance to ubiquitination (Naelitz and Sharifi, 2020).

DHEA and DHEA(S) in the central nervous system

Early investigations pointed DHEA as a neurosteroid - a hormone locally produced in the brain (Baulieu and Robel, 1998). Although peripheral DHEA can freely cross the brain-blood barrier, DHEA(S) as a hydrophilic molecule cannot (Starka et al., 2015). Carriers such as the organic anion transporting polypeptide (OATP), ATP-binding cassette, and solute carriers are involved in the cellular uptake of DHEA(S) (Kullak-Ublick et al., 1998; Starka et al., 2015). DHEA(S) might be locally un-sulphated in cellular tissues by steroid sulfatases (Reed et al., 2005) before being converted into other metabolites.

The first demonstration suggesting that DHEA(S) might have a role in neuromodulation came from the findings of the androgen expression in rat brains (Corpéchot et al., 1981), once a systemic production is absent or very low in rats (Baulieu and Robel, 1998; Baulieu, 1996; Corpéchot et al., 1981; Cutler et al., 1978). In fact, in a recent post-mortem study was shown that the mRNA and the immunostaining of CYP17 is diminished in the anterior cingulate cortex of depressed patients, while the SULT2A1 mRNA is increased in the dorsolateral prefrontal cortex. Thus, showing an imbalance in DHEA and DHEA(S) brain metabolism (Qi et al., 2018). Besides, evidences show the brain expression of DHEA in fashion that its concentration is higher than the plasmatic levels (Lacroix et al., 1987). DHEA levels found in the brain are understood to be mainly synthesized de novo (Baulieu and Robel, 1998; Baulieu, 1996). The production is unrelated to the circadian endocrine regulation (Robel et al., 1986) as neither the treatment with dexamethasone, nor adrenalectomy diminishes DHEA(S) levels in the brain; and treatment with corticotrophin failed to modulate it (Corpéchot et al., 1981).

Studies on animal models support the local synthesis of DHEA as brain cells express the sterodoigenic cytochrome enzimes CYP11A1 and CYP17 (Kohchi et al., 1998; Manca et al., 2012; Ukena et al., 1998; Maninger et al., 2009), the first step in the biosynthesis of steroid hormones. Further support to the local production of DHEA is the fact that hippocampal cells convert pregnenolone into DHEA (Hojo et al., 2004). Another alternative pathway for brain DHEA production could involve oxidative stress. In human brain cell cultures (Brown et al., 2000) and in brain tissue (Rammouz et al., 2011; Brown et al., 2003) DHEA was synthetized through oxidative stress-mediated metabolism and independent of the CYP17 activity.

DHEA and depression – observational studies

Depression

Depression is a mental condition of massive global impact, with more than 320 hundred million people suffering from it. Common systemic impacts related to depression are to mood variations, sadness, loss of pleasure and feelings, anxiety, sleep disturbances, amongst others. It is the worldwide leading cause of disability and suicide (WHO, 2017). Current treatments have not been successful to a limited proportion of individuals. Despite the fact that depression is associated with neurotransmitter disturbances, inflammatory processes, and dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis (Jain et al., 2018), in depth aetiological and pathophysiological mechanisms are yet to be described.

DHEA and DHEA(S) levels in depression

Most mental health disorders start during adolescence and the incidence of emotional disorders rises dramatically between 11 and 18 years (Joinson et al., 2017). It is well established that DHEA have different levels between men and women. In both genders the production peak is reached around the third decade of life, with a consequent age-related decline of approximately 2% a year (Racchi et al., 2003).

Cross-sectional studies of DHEA and DHEA(S) in major depressive disorder

The association between DHEA and/or DHEA(S) in major depressive disorder (MDD) are still conflicting (Table 1). Studies which show DHEA and/or DHEA(S) levels are decreased (Barrett-Connor et al., 1999; Goodyer et al., 1996; Michael et al., 2000; Morsink et al., 2007; Souza-Teodoro et al., 2016; Zhu et al., 2015) in depression; but increased (Assies et al., 2004; Heuser et al., 1998) and no association have also been reported (Hsiao, 2006b; Osran et al., 1993; Young et al., 2002). The exact reason for controversial findings is unknown, but may be related to gender, biological substrate where DHEA(S) was analysed (serum/plasma or saliva) and inclusion of medicated patients. Studies conducted only in women found that DHEA(S) was decreased in major depressive disorder (Barrett-Connor et al., 1999; Lopes et al., 2012), but not all (Erdinçler et al., 2004). DHEA levels were increased when both genders were analysed together in medicated patients, but decreased in medicated depressed men when gender was separately analysed (Kurita et al., 2012).

Table 1
Summary of cross-sectional studies evaluating DHEA and/or DHEA(S) levels in patients with major depressive disorder (MDD) in A) plasma/serum and B) saliva.

A) Plasma/Serum/Urine			
Author	Participants	Sample	Results
Men and women			
(Osran et al., 1993)	9 MDD 9 HC	Serum Urine	→
(Heuser et al., 1998)	26 severe MDD 33 controls	Plasma	↑
(Hsiao, 2006b)	28 MDD	Serum	→
(Markopoulou et al., 2009)	28 severe MDD 40 HC	Plasma	→
(Phillips et al., 2011)	185 MDD 3755 HC	Serum	→
(Kurita et al., 2012)	90 MDD 128 HC	Serum	↑
(Morita et al., 2014)	24 MDD 24 HC	Plasma	↑
Men			
(Kurita et al., 2012)	90 MDD 128 HC	Serum	↓ DHEA(S) in men
(Šrámková et al., 2017)	20 MDD 30 HC	Plasma	↓
(Uh et al., 2017)	117 MDD	Serum	↑ in mild to moderate depression ↓ severe depression
Women			
(Barrett-Connor et al., 1999)	31 MDD 93 HC	Plasma	↓
(Erdinçler et al., 2004)	34 MDD 40 HC	Plasma	→
(Lopes et al., 2012)	38 MDD 15 HC	Serum	↓
B) Saliva			
Author	**Participants**	**Sample**	**Results**
Men and women			
(Goodyer et al., 1996)	82 MDD children 40 HC	Saliva	↓
(Michael et al., 2000)	44 MDD 41 HC	Saliva	↓
(Young et al., 2002)	39 drug-free MDD 41 controls	Saliva	→
(Assies et al., 2004)	13 MDD 13 HC	Saliva	↑
(Jiang et al., 2017)	38 MDD 43 HC	Saliva	→

Legend: DHEA – Dehydroepiandrosterone; DHEA(S) Dehydroepiandrosterone sulphate; MDD major depressive disorder; HC healthy control. Arrows represent increased, decreased or no change of DHEA and/or DHEA(S) levels of depressive symptoms in depressed patients compared to health/group control.

Indeed, meta-analysis studies confirm an inverse association between DHEA and/or DHEA(S) levels and depression (Zhu et al., 2015). Ten studies with clinic diagnosed depressed patients were evaluated in each meta-analysis, and five studies were included in both (Hu et al., 2014; Zhu et al., 2015). Differences amongst ethnicity, sex and sample size were not related to the heterogeneity of results in the association between depressive symptoms and DHEA(S) levels according to the meta-analysis. No significant bias related to detection method was observed (Zhu et al., 2015). But Hu et al. (2014) found the inverse relationship between depression and levels of DHEA(S) in studies analysing plasma and serum, but not in saliva.

Cross-sectional studies of a correlation between DHEA and DHEA(S) and depressive symptoms

DHEA and/or DHEA(S) levels have also been investigated in larger groups of individuals with depressive symptoms with more consistent results. Most studies report a negative cross-sectional correlation between DHEA(S) and depressive symptoms (Morsink et al., 2007), (ó Hartaigh, 2012), (Souza-Teodoro et al., 2016) but no correlation also exist (Veronese et al., 2015). Some studies have looked exclusively at one gender only. They report negative correlation between DHEA and/or DHEA(S) and depressive symptoms when investigated in men only (T'Sjoen et al., 2005; (Wong et al., 2011) and in women only (Barrett-Connor et al., 1999) (Barrett-Connor et al., 1999).

Longitudinal studies

Information from longitudinal studies emphasizes the relationship between depression and DHEA and/or DHEA(S), by more consistently demonstrating that these hormones could be a predictor of depression development although controversies in relation to gender differences exist (Table 2B) Yaffe et al. (1998). conducted a prospective (4 – 6 years) study with elderly women in which there was not an association between DHEA(S) and depressive symptoms. Nevertheless, they analysed a subset of women who did not have detectable levels of DHEA(S), and it was shown that these women had higher depressive symptoms (Yaffe et al., 1998). In a 4-year longitudinal study with men and women, there was an association between low DHEA(S) levels and depression in women, but not in men (Berr et al., 1996). The opposite was also observed, i.e. reduced DHEA(S) levels were associated to further development of depression (1-year follow-up) only in men, amongst Japanese (Michikawa et al., 2013) and Taiwanese (Goldman and Glei, 2007) cohorts with both genders (3 years follow-up) Veronese et al. (2015). showed an inverse association with depression in both men and women (4.4 years follow-up), but the severity of depression was associated to DHEA(S) levels only in men (Veronese et al., 2015). The largest study to date of a community-dwelling of men and women shows DHEA (S) is a predictor (4 years follow-up) of depression in both genders (Souza-Teodoro et al., 2016).

Table 2
Summary of A) cross-sectional and B) longitudinal cohort studies evaluating the relationship between depressive symptoms and DHEA and/or DHEA(S) levels.

A) Cross-sectional			
Author	Participants	Is DHEA(S) anddepressive symptoms inversely correlated?	
Men and women			
(Morsink et al., 2007)	2855	Yes	
(ó Hartaigh, 2012)	608	Yes	
(Veronese et al., 2015)	789 elderly	No	
(Souza-Teodoro et al., 2016)	3083 elderly	Yes	
Men			
(T'Sjoen et al., 2005)	236 elderly	Yes	
(Wong et al., 2011)	1147 elderly	Yes	
Women			
(Barrett-Connor et al., 1999)	699	Yes	
(Haren, 2007)	244	Yes	
B) Longitudinal			
Author	**Participants**	**Time of Follow-up**	**Is DHEA(S) and depressive symptoms inversely correlated?**
Men and women			
(Berr et al., 1996)	622	4 years	No, in men Yes, in women
(Goldman and Glei, 2007)	841	3 years	Yes, in men No in women
(Michikawa et al., 2013)	554	1 year	Yes, in men No, in women
(Veronese et al., 2015)	789	4.4 years	Yes
(Souza-Teodoro et al., 2016)	3083 elderly	4 years	Yes
Men			
(T'Sjoen et al., 2005)	236 elderly	3 years	No
Women			
(Yaffe et al., 1998)	394	4–6 years	Yes

DHEA and depression – interventional studies

Does antidepressant treatment modulate DHEA(S) levels as part of their therapeutic benefit?

The association between DHEA and MDD/depressive symptoms has led to the speculation that antidepressants modulate DHEA and/or DHEA(S) levels. Some studies have attempted to answer this question by analysing the effect of antidepressants of different classes on DHEA and/or DHEA(S) levels(Table 3). Overall, most studies show that treatment with antidepressants of different classes decrease DHEA and/or DHEA (S) levels (Morita et al., 2014), (Hsiao, 2006a), (Schule et al., 2009), Paslakis et al., 2010, (Zhu et al., 2015). Some studies showing no association (Hough et al., 2017), Wijaya et al. (2018) or association dependant upon the mechanism of action of drug used (Deuschle et al., 2004) also exist. Most of these studies did not take antidepressant response or remission into account.

The evidence that antidepressants modulate DHEA and/or DHEA(S) particularly in those who decreased or remitted their depressive symptoms is controversial Paslakis et al., 2010. showed that only in patients who remitted antidepressants decreased DHEA(S) levels. Whereas

Table 3
Summary of studies analysing the effects of clinical antidepressants upon DHEA and/or DHEA(S) levels.

Author	Participants	Sample	Treatment period (weeks)	Treatment	Result
Men and women					
(Deuschle et al., 2004)	80 MDD	Serum	5	Paroxetine Amitriptyline	→ ↓
(Hsiao, 2006a)	34 MDD	Plasma	12	Venlafaxine	↓
(Schule et al., 2009)	23 MDD	Plasma	5	Mirtazapine	↓
(Paslakis et al., 2010)	70 MDD	Serum	4	Mirtazapine Venlafaxine	↓ ↓
(Morita et al., 2014)	24 MDD 24 HC	Plasma	25	Several	↓
(Zhu et al., 2015)	46 MDD 55 HC	Serum	8	Serotonin + Citalopram	↓
(Hough et al., 2017)	36 MDD 75 HC	Serum	8	Several SSRI	→
(Wijaya et al., 2018)	47 MDD 41 HC	Urine	Not specified	Several (SSRI, SNRI, NaSSA, DNRI, agomelatine, vortioxetine, quetiapine)	→

DHEA – Dehydroepiandrosterone; DHEA(S) – Dehydroepiandrosterone sulfate; SSRI – Selective serotonin reuptake inhibitor; SNRI – Serotonin–noradrenaline reuptake inhibitor; MDD – major depressive disorder; HC – healthy controls. Arrows represent increased, decreased or no change of DHEA and/or DHEA(S) levels of depressive symptoms in depressed patients compared to health/group control.

Hough et al., 2017 showed that patients remitted patients had higher levels of DHEA(S) than non-remitted patients after 8-weeks of treatment with open-label SSRI Hsiao et al., 2006a. reported DHEA levels decreased in remitted patients, but did not have non-remitted patients to compare. They also positively correlated with improvement of the symptoms in remitted patients (Hsiao, 2006a).

It is possible that antidepressants of different mechanism of action exert different effects on DHEA and/or DHEA(S) Wijaya et al. (2018). did not find differences in DHEA(S) in response to antidepressant treatment when patients received treatment with antidepressants of different classes (Wijaya et al., 2018) Morita et al., 2014., on the other hand, found decreased DHEA(S) levels after 8 weeks of antidepressant use regardless of the class of antidepressants used (Morita et al., 2014). (Deuschle et al., 2004) observed that the tricyclic antidepressant amitriptyline decreased DHEA(S) levels, but not paroxetine. Whether antidepressants necessarily need to decrease DHEA(S) levels to exert its therapeutic benefit is still unknown. To our knowledge, there has been no study that evaluated whether levels of DHEA and/or DHEA(S) increase *before* the therapeutic benefit of antidepressants occur. More studies are needed to clarify the role of DHEA and/or DHEA(S) in antidepressant treatment.

Whether the alteration in DHEA(S) levels in response to antidepressant are a biological component in depression amelioration or if it is related to a direct action on HPA remains to be clarified. In these regard, hormone levels should also be further explored in terms of remission. A disturbance in HPA system is the more consistent finding amongst depressed patients, typically demonstrated by disturbances in cortisol levels. Different responses related to HPA activity is observed in relation to antidepressants (Nandam et al., 2020), and cortisol levels may predict treatment outcome (Carvalho and Pariante, 2008; Jain et al., 2018).

Thus, considering DHEA(S) levels at baseline could also be a trait to be relevant to understand the response to treatment, i.e., patients with depressed symptoms associated to low levels of DHEA(S) may present a different response to antidepressants when compared to those with normal or either elevated levels of the hormone.

Could DHEA be used as a treatment to depression?

The role of exogenous DHEA as a treatment for depressive symptoms was investigated (Table 4).

A systematic review showed that DHEA treatment for depression and depressive symptoms in people with other psychiatry pathologies and medical conditions (Peixoto et al., 2014). Twenty-two studies met the eligibility criteria, and the administration of DHEA led to an overall improvement in depressive symptoms. Moreover, DHEA decreased depressive symptoms on diseases such as schizophrenia, adrenal insufficiency, HIV, and anorexia. Results regarding patients with autoimmune diseases were not conclusive, and the amelioration of depressive symptoms was not observed in patients with fibromyalgia. In a more recent systematic review and meta-analysis evaluating randomised clinical trials for depression in the absence of other medical illnesses showed that DHEA used as a treatment indeed ameliorate depression when compared to placebo (Peixoto et al., 2018).

Studies present a large variation in the concentration of DHEA used for depressive symptoms. Evidence show that patients taking DHEA (30 – 90 mg/day, 4 weeks) had an improvement in their depressive symptoms (Wolkowitz et al., 1997). They also made a 2-step approach to a patient who was treatment-resistant. Firstly, they administered 60 mg/day of DHEA for 4 months. Secondly, they raised the DHEA dose to 90 mg/day for 2 months. At the end of the 6-month treatment, both memory performance and depression rating were improved, in a fashion that this improvement was correlated to the augmented DHEA and DHEA(S) levels. Similar findings were reproduced in a further study of the same group, in which they expanded their samples and conducted a double blinded, placebo-controlled trial of DHEA administration to patients with depression (Wolkowitz et al., 1999). It is possible that a U-shape relationship of treatment-effect exist as animal studies show DHEA only caused improvement in memory retention and neuronal survival for the intermediate concentrations (Samardzic et al., 2017).Of note, most patients were not medication-free which may have contributed to the results.

The positive effects of DHEA (90 mg/day for 3 weeks, following 450 mg/day for 3 weeks) as a monotherapy was evaluated in chronic depressed. In this study, DHEA also led to an amelioration of depressive symptoms (Bloch et al., 1999), accompanied of increases on DHEA and DHEA(S) levels. A more robust result of this research group was further published (Schmidt et al., 2005), in which they used the same treatment design, and emphasized the benefits of using DHEA as a monotherapy for the amelioration of depressive symptoms. Furthermore, in depressed patients with the human immunodeficiency virus (HIV), DHEA (100 – 400 mg/day for 8 weeks) treatment also reduced the symptomatology of depression (Rabkin et al., 2006).

DHEA and depression - Potential mechanisms

Classically, DHEA and DHEA(S) effects are related to its conversion in specific tissues into androgens or oestrogens, as these hormones have higher affinity to nuclear receptors than DHEA (Prough et al., 2016). However, the evidence suggesting a protective role of the circulating DHEA and/or DHEA(S) preventing development of depression, led to investigations of possible mechanisms of action in this relationship, including those exploring the synthesis and actions of DHEA levels in the central nervous system. DHEA and/or DHEA(S) are being observed as showing opposing effects to cortisol, presenting direct and indirect actions as a neuromodulator, and being involved with inflammatory responses.

It is believed that DHEA and DHEA(S) and cortisol exert opposing protective/toxic effects and, thus, the analysis of the ratio DHEA/cortisol may be important for psychiatric disorders. DHEA is an ACTH-regulated steroid that possesses anti-glucocorticoid properties (Kalimi et al., 1994) partly by inhibiting the 11 Beta hydrosysteroid dehydrogenase type 1 enzyme which converts the inactive cortisone to the active cortisol (Tomlinson et al., 2004). Studies show that DHEA protects hippocampal cells against neurotoxicity induced by cortisol (Kimonides et al., 1999). A similar finding was observed in neurotoxicity glutamate-induced, in which the protective DHEA role was suggested to be related to an inhibition on nuclear levels of glucocorticoid receptors (Cardounel et al., 1999). DHEA administration is also able to reverse the increased glucocorticoid receptor expression induced by stress and presented anti-stress activity once DHEA treatment inhibited the translocation of stress-activated protein kinase type 3 (Hu et al., 2000; Kimonides et al., 1999).

Studies have shown that DHEA levels may acutely increase in response to stress stimuli but returning to baseline levels after stress recovery in healthy subjects (Lennartsson et al., 2012; Lenartsson, 2013). Such Increased levels of cortisol and low DHEA(S) contribute to the maladaptive responses to stress in several biological systems - named allostatic load - offer risks such as cardiovascular and psychiatric

Table 4
Summary of intervention studies on effects of either exogenous DHEA for depressive symptoms.

Author	Participants	Treatment (dose)	Study design	Treatment period (weeks)	Depressive symptoms
Men and women					
(Wolkowitz et al., 1997)	6 MDD	DHEA (up to 90 mg/day)	Open-label	6	↓
(Wolkowitz et al., 1999)	22 MDD	DHEA (up to 90 mg/day)	RCT	4	↓
(Bloch et al., 1999)	17 dysthymia	DHEA (up to 450 mg/day)	Cross-over RCT	6	↓
(Schmidt et al., 2005)	46 MDD	DHEA (up to 450 mg/day)	Cross-over RCT	6	↓
(Rabkin et al., 2006)	145 HIV patients with depression or dysthymia	DHEA (up to 400 mg/day)	RCT	8	↓
(Kritz-Silverstein et al., 2008)	115 healthy elderly	DHEA (50 mg/day)	RCT	52	→
Women only					
(Collomp et al., 2018)	10 athletes' women	DHEA (100 mg/day)	RCT	4	→

DHEA – Dehydroepiandrosterone; DHEA(S) – Dehydroepiandrosterone sulfate; HIV – Human immunodeficiency virus; RCT- randomised controlled trial, MDD- major depressive disorder. Arrows represent increased, decreased or no change of DHEA and/or DHEA(S) levels of depressive symptoms in depressed patients compared to healthy/groupcontrol.

disorders (Maninger et al., 2009; McEwen and Gianaros; 2011). Adults exposed to long-term stress or clinical burnout showed attenuated DHEA (S) levels and a higher cortisol/DHEA(S) ratio, suggesting that under chronic stress, steroidogenesis suffers a shunt favouring cortisol synthesis and down-regulating DHEA and/or DHEA(S) (Kamin and Kertes, 2017).

DHEA/cortisol and cortisol/DHEA ratios in depression

It has been proposed that the counter effects between DHEA and/or DHEA(S) and cortisol may be involved in the development of psychiatric disorders, such as depression (Butcher et al., 2005; Gallagher and Young, 2002), and this ratio might be a more consistent and relevant tool than the levels of these hormones alone to evaluate depression. In un-medicated patients with unipolar depression, neither cortisol nor DHEA levels on their own were associated to depression, while cortisol/DHEA ratio was significantly greater amongst those depressed (Young et al., 2002). In medicated depressed patients, higher cortisol/DHEA ratio was found in remitted patients compared to healthy subjects (Michael et al., 2000). In depressed adolescents with post-traumatic stress disorder (PTSD), DHEA(S)/cortisol was able to predict therapy response (Eye Movement Desensitization and Reprocessing - EMDR) (Usta et al., 2018), and higher cortisol/DHEA ratio in children and teenagers (8 to 16 years old) predicts persistent depression up to 36 weeks, while the measure of the hormones alone could not (Goodyer et al., 1998). In addition, cortisol/DHEA(S) ratio is a predictor of up to 10 years of recurrence (Mocking et al., 2015). Others corroborate the finding that depression is associated to higher cortisol/DHEA ratio (Kahl et al., 2006; Osran et al., 1993).

The differences between cortisol and DHEA are also observed in other psychiatric conditions. Higher salivary levels of cortisol are associated to enhanced anxiety, while elevated DHEA levels were associated to lower anxiety (van Niekerk et al., 2001). Patients with Cushing's syndrome show decreased DHEA(S) levels (Yener et al., 2015). Acute stress test is followed by an enhancement of cortisol levels (Kidd et al., 2014) while Trier Social Stress Test led to diminished DHEA(S) levels on participants with higher perceived stress at work (Lennartsson et al., 2013). The Trier Social Stress Test also led to attenuated responses of DHEA and DHEA(S) in depression comparison to healthy participants (Jiang et al., 2017). It has been suggested that the ratio cortisol/DHEA provides a better prediction of mortality or health, than the levels of these molecules on their own (Kamin and Kertes, 2017; Phillips et al., 2010; Sollberger and Ehlert, 2016).

The role of pharmacologic treatment in the regulation of these steroids was also evaluated. Noradrenergic and specific serotonergic antidepressants reduced both cortisol and DHEA(S), suggesting that the antidepressant led to a diminishment on hypothalamic-pituitary-adrenal (HPA) function. Nevertheless, the treatment did not affect the cortisol/DHEA(S) ratio. Interestingly, only the reduction on DHEA(S) levels was associated to the diminishment of depressive symptoms (Schule et al., 2009). Others observed that remission was associated to a reduction on DHEA(S) levels, and an enhancement on cortisol/DHEA(S) ratio (Paslakis et al., 2010). In addition, the administration of L-tryptophan to healthy subjects and depressed patients neither altered the levels of the hormones alone nor the cortisol/DHEA ratio (Porter et al., 2003). In the study case of Wolkowitz et al. (1997), in which DHEA was administrated, both DHEA/cortisol and DHEA(S)/cortisol ratios were negatively correlated to depressive symptoms (Wolkowitz et al., 1997).

DHEA as a neuromodulator

Emerging evidences have been showing that DHEA(S) can activate directly G-protein coupled receptors. For instance, DHEA(S) modulates the expression of tight junctions of the blood brain barrier (Papadopoulos and Scheiner-Bobis, 2017).

Relevant roles are associated to DHEA and/or DHEA(S) in the central nervous system and in psychiatric conditions. Studies showed that DHEA and/or DHEA(S) improve synapse efficacy (Moriguchi et al., 2013), enhance neuronal survival and differentiation (Bologa et al., 1987; Roberts et al., 1987), have a neuroprotective role against oxidative stress (Bastianetto et al., 1999), and display neurogenic and neurotrophic activity (Moriguchi et al., 2013; Sakr et al., 2014). Moreover, these hormones interact directly and indirectly with neuronal circuitry.

GABAergic and serotonergic systems

The gamma-aminobutyric acid (GABA) signalling is involved in the development of psychiatric conditions such as anxiety, depression, and stress-related responses through exerting neural inhibitory activity (Kalueff and Nutt, 2007; Luscher et al., 2011), and GABA receptors have their signalling affected by DHEA. For instance, animal models of depression showed that DHEA treatment decreased depressive-like behaviour in the immobility swim paradigm due to DHEA inhibitory effect on GABAA receptors (Genud et al., 2009). DHEA(S) neuroprotective role was demonstrated in an ischaemic model of mild to medium oxygen-glucose deprivation. This protective effect was inhibited by either GABAA agonist pentobarbital or GABAA antagonist picrotoxin (Kaasik et al., 2001), emphasizing a crosstalk in this signalling. Recently, it was demonstrated that DHEA(S) inhibits GABAA effects through stabilizing the receptor into a nonconductive state (Pierce et al., 2022).

Another pathway by which DHEA can have neuromodulatory effects involves the serotonergic signalling. The imbalance in the serotoninergic system has been one of the most stablished pathways involved in psychiatric conditions such as depression (Albert et al., 2012; Yohn et al., 2017). DHEA and DHEA(S) diminish the inhibitory response of GABAA receptors upon serotonin-rich neurons in the dorsal raphe nucleus (Gartside et al., 2010). This effect indicates that DHEA may modulate serotonergic transmission via its modulation of GABA receptors. Besides, treatment with DHEA increases serotonin turnover in the nucleus accumbens (Perez-Neri et al., 2008), and decreases the activity of monoamine oxidase (Perez-Neri et al., 2009).

NMDA and sigma receptors

DHEA also has an involvement with neuronal survival and synaptic efficiency and may impact depression via such modulation. DHEA protects against neurotoxicity induced by the activation of N-methyl-D-aspartic acid (NMDA) receptors in cultured neurons from the hippocampus (Kimonides et al., 1998). DHEA(S) can also increase synaptic efficiency by eliciting calcium ions and increasing long-term potentiation (Chen et al., 2006). DHEA can also increase the firing-rate of NMDA receptors (Bergeron et al., 1996).

Sigma receptors have been demonstrated to display an antidepressant role, and their activation by DHEA and/or DHEA(S) is one the most consistent role of these hormones as neurosteroids. In mice, studies show that depressive behaviour has the involvement of sigma non-opioid intracellular receptor 1, and the interaction with DHEA and/or DHEA (S) ameliorates this condition (Urani et al., 2001). In an animal model of depression using olfactory bulbectomized mice, chronic DHEA treatment increases neurogenesis, reduces depressive behaviour through activating sigma non-opioid intracellular receptor 1 (Moriguchi et al., 2013), and ameliorates cognitive impairment (Moriguchi et al., 2011).

Immune system and inflammation

DHEA(S) may exert an additional neuroprotective role in depression by decreasing inflammation – yet another pathway disturbed in patients with depression (Setiawan et al., 2015). In astrocytes and microglia, DHEA and/or DHEA(S) reduces the levels of tumour necrosis factor (Di Santo et al., 1996; Kipper-Galperin et al., 1999). DHEA inhibits production of interleukin (IL)−6 (Kipper-Galperin et al., 1999), while

DHEA(S) treatment reduced the transcription of pro-inflammatory markers such as tumour necrosis factor and IL-1B in animal models (Maingat et al., 2013).

Discussion and conclusion

The role of DHEA and/or DHEA(S) in relation to depression has been explored in the past decades, and in spite of the lack of consensus, there seems to be an inverse association between the circulating levels of these hormones and depression. Questions, however, remain to be clarified. Studies have not explored the direction of this relationship, i.e., diminished levels of DHEA and/or DHEA(S) are a part of depression development or are one of the consequences of the disease? Moreover, meta-analysis evaluating cross-sectional studies indicates that further steps could benefit from measuring these hormones in serum or plasma, rather than in saliva, which offers more results variability.

DHEA and/or DHEA(S) were also found to be inversely associated to depression in longitudinal studies, what may also suggest that this relationship is causal. Corroborating this hypothesis, evidences showed that patients receiving DHEA as a treatment for depression had an amelioration of symptoms in the studies observed. Of notice, this finding was not replicated by all the studies, but was confirmed in a meta-analysis. Nevertheless, a standardization of this treatment (dose, time of treatment) is not stablished.

Systemically, the relationship of these hormones with cortisol has been shown as a relevant trait to a better understanding of the adrenal function, and may reflect depression prognosis. The opposing effects/ratio of these hormones have been explored, and some authors claim that this ratio could play as a more robust indicator of depression than any of these hormones alone. Moreover, novel evidences pointing to both synthesis and direct actions of DHEA and/or DHEA(S) in the central nervous emphasize the importance of continuous investigation regarding the contribution of these hormones to depression development. There is plenty of evidence showing that DHEA and/or DHEA(S) may affect classic neurotransmitters relevant to the disease.

In sum, DHEA shows potential to ameliorate depressive symptoms. Further studies should focus on understanding who would particularly benefit from such treatment, for how long and in which concentration.

Declaration of Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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