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THE ROLE OF DEHYDROEPIANDROSTERONE (DHEA) IN SCHIZOPHRENIA

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SUMMARY

Neurosteroid dehydropiandrosterone (DHEA) and its sulphate (DHEAS) are reported to have modulatory effects on neuronal excitabillity and synaptic plasticity. DHEA and DHEAS are synthesized in central and peripheral nervous system from cholesterol or steroidal precursors imported from peripheral sources. There is accumulating evidence that alterations in DHEA(S) levels may be involved in the pathophysiology of schizophrenia. The possible effects of DHEA(S) as augmentation therapy in schizophrenia, related to psychological and somatic aspects of this disease, are discussed.

Key words: *schizophrenia – dehydroepiandrosterone – DHEA – DHEAS - augmentation therapy*

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Introduction

Neurosteroid dehydropiandrosterone (DHEA) and its sulphate (DHEAS) are reported to have modulatory effects on neuronal excitabillity and synaptic plasticity. They also have many other functions associated with neuroprotection, response to stress, mood regulation and cognitive performance. Furthermore, these neurosteroids have been linked to, and their levels are altered in, various psychiatric disorders (Ritsner 2010).

Schizophrenia is a chronic and disabling mental disorder characterized by psychopathological symptoms, elevated emotional distress and a significant decline in cognition, quality of life and psychosocial functioning. Although the molecular mechanisms of neurodegeneration and pathogenesis of schizophrenia remain largely unknown, a significant body of literature indicates that the main mechanism may include apoptosis, excitotoxicity and oxidative stress (Berger et al. 2003, Ciobica et al. 2011).

Despite the advances in schizophrenia research and drug development currently available, antipsychotic agents continue to treat symptoms rather than provide a cure and overall clinical response remains insufficient and incomplete (Plesničar 2015, Šagud 2015). The development of more effective treatment is an important research goal. One promising direction is the use of neurosteroids, substances produced in the brain and neuroactive steroids, produced in adrenal gland and gonads. Recently, there has been a great deal of interest in the possible involvement of neurosteroids in the pathogenesis and pharmacotherapy of schizophrenia (Frau et al. 2015).

DHEA and DHEAS are synthesized in the central and peripheral nervous system from cholesterol or steroidal precursors imported from peripheral sources (Baulieu 1998). DHEA(S) concentrations in the human brain were found to be much higher than in peripheral circulation and also exceeded their very low cerebrospinal fluid levels. DHEA(S) are the most abundant neurosteroids in humans. Levels of DHEA(S) decrease with age, and their levels in elderly population are reduced to 20 to 30% of peak levels in young adulthood. DHEA(S) concentration rise during puberty, peak in early twenties in men and thirties in woman, and decline from the third decade onward (Orentreich et al. 2002).

Biological actions of DHEA(S) include neuroprotection against apoptosis, excitotoxicity mediated by N-methyl-D-aspartat (NMDA) or oxidative damage, promotion of neurite growth, opposition of glucocorticoids, effects on oxidants and glucocorticoids, a modulatory effect on neuronal excitability and synaptic plasticity (Ritsner et al. 2008, Mellon 2007, Maninger et al. 2009).

DHEA(S) is produced at high concentration in the human embryo enhancing neuronal development but its production rate and levels in serum and brain, as we mentioned before, decrease gradually with advancing age. This decline was associated to age related neuronal dysfunction and degeneration, suggesting a neuroprotective effect of endogenous DHEA against noxious agents (Charalampopoulos et al. 2008). DHEA(s) exibit reduction of risk of age-related neurodegenerative disorders. This specificaly reffers to a protective effect of DHEA(S) on the hippocampus which supports the proposed antiglucocorticoid effect of DHEA(S). Morgan et al. (2004) provide prospective empiric evidence that the DHEA(S) levels are increased by acute stress in healthy humans and that the DHEA(S) to cortisol ratio may index the degree to which an individual is buffered against the negative effect of stress.

The role of DHEA and DHEAS in the etiopathogenesis of schizophrenia

The decline of neurosteroid levels during aging and schizophrenia may leave the brain unprotected against neurotoxic challenges. In animal models, DHEA(S) stimulate hypothalamic-pituitary–adrenal (HPA) axis activity and cerebral brain–derived neurotrophic factor (BDNF) protein levels. These results strongly suggest that part of the HPA axis and antidepressant effects of neuroactive steroids could be mediated by BDNF, particularly on the amygdala levels (Naert et al. 2007). DHEA(S) demonstrates neuroprotective effects on NMDA-induced neurotoxicity in primary cultured rat hippocampal neurons, as well as a blockage of the neurotoxic effects of cortisol on hippocampal cells, and protection of neurons against glutamate and amyloid beta protein toxicity (Cardounel et al. 1999).

At the cellular level, neurosteroids have modulatory effect on the release of multiple neurotransmitters like glutamate, GABA, acetylcholine, norepinephrine, dopamine and 5-HT (Zheng 2009). They directly affect major CNS receptors, especially gamma-aminobutyric acid (GABA A), NMDA, and sigma receptors. There is accumulating evidence that alterations in DHEA(S) levels may be involved in the pathophysiology of schizophrenia (e.g., Beyazyuz et al. 2014).

Blood DHEA and DHEAS levels of schizophrenia patients and healthy subjects were found to differ across studies, ranging from normal to low and to high levels (Tourney & Erb 1979, Oades & Schepker 1994, Ritsner et al. 2009, Galagher et al. 2007). Ritsner et al. (2010) showed higher levels of DHEA in medicated schizophrenia patients in comparison to healthy subjects. They also concluded that DHEA may more probably act as an trait marker of impaired hormonal response to stress in schizophrenia and that DHEA concentrations are not related to specific diagnoses, but more general psychological states such as anxiety that can occur in various disorder. Results of the study performed by our team (Vuksan-Cusa 2010) demonstrated no statistically significant difference between DHEA levels in psychotic patients treated with SGAs compared to healthy controls. Furthermore, we found no associations of baseline cortisol levels, DHEA levels and the cortisol/DHEA ratio with the presence of metabolic syndrome (MetS) in a sample of psychotic patients (Vuksan-Cusa et al. 2014). Another recent study exhibited higher values of DHEAS in the first-episode male shizophrenia patients, but not among those with subsequent episodes (i.e., acute exacerbation phases of illness (Beyazyuz et al. 2014).

Since the majority of schizophrenia patient are medicated, it is very impotant to know whether antipsychotic treatment could possibly affect DHEA(S) circulatory levels in these patients. It seems that patients who received first–generation (FGAs), second generation (SGAs) and both types of antipsychotic agents had no significant differences in the cortisol to DHEAS and cortisol to DHEAS ratios (Ritsner et al. 2004). On the other hand, there are some findings suggesting that imbalances in serum DHEA(S) may be related to responsiveness to antipsychotic treatment, meaning that drug responders had significantly higher base levels of DHEA(S) compared to non-responders (Ritsner et al. 2005). There is the need for developing novel treatment strategies, such as neuroprotective strategies, using neurosteroids which should help overcome the limitations of current antipsychotic drugs and improve cognitive deficits and negative symptoms in schizophrenia patients. Clinical studies investigating the effects of DHEA(S) as augmentation therapy in schizophrenia (negative, positive, cognitive and extrapyramidal symtoms) showed, in clinical terms, inconsistent results (Ritsner 2011).

The role of DHEA and DHEAS in the treatment of schizophrenia

Several randomized, double-blind, placebo-controlled clinical trials have been conducted with DHEA(S) for the augmentation treatment of schizophrenia. However, the results are conflicting (Strous et al. 2003, 2007, Ritsner 2010). The authors reported a decrease in anxiety, depression and negative symptoms among the DHEA treated patients (Strous et al. 2003), favourable effect on parkinsonism (Nachshoni 2005), but no effect on the overall symptom as measured by PANSS (Strous et al. 2007). Ritsner at al. (2010) conducted an 8-week, double blind, randomized, placebo controled study comparing 400 mg/d of DHEA and placebo as an adjunctive treatment among 58 chronic schizophrenia or schizoaffective disorder patients. The outcome measures were symptomatic and neurocognitive changes, functioning and tolerability. In this study DHEA was superior to placebo in improving extrapiramidal side effects. In the study of Strous et al. (2003) patients were administered DHEA or placebo in addition to a constant dosage of antipsychotic agents for the 6-week trial period. The authors noted a decrease in anxiety, depression and negative symptoms among the DHEA treated patients. In the study of Nachsoni et al. (2005) the authors investigated the effect of DHEA administration during a period of only 7 days on medication induced EPS among inpatients with schizophrenia and schizoaffective disorders. Patients were randomized in a double–blind fashion to receive either 100 mg DHEA or placebo in addition to a constant dosage of antipsychotic medications. The authors reported that DHEA caused significant favourable effect on parkinsonism. A study of Strous et al. (2007) included 40 patients with chronic schizophrenia stabilized on olanzapine. The subjects were randomized in a double blind fashion to receive either DHEA (150 mg/d) or placebo augmentation for a period of 12 weeks. DHEA was not superior to placebo in improving scores on the scale for the assesment of negative symptoms, positive symptoms, and measures of side effects.

Generally, it has been shown that DHEA replacement tends to promote somatic health by decreasing insulin resistance and lowering inflammatory cytokines (Weiss et al. 2011), which is a common burden among patients with schizophrenia (Vuksan-Cusa et al. 2013, Lasić et al. 2014). Its levels are also associated with the degree of quality of life, well-being and physical disability, especially in female populations (Haren et al. 2007). Furthermore, some animal-model studies have demonstrated a significant role of DHEA in decreasing cognitive decline (e.g., decreased attention span, impaired long-term memory) (Sorwell & Urbanski 2010), another hallmark of schizophrenia, although future studies need to confirm its cognition-related specific role in this population.

The clinically significant benefits of DHEA augmentation still remain unclear. It is crucial to replicate these trials with larger clinical samples and for the longer duration of treatment. The relative inefficacy of DHEA replacement therapies among patients could be explained by age-related changes within the DHEA metabolic pathway in humans (Sorwell & Urbanski 2010). Future studies should monitor hormonal alterations in drug–free patients and maybe include examination of cortisol to DHEA(S) ratio during the administration of DHEA(S). Further research should include long-term monitoring of the relationship between hormonal alterations and specific psychotic symptomatology, depressive manifestations, agressive-suicidal behaviour, negative symptoms and cognitive deficits in first-onset and chronic schizophrenia patients.

Conclusion

Neurosteroids such as dehidroepiandrosterone and its sulfate display multiple effects on the central nervous system. Experimental and clinical observations support the speculation that neurobiological alterations in DHEA(S) are related to the patophysiology of schizophrenia. It is also possible to conclude that DHEA(S) might play a relevant role in the expressions of stress response, anxiety, cognitive deficits, and physical health in schizophrenia.

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