The effect of fludrocortisone on emotional information processing in healthy volunteers

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To investigate the effects of a single dose of fludrocortisone, a mineralocorticoid receptor agonist, on emotional information processing in healthy female participants.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Mood disorders and disturbances NEC
Study type	Interventional

Summary

ID

NL-OMON37623

Source
ToetsingOnline

Brief title
Fludrocortisone and emotional information processing

Condition

- Mood disorders and disturbances NEC

Synonym
depression, mood disorder

Research involving
Human

Sponsors and support

Primary sponsor: Universiteit Leiden
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: antidepressant, emotional information processing, fludrocortisone, mineralocorticoid receptor

Outcome measures

Primary outcome

. Performance on a test battery of emotional information processing, in

particular:

- accuracy of recognition of facial expressions of emotion

- memory for positive vs. negative information

Secondary outcome

Modifiability of attention to positive and negative information (positive

effect expected).

Positive and negative mood states (no effect expected)

Study description

Background summary

The hypothalamic-pituitary-adrenal (HPA) axis plays a central role in the regulation of the stress response while the reactivity of the HPA-axis shows large individual differences (DeRijk, 2009). Cortisol, a main stress hormone produced and secreted by the adrenals, exerts effects on almost all nucleated cells in the body. However, chronic stress dysregulates the HPA-axis, which leads to an increased vulnerability for disease (Sapolsky et al., 1996, 2000; Lupien et al., 2007, 2009). More specifically, it is hypothesezed that chronic stress and impaired HPA-axis regulation are involved in the pathophysiology and course of depression (Holsboer, 2000, 1999).

The mineralocorticoid receptor seems to be involved in the appraisal processes of psychological stressors. These processes including higher mental functions like emotion, cognition, and behaviour determine the release of corticotrophin

releasing hormone (CRH) from the hypothalamic paraventricular nucleus (PNV) (Holsboer & Ising, 2010). Next, CRH stimulates the release of adrenocorticotropic hormone (ACTH) from the pituitary gland. Additionally, arginine vasopressin (AVP) stimulates synergistically with CRH the release of ACTH (Swaab et al, 2005). Subsequently, ACTH is binding to specialized receptors at the adrenal gland to cause glucocorticoid production and secretion from the adrenal cortex in a pulsatile fashion: amplitude and frequency of these secretory bursts are heightened under stressful conditions (Holsboer & Ising, 2010). Once the perceived stressor has disappeared, the glucocorticoids act in a negative feedback loop on the hypothalamus and the pituitary gland in order to suppress the production of CRH and ACTH, enabling return to homeostasis (De Kloet et al, 2005, 2007; Lupien et al., 2007, 2009).

Cortisol, which is the most important human glucocorticoid, exerts its effects through two corticosteroid receptors: the glucocorticoid receptor (GR) and mineralocorticoid receptor (MR). MRs bind cortisol with a ten-fold higher affinity than GRs, which implicates that MRs are sensitive to low levels of glucocorticoids. In the brain MRs are involved in the determination of the onset of the stress response by appraising psychosocial stressors and modulating behavioral flexibility (Brinks et al., 2009; Klok et al., 2011), whereas GRs terminate stress responses and contribute to recovery and memory storage for coping with future events (De Kloet et al., 2005, 2007; Otte et al., 2007). Furthermore, MRs seem to be important for cognitive processes like selective attention and emotions like fear (Otte et al., 2007; Brinks et al., 2007). This is consistent with other findings that MRs are located especially in the hippocampus, septum and amygdala: these limbic regions of the brain are crucial for memory formation and emotional response, whereas GRs are distributed ubiquitously in the brain (De Kloet, 2005). An imbalance in mediated actions by these receptors results in cortisol responses of less optimal magnitude and duration, which might increase vulnerability to mental disorders like depression (De Kloet et al., 2005, 2007; Holsboer, 2000, 1999). Another indication for the relation between depression and the mineralocorticoid receptor is discovered in post-mortem brain tissue of patients diagnosed with major depressive disorder (MDD). We found in depressed individuals, compared with non-depressed controls, that MRs had a decreased (approximately -30%) expression in hippocampus, inferior frontal gyrus and cingulate gyrus. It is proposed that decreased expression of MRs is part of the underlying pathological process in depression (Klok et al., 2011).

Recent studies have revealed considerable interpersonal differences with regard to the functioning of the MRs. Firstly, common MR gene polymorphisms influence the cortisol awakening response (CAR; Klok et al., 2011; Pruessner et al., 1997). Secondly, clinical populations differ in observed depressive symptoms as a function of MRI180V genotype (Kunningas et al., 2006). This MR I180V gene variant showed less activity in vitro, which suggests that functionality in vivo is decreased (DeRijk et al., 2006). Finally, MR haplotype 2, which is prevalent in 35% of the Caucasian population, enhances the transcription,

translation and transactivation of the MR (Klok et al., 2009, 2011). This haplotype is associated with higher dispositional optimism, fewer thoughts of hopelessness and lower risk of major depression. These effects are restricted to pre-menopausal women (Klok et al., 2011). This suggests that female sex steroids may interact with the MR gene, thereby modulating resilience (Klok et al., 2009, 2011). Indeed, it has been shown that progesterone and oestrogen modulate MR-expression in rats (Castrén et al., 1995). Taken together, mineralocorticoid receptors in the brain are considered to be a new target for the treatment of stress related disorders like depression.

Fludrocortisone (9α fluoro-hydrocortisone) is a specific MR-agonist currently used to treat diseases of the adrenal cortex (Coursin & Wood, 2002), septic shock (Russel, 2008) and occasionally orthostatic hypotension (Schatz, 2001). Consistent with the idea that the stimulation of the MR might be useful in the treatment of depression, fludrocortison accelerated the antidepressant effects of the SSRI escitalopram, at least in those patients who responded to escitalopram (Otte et al., 2010). This is in line with a previous observation that spironolactone, a MR antagonist, decreased the efficacy of the antidepressant amitriptyline in depressed patients (Holsboer et al., 1999). Both studies show that stimulation of the MR might be a useful addition to the treatment of depression. Though, the explanatory mechanism behind these observations remains unclear.

In the present experiment we will investigate the effects of acute administration of 500 µg fludrocortisone (FC) in healthy, female, unmedicated volunteers. This project is a first step in investigating the potential antidepressant effects of MR stimulation by fludrocortison. We will test the effects of FC on indices of emotional information processing in healthy volunteers, which is a recently validated model of antidepressant drug action (Harmer et al., 2009). It has been demonstrated repeatedly that a single dose of an antidepressant changes the processing of emotionally relevant information in healthy volunteers, within a few hours after administration. For instance, one dose of citalopram improved the recognition of facial expressions of fear and happiness relative to placebo in healthy female volunteers (Harmer et al., 2003). This finding has been replicated with different antidepressants and different populations (see Harmer et al., 2009).

Study objective

To investigate the effects of a single dose of fludrocortisone, a mineralocorticoid receptor agonist, on emotional information processing in healthy female participants.

Study design

Randomized double-blind, placebo-controlled trial.

Stratification on current use of oral contraceptives (yes/no).

Intervention

Fludrocortisone 500 µg, single dose, oral.

Study burden and risks

Fludrocortisone may decrease plasma ACTH and cortisol and slightly increase blood pressure and transiently enlarge sodium and water retention. Other side-effects are not expected since these have only been described over longer periods of intake.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age

Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Healthy females
- Age 18-35yrs
- BMI between 18 and 30
- Fluent in Dutch
- North-West European ancestry

Exclusion criteria

- Major physical illness (infections, diabetes, thyroid disease, epilepsy, multiple sclerosis, pituitary disease or any other serious medical condition).
- Hypertension or history of stroke. Increased blood clot formation.
- Any current or past psychiatric disorder.
- Use of medication likely to interfere with the study (e.g., benzodiazepines, St John*s Wort).
- Pregnancy or breastfeeding.
- Use of soft drugs (hash, marijuana) in the three months prior to the study.
- Any hard drug use during life time (including XTC).
- Alcohol use of more than 14 units per week or more than 4 units on any day during the week prior to the study.
- Regular smoker during past year or use of any nicotine products during past week

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	02-05-2012

Enrollment:	40
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	florinef
Generic name:	fludrocortisone acetate
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	10-02-2012
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	24-04-2012
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2011-005205-71-NL

Register	ID
CCMO	NL38980.058.11