Neuroscience 286 (2015) 412–422

MINERALOCORTICOID RECEPTOR HAPLOTYPE, ORAL CONTRACEPTIVES AND EMOTIONAL INFORMATION PROCESSING

D. A. HAMSTRA, [a,b]* **E. R. DE KLOET,** [d] **A. M. VAN HEMERT,** [c] **R. H. DE RIJK** [e] **AND A. J. W. VAN DER DOES** [a,b,c]

[a] *Institute of Psychology, Leiden University, The Netherlands*

[b] *Leiden Institute of Brain and Cognition, Leiden University, The Netherlands*

[c] *Department of Psychiatry, Leiden University Medical Center, The Netherlands*

[d] *Leiden Academic Centre of Drug Research, Leiden University, The Netherlands*

[e] *DynaCorts Therapeutics, Leidschendam, The Netherlands*

Abstract—*Background:* Oral contraceptives (OCs) affect mood in some women and may have more subtle effects on emotional information processing in many more users. Female carriers of mineralocorticoid receptor (MR) haplotype 2 have been shown to be more optimistic and less vulnerable to depression.

***Aim:* To investigate the effects of oral contraceptives on emotional information processing and a possible moderating effect of MR haplotype.**

***Methods:* Cross-sectional study in 85 healthy premenopausal women of West-European descent.**

***Results:* We found significant main effects of oral contraceptives on facial expression recognition, emotional memory and decision-making. Furthermore, carriers of MR haplotype 1 or 3 were sensitive to the impact of OCs on the recognition of sad and fearful faces and on emotional memory, whereas MR haplotype 2 carriers were not.**

***Limitations:* Different compounds of OCs were included. No hormonal measures were taken. Most naturally cycling participants were assessed in the luteal phase of their menstrual cycle.**

***Conclusions:* Carriers of MR haplotype 2 may be less sensitive to depressogenic side-effects of OCs.**

Key words: mineralocorticoid receptor, oral contraceptives, cognition, emotional information processing.

INTRODUCTION

Hormonal oral contraceptives (OCs) have been on the market for over 50 years now and are used by approximately 100 million women worldwide (Hather et al., 2007). Early studies investigating the association between OC use and depression revealed inconsistent findings (Oinonen and Mazmanian, 2002): varying from increased to decreased rates of depressed mood in OC users (Cullberg, 1972; Deijen et al., 1992). Some studies found no association (e.g., Vessay et al., 1985). More recent studies have shown that in most women OCs reduce the variability of affect across the entire menstrual cycle. This is due to the suppression of cyclical changes in ovarian hormones (Kornstein and Clayton, 2002). OCs also prevent negative affect during menstruation (Oinonen and Mazmanian, 2002). Recent cohort studies have also shown that OCs may protect against depression (Svendal et al., 2012; Toffol et al., 2012). However, depressogenic side effects remain one of the major reasons for discontinuation of OCs (Oinonen and Mazmanian, 2002; Boron and Boulpaep, 2012). In experimental research, OC users showed a blunted response in positive affect (i.e., reduced positive affect variability) when exposed to emotional stimuli (Jarva and Oinonen, 2007).

Recently, subtle psychological consequences of OC use have been discovered that may also affect users who do not experience subjective effects on mood (Pletzer et al., 2010; Cobey and Buunk, 2012). For example, OCs induce a preference for less masculine faces (Little et al, 2013; Bobst et al., 2014). Partnered women using OCs reported significantly higher levels of jealousy than naturally cycling (NC) partnered women in their non-fertile cycle phase (Cobey et al., 2012). Furthermore, endogenous and/or exogenous female hormones affect not only psychological processes and the associated brain activity patterns, but also brain structure (Pletzer et al., 2010; DeBondt et al., 2013; Pletzer et al., 2014). Taken together, psychological effects of OCs may have implications on both societal and individual levels.

Previously we have detected that OC users make more errors in the recognition of facial expressions of sadness, anger and disgust (Hamstra et al., 2014). Natural variations in estrogens and progesterone also

*Corresponding author. Address: Institute of Psychology, Clinical Psychology Department, Leiden University, Wassenaarseweg 52, 2333 AK Leiden, The Netherlands. Tel: +31-71-527-8482; fax: +31-71-527-3691.

E-mail address: d.a.hamstra@fsw.leidenuniv.nl (D. A. Hamstra).

Abbreviations: DMT, decision-making task; EMT, emotional categorization and memory task; FERT, facial expression recognition task; GR, glucocorticoid receptor; HPA, hypothalamic–pituitary–adrenal; LEIDS-R, Leiden Index of Depression Sensitivity-Revised; MANOVA, multivariate analyses of variance; MR, mineralocorticoid receptor; NC, naturally cycling; NEO-FFI, NEO Five-Factor Inventory; OCs, oral contraceptives; PANAS, Positive and Negative Affect Schedule (state); RTs, reaction times.

http://dx.doi.org/10.1016/j.neuroscience.2014.12.004
0306-4522/

affect emotional information processing. For instance, stress vulnerability fluctuates during the menstrual cycle (Ossewaarde et al., 2010). Sex hormones influence also facial emotion recognition: specifically, estrogen seems to be implicated in the recognition of negative emotions such as sadness, anger and fear (Guapo et al., 2009). Furthermore, recognition errors for facial expressions of sadness and disgust were significantly higher in the follicular phase than in the luteal phase, when progestins dominate the female cycle (Gasbarri et al., 2008). Not only emotion recognition, but also the reactivity of the reward system is moderated by the menstrual cycle phase (Ossewaarde et al., 2011). In the mid-follicular phase of the menstrual cycle, when estrogen is unopposed by progesterone, more reward anticipation in the monetary incentive delay task was observed (Dreher et al., 2007). Since the most frequently used OCs contain a synthetic progestin and estrogen (Hather et al., 2007), these findings may also be relevant for research into the influence of OCs on information processing.

OCs suppress the release of endogenous female hormones by the hypothalamic–pituitary–gonadal axis. OCs feed back at the hypothalamus, decreasing the secretion of gonadotropin releasing hormone (GnRH), and at the gonadotrophs in the anterior pituitary, resulting in low levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH), disabling normal folliculogenesis and ovulation (Rivera et al., 1999; Boron and Boulpaep, 2012). Hormonal contraceptives suppress endogenous hormonal levels: concentrations of estrogen and progesterone are significantly lower in OC-users than in NC women in the mid-luteal phase of the menstrual cycle (days 18–25) (DeBondt et al., 2013). Furthermore, regardless of the estrogen or progestin type, combined OCs reduce total and free testosterone levels (Alexander et al., 1990; Zimmermann et al., 2013).

Exogenous gonadal hormones also influence the responsiveness of the hypothalamic–pituitary–adrenal (HPA) axis. OCs decrease HPA axis activity and cortisol response to a stressor in women (Kirschbaum et al., 1999; Nielsen et al., 2013). OCs may also suppress cortisol secretion by affecting the feedback action of cortisol in the brain, which is mediated by mineralocorticoid receptors (MR) and glucocorticoid receptors (GR). Previous studies in rats revealed that endogenous estrogen and particularly progesterone affect the expression and binding characteristics of the MR in the brain, which may explain the effects of the MR on HPA axis activity (Carey et al. 1995; Quinkler et al., 2002). It is not known to what extent the synthetic estrogens and progestins may interact with the MR and GR. The MR in particular was found to be associated with the processing of emotional information (Joëls et al., 2012) and stress reactions (Otte et al., 2007).

More specifically, the MR seems to be involved in the regulation of initial psychological stress reactions like vigilance, selective attention, emotional expressions and formation of emotional memory (Otte et al., 2007). This is consistent with the fact that the MR is located especially in limbic structures such as the subgenual anterior cingulate cortex, amygdala and hippocampus, which are crucial for processing of stressful information (De Kloet et al., 2005). In depressed individuals MR expression is approximately 30% lower in the hippocampus, inferior frontal gyrus and cingulate gyrus than in non-depressed controls (Klok et al., 2011b). Recent studies have revealed that MR haplotype 2 is associated with higher dispositional optimism, fewer thoughts of hopelessness during sad moods and lower risk of depression. These effects are restricted to premenopausal women suggesting a moderating effect of female gonadal steroids on the function of the MR (Klok et al, 2011b). The observed differences in sensitivity between different MR-haplotypes may also explain why some women experience depression-like side-effects of OCs whereas others do not (Oinonen and Mazmanian, 2002; Boron and Boulpaep, 2012).

The goal of the current study was to further investigate the effects of OC use on information processing (Hamstra et al., 2014), taking into account potential moderating effects of MR haplotypes. Firstly, OC-users were compared with NC women on indices of emotional information processing. Secondly, we hypothesized that performance on these tasks would be moderated by MR haplotype. Specifically, we hypothesized that the effects of OCs on emotional information processes would be larger in carriers of MR haplotype 1 and 3 than in MR haplotype 2.

EXPERIMENTAL PROCEDURES

Participants

Eligible participants were women of North-Western European origin with a regular menstrual cycle (between 25 and 35 days). Age limits were between 18 and 35 years. Users of hormonal contraceptives other than hormonal pills were excluded. Further exclusion criteria were pregnancy or lactation, dyslexia, alcoholism, habitual smoking, a history of regular use of (hard) drugs including XTC and cannabis and use of medication likely to interfere with the study (e.g., antidepressants, St John's Wort, benzodiazepines, ADHD medication). Participants were recruited at various sites at Leiden University. All participants provided written informed consent before the start of the study and received course credit or 15 euro. The study was approved by the Ethics Committee Psychology of Leiden University (CEP 7099926055).

Design and procedure

This study had a cross-sectional, parallel-group design. Participants completed a test battery in a psychology laboratory. NC women were tested between day 6 and 26 of their menstrual cycle. OC users were tested outside their pill-free week. OC brand name and chemical compound, duration of OC use and in case of NC women first day of last menses were registered.

Instruments

Clinical characteristics. Mood state was assessed by the 20-item state version ('today') of the Positive and Negative Affectivity Scales (PANAS) prior to testing (Watson et al., 1988). Personality traits were assessed by the NEO Five-Factor Inventory (NEO-FFI) (Hoekstra et al, 1996). Depression vulnerability was measured with the