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Mineralocorticoid receptor haplotype, estradiol, progesterone and emotional information processing

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ABSTRACT

Background: Carriers of MR-haplotype 1 and 3 (GA/CG; rs5522 and rs2070951) are more sensitive to the influence of oral contraceptives (OC) and menstrual cycle phase on emotional information processing than MR-haplotype 2 (CA) carriers. We investigated whether this effect is associated with estradiol (E2) and/or progesterone (P4) levels.

Method: Healthy MR-genotyped premenopausal women were tested twice in a counterbalanced design. Naturally cycling (NC) women were tested in the early-follicular and mid-luteal phase and OC-users during OC-intake and in the pill-free week. At both sessions E2 and P4 were assessed in saliva. Tests included implicit and explicit positive and negative affect, attentional blink accuracy, emotional memory, emotion recognition, and risky decision-making (gambling).

Results: MR-haplotype 2 homozygotes had higher implicit happiness scores than MR-haplotype 2 heterozygotes ($p=0.031$) and MR-haplotype 1/3 carriers ($p<0.001$). MR-haplotype 2 homozygotes also had longer reaction times to happy faces in an emotion recognition test than MR-haplotype 1/3 ($p=0.001$). Practice effects were observed for most measures.

The pattern of correlations between information processing and P4 or E2 differed between sessions, as well as the moderating effects of the MR genotype. In the first session the MR-genotype moderated the influence of P4 on implicit anxiety ($sr=-0.30$; $p=0.005$): higher P4 was associated with reduction in implicit anxiety, but only in MR-haplotype 2 homozygotes ($sr=-0.61$; $p=0.012$). In the second session the MR-genotype moderated the influence of E2 on the recognition of facial expressions of happiness ($sr=-0.21$; $p=0.035$): only in MR-haplotype 1/3 higher E2 was correlated with happiness recognition ($sr=0.29$; $p=0.005$). In the second session higher E2 and P4 were negatively correlated with accuracy in lag2 trials of the attentional blink task ($p<0.001$). Thus NC women, compared to OC-users, performed worse on lag 2 trials ($p=0.041$).

Conclusion: The higher implicit happiness scores of MR-haplotype 2 homozygotes are in line with previous reports. Performance in the attentional blink task may be influenced by OC-use. The MR-genotype moderates the influence of E2 and P4 on emotional information processing. This moderating effect may depend on the novelty of the situation.

1. Introduction

Female hormones modulate the impact of stress on mood. For instance, high estradiol (E2) concentrations attenuate the negative influence of a psychosocial stressor on mood and promote fear inhibition (Albert et al., 2015; Lebron-Milad and Milad, 2012; Milad et al., 2010). Furthermore, reward-sensitivity and emotional information processing are influenced by the menstrual cycle, probably depending on female hormones like estradiol (E2) and progesterone (P4) (Hamstra et al., 2016; Bayer et al., 2013; Dreher et al., 2007).

Oral contraceptives (OC) contain synthetic estrogens and progestins that also influence human cognition. Better performance on verbal memory, associative learning and spatial attention tasks was observed in OC-users (Gogos et al., 2014; Sundstrom Poromaa and Gingnell, 2014). OC-use may also affect emotion processing, in par-

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ticular the recognition of negative facial and bodily expressions of emotions as well as decision-making (Suslow et al., 2015; Hamstra et al., 2016, 2015, 2014; Maner and Miller, 2014; Gingnell et al., 2013; Pearson et al., 2009). Cognitive function in post-menopausal women was not improved by hormone replacement therapy with naturally occurring estrogens and a (synthetic) progestin (Lethaby et al., 2008).

The observed effects of OC and female hormones on emotional information processing may be mediated by estrogen and progesterone receptors, which are abundantly expressed in limbic brain structures (Handa and Weiser, 2014). In these limbic areas the sex steroids may modulate the function of mineralocorticoid receptors (MR), that mediate the action of cortisol on vigilance and selective attention (Hermans et al., 2014; Cornelisse et al., 2011) as well as on encoding of spatial (Arp et al., 2014) and emotional memory performance in animal and human studies (Otte et al., 2015; Zhou et al., 2010; Joels et al., 2008; Otte et al., 2007; De Kloet et al., 2005). Progesterone (P4) binds to the MR with nearly the same affinity as aldosterone and cortisol, and acts as a competitive antagonist (Quinkler et al., 2002; Carey et al., 1995). E2 suppresses the synthesis and transactivation of the MR in brain and vascular endothelial cells (Barrett Mueller et al., 2014; Carey et al., 1995). Consequently, the MR is of relevance in candidate gene studies investigating the influence of female hormones on emotional information processing.

Recent research has identified a common functional MR-haplotype block that is located at the 5'promoter of the gene and is based on two single nucleotide polymorphisms: MR-2G/C (rs2070951) and MR-I180 V (A/G, rs5522) (Van Leeuwen et al., 2011). Female carriers of MR-haplotype 2 (MR-2C/I180: CA) appeared to have a lower risk of depression during their reproductive years (Klok et al., 2011). Consistent with this, observations in a population-based sample (n = 665) and a clinical cohort from the Netherlands Study of Depression and Anxiety (NESDA; n = 1639) revealed that female carriers of MR-haplotype 2 who reported childhood maltreatment were less likely to develop depression than MR-haplotype 3 carriers who reported maltreatment (Vinkers et al., 2015). The MR-haplotype also moderates the impact of the menstrual cycle and OCs on emotional information processing. MR-haplotype 1/3 carriers were sensitive to the impact of OC on recall and on the recognition of sad and fearful facial expressions (Hamstra et al., 2015). Within the MR-haplotype 1/3 carriers, OC-users recognized fewer emotions than non-users in the mid-luteal phase of the menstrual cycle (Hamstra et al., 2016). These effects were not observed in MR-haplotype 2 carriers. These observations might explain why some women experience more mood-swings during the menstrual cycle and/or depression-congruent side effects of OC, whereas others do not (Boron and Boulpaep, 2012; Kulkarni, 2007).

The aim of the present study was to investigate the effect of menstrual cycle phases and OC use on emotional information processing in healthy women and the possible moderation of this effect by MR-genotype. Contrary to most previous studies, we used a longitudinal, within-person design. We measured estradiol (E2) and progesterone (P4) concentrations in saliva. We hypothesized that variations in female sex steroid levels affect emotional information processing more strongly in MR-haplotype 1/3 carriers than in MR-haplotype 2 carriers.

2. Methods

2.1. Participants

Participants were recruited through social media and at Leiden University campus. Eligible participants were healthy, non-smoking female university students (18–35 years) of Northwestern European origin. Naturally cycling (NC) participants had a regular menstrual cycle of between 25-35 days, had not used any hormonal contraceptives for at least three months and did not have pre-menstrual syndrome (PMS) as determined by the MDQ (Menstrual Distress Questionnaire; Moos, 1968). OC-users took mono-phasic OCs with as compounds ethinylestradiol (EE; 0.03)/levonorgestrel (LNG; 0.15) for more than three months and applied a pill-free week. Mental health was screened with the General Health Questionnaire 12 item-version, with a cut-off score of X > 2 (Goldberg et al., 1997). Exclusion criteria were self-reported current psychological or psychiatric treatment; pregnancy or lactation; drinking >14 units alcohol per week; use of cannabis in the past three months; use of MDMA (3,4-methyleendioxymethamfetamin) (> 1 per month during the past three months or any during the past month); any other illegal drug (lifetime); smoking; and current use of prescribed medication likely to interfere with female hormonal levels.

2.2. Procedure

2.2.1. Design

This study had a counterbalanced within-subject design. All data were collected from March till June 2015. OC-users were tested in a counterbalanced entry-order: once in the second week of active OC-use (day 8–14) and once during inactive OC-use (day 4–7 of the pill-free week). Naturally cycling (NC) participants were tested at two counterbalanced time-points that are characterized by relatively stable hormone levels of E2 and P4. Once in the early follicular phase (day 2–6), when both hormones are low, and once in the middle of the luteal phase (3–10 days before the onset of the new cycle) when the concentration of P4 is at its maximum and E2 reaches a second peak (Bayer et al., 2014; Boron and Boulpaep, 2012). At intake the average cycle duration of the NC participants was registered. After confirmation of the start of the new cycle, test data were scheduled and adjusted to the individual cycle-duration, reasoning that the luteal phase always lasts two weeks (Boron and Boulpaep, 2012). Participation ended after confirmation of the start of the new cycle. This cycle onset information was used to confirm whether participants had been tested on the right moment.

2.2.2. Clinical characteristics

Personality traits (NEO-Five Factor Inventory; Costa and McCrae, 1992) were assessed at the first session. Mood state was assessed by the 20-item state version of the Positive and Negative Affect Schedule (PANAS) (Watson et al., 1988), after assessment of the IPANAT (see 2.3.1). Participants were screened for premenstrual syndrome as determined by the MDQ (Menstrual Distress Questionnaire; Moos, 1968) after completion of the second session.

2.3. Biological measures

2.3.1. Hormonal assessment

E2 and P4 were assessed in saliva, which was collected at three time-points with 30 min intervals. In order to control for pregnancy estriol level in saliva was assessed as well. Participants were instructed to avoid eating, drinking, chewing gum 30 min prior to participation. Just before saliva collection they were asked to rinse the oral cavity with water. Each sample contained approximately 2 ml saliva, collected by polypropylene straws in IBL ultrapure polypropylene tubes (SaliCap Sets; Innovation Beyond Limits, Hamburg, Germany). Samples were immediately stored and kept frozen at −20 °C until the day of assaying. The three samples were pooled and analyzed with highly sensitive luminescence assays of IBL at Ganzimmun Diagnostics AG (D). Reference values of free E2 in saliva were: follicular phase 0.2–10.4 pg/ml; ovulation