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Relationship between the hypothalamic—pituitary—adrenal-axis and fatty acid metabolism in recurrent depression

Roel J.T. Mocking[a,*], Henricus G. Ruhé[a], Johanna Assies[a], Anja Lok[a], Maarten W.J. Koeter[a], Ieke Visser[a], Claudi L.H. Bockting[b], Aart H. Schene[a]

[a] *Program for Mood Disorders, Department of Psychiatry, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands*
[b] *Department of Clinical Psychology, University of Groningen, Groningen, The Netherlands*

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Summary Alterations in hypothalamic—pituitary—adrenal (HPA)-axis activity and fatty acid (FA)-metabolism have been observed in (recurrent) major depressive disorder (MDD). Through the pathophysiological roles of FAs in the brain and cardiovascular system, a hypothesized relationship between HPA-axis activity and FA-metabolism could form a possible missing link accounting for the association of HPA-axis hyperactivity with recurrence and cardiovascular disease in MDD.

In 137 recurrent MDD-patients and 73 age- and sex-matched controls, we therefore investigated associations between salivary cortisol (morning and evening) and the following indicators of FA-metabolism measured in the red blood cell membrane: (I) three main FAs [eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and arachidonic acid (AA)], and (II) structural FA indices (unsaturation, chain length, peroxidation) calculated from concentrations of 29 FAs to delineate overall FA-characteristics. In addition, we compared these associations in patients with those in controls.

In patients, evening cortisol concentrations were significantly negatively associated with DHA ($B = -1.358$; SE = 0.499; $t = -2.72$; $p = .006$), the unsaturation index ($B = -0.021$; SE = 0.009; $t = -2.42$; $p = .018$), chain length index ($B = -0.060$; SE = 0.025; $t = -2.41$; $p = .019$), and peroxidation index ($B = -0.029$; SE = 0.012; $t = -2.48$; $p = .015$). The relations between cortisol and the latter three variables were significantly negative in patients relative to controls. Significance remained after correction for confounders.

Our results suggest a relationship between HPA-axis activity and FA-metabolism in recurrent MDD. Future randomized experimental intervention studies using clinical outcome measures could help to further elucidate the suggested effects of hypercortisolemia in the brain and cardiovascular system in recurrent MDD.

* Corresponding author at: Department of Psychiatry, Academic Medical Centre, Meibergdreef 5, Amsterdam 1105 AZ, The Netherlands. Tel.: +31 208913694.
E-mail address: R.J.Mocking@amc.uva.nl (R.J.T. Mocking).

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1. Introduction

Major depressive disorder (MDD) accounts for an overwhelming global burden of disease. This is mainly due to its (I) lifelong recurrent nature (Greden, 2001), and (II) association with cardiovascular comorbidity (Charlson et al., 2011). Yet, pathophysiological pathways underlying the recurrent nature of MDD and its association with cardiovascular disease remain unclear. A potential missing link could be a relationship between hypothalamic–pituitary–adrenal (HPA)-axis activity and fatty acid (FA)-metabolism.

The HPA-axis is the principal endocrinological stress axis, with the glucocorticoid hormone cortisol as the primary end product of its activation. Although mixed results exist, the extensive literature on cortisol in MDD mainly shows that MDD-patients exhibit higher cortisol concentrations than healthy controls (Stetler and Miller, 2011; Herbert, 2012), both during MDD-episodes and in remission, suggesting an endophenotype (Lok et al., 2011).

This hypercortisolemic trait has been proposed to contribute to the development of both MDD-episodes and cardiovascular disease in MDD. Specifically, hypercortisolemia predicts the development of a first MDD-episode in subjects at risk (Goodyer et al., 2000), as well as recurrent episodes in remitted MDD-patients (Appelhof et al., 2006), possibly through the effects of excess cortisol on the brain, particularly the hippocampus (Sapolsky, 2000; Kronmüller et al., 2008; Ursache et al., 2012). However, mixed results have also been observed (Bockting et al., 2012). In addition, hypercortisolemia is predictive of prospective death from cardiovascular disease in MDD-patients (Jokinen and Nordström, 2009). Nevertheless, the precise (patho)physiological pathways underlying the origin of hypercortisolemia and these associations with recurrence and cardiovascular disease in MDD remain unclear.

As for the HPA-axis, disturbed FA-metabolism has been consistently reported in MDD (Assies et al., 2010; Lin et al., 2010; Yager et al., 2010), both in acutely depressed and remitted patients (Assies et al., 2010). Main findings are lower concentrations of ω3 long chain polyunsaturated fatty acids (LCPUFA) [e.g. eicosapentaenoic acid (C20:5ω3; EPA) and docosahexaenoic acid (C20:6ω3; DHA)] (Assies et al., 2010; Lin et al., 2010), and decreased overall FA unsaturation, chain length and peroxidizability (Mocking et al., 2012b).

FAs have important structural and functional (patho)physiological roles in both the nervous and cardiovascular system (Piomelli et al., 2007; Mozaffarian and Wu, 2011; McNamara, in press; Samieri et al., 2012). Structurally, FAs are major components of (neuronal) membranes (Piomelli et al., 2007). Unsaturation and chain length of membrane FAs determine membrane fluidity, which on its turn influences functioning of membrane bound proteins, e.g. neurotransmitter receptors and cardiac ion channels (Piomelli et al., 2007). Moreover, membrane FA peroxidizability determines membrane susceptibility to oxidative stress (Mocking et al., 2012b). Functionally, FAs [particularly EPA, DHA and arachidonic acid (C20:4ω6; AA)] are involved in inflammatory regulation (Hibbeln and Salem, 1995; Mozaffarian and Wu, 2011), and maintenance of brain cytoarchitecture (Rao et al., 2006; McNamara, in press).

Previous studies have found a modulating effect of HPA-axis activity on FA-metabolism. Cortisol influences mobilization (Conner et al., 1996; Brenner et al., 2001; Macfarlane et al., 2008), lipolysis (Brenner et al., 2001), oxidation (Hibbeln and Salem, 1995; Flerov et al., 2003), and synthesis (Hibbeln and Salem, 1995; Brenner et al., 2001) of FAs. For example, cortisol inhibits Δ5- and Δ6-desaturase-activity (de Alaniz and Marra, 2003), enzymes responsible for unsaturation of FA chains. In addition, oxidative stress associated with hypercortisolemia (Sato et al., 2010) could influence FA concentrations (Hibbeln and Salem, 1995; Flerov et al., 2003; Yager et al., 2010). These influences seem to have differential effects on specific FAs (Hibbeln and Salem, 1995; Conner et al., 1996; de Alaniz and Marra, 2003; Gounarides et al., 2008), in such a way that high cortisol concentrations are associated with a decrease in ω3 LCPUFA concentrations and FA unsaturation, chain length and peroxidizability.

Vice versa, FAs also seem to affect the HPA-axis (Lanfranco et al., 2004). Dietary supplementation of ω3 LCPUFA (e.g. EPA) reduced cortisol concentrations in rats (Song et al., 2003), healthy subjects (Delarue et al., 2003), and MDD-patients (Jazayeri et al., 2010; Mocking et al., 2012a). In addition, a maternal preweaning ω3 PUFA deficient diet induces HPA-axis hyperactivity in rat offspring (Chen and Su, 2012). Furthermore, in chronically stressed monkeys, the ω6/ω3 ratio was positively associated with cortisol response to acute stress (Laugero et al., 2011). Supplementation of ω3 LCPUFA increases concentrations of EPA and DHA (polyunsaturated FAs with a long chain length), and decreases concentrations of AA. These FA-alterations may alter the feedback of the HPA-axis in three ways: (I) FAs influence glucocorticoid receptor functioning, depending on their degree of unsaturation and chain length (Vallette et al., 1991), (II) EPA and AA modulate p-glycoprotein function and thereby cortisol transport across the blood–brain barrier (Murck et al., 2004), and (III) the AA/EPA ratio regulates production of pro- or anti-inflammatory eicosanoids, which can influence HPA-axis activation [via corticotrophin releasing hormone (CRH) secretion] and feedback (through induction of glucocorticoid receptor resistance) (Hibbeln and Salem, 1995; Schiepers et al., 2005).

Based on this literature, a relationship between the HPA-axis and FA-metabolism can be expected. Through the effects of FAs in the brain and cardiovascular system, this relationship might play an important role in the reinforcement and explanation of recurrence and cardiovascular disease in recurrent MDD.

However, the association between cortisol and FA-metabolism has never been investigated in MDD, especially not in comparison with controls. Therefore, we aimed to study the supposed relationship between HPA-axis activity and FA-metabolism in MDD by testing the associations between cortisol and FA-concentrations in patients with recurrent MDD and matched controls. We hypothesized that cortisol would be negatively associated with (I) concentrations of ω3 LCPUFAs (e.g. EPA and DHA), and (II) indicators of overall FA-metabolism (e.g. unsaturation, chain length and peroxidizability). In addition, we hypothesized that these associations would be more negative in patients with recurrent MDD than in controls.