Fatty acids in context

Neurometabolic perspectives on depression vulnerability

Mocking, R.J.T.

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Discussion of neuroendocrinological stress

Summary of our findings
In sum, in our sample of patients with recurrent MDD we observed an endophenotypic trait consisting of higher diurnal cortisol compared to controls that did not change during new depressive episodes or stress, but could be influenced by cognitive therapy. In addition, we found a profile of steeper DHEAS-decline and a flattened diurnal cortisol/DHEAS-ratio, that was also unaffected by depressive episodes, but showed an interaction with cognitive therapy to predict recurrence over a 10-year follow-up.

These findings contribute to the understanding of HPA-axis alterations in MDD-pathophysiology, by providing insight in cross-sectional and longitudinal heterogeneity. The interaction of cortisol/DHEAS-ratio with cognitive therapy to predict recurrence suggest inroads for personalization of therapy and prognosis. In addition, they may point to targets to augment therapy response. For example, patients with a high cortisol/DHEAS ratio seem to be less likely to respond favourably to preventive cognitive therapy, asking for other preventive interventions for this subgroup.

Relation with other literature
The HPA-axis still is an active topic of investigation in MDD. A meta-analysis summarized four decades of HPA-axis research, and is in line with our findings of overall higher cortisol. Nevertheless, several inconsistencies remain. For example, in our DELPHI study including acutely depressed unmedicated patients, we observed no baseline HPA-axis alterations compared to controls. Population characteristics as depression severity, duration, subtype, and comorbidity have been suggested as explanations for these inconsistencies. However, given the characteristics of the DELPHI study population (predominantly severe melancholic depression without comorbidity), these explanations do not necessarily explain the lack of HPA-axis alterations in this sample. These inconsistencies show that even one of the most extensively studied topics in biological psychiatry remains so far incompletely understood. Besides improved phenotyping of study populations, new assessment methods as hair cortisol and a focus on resilience instead of disease, while applying a developmental perspective that includes (epigenetic) effects of perinatal programming, early life stress, and gender seems pivotal in grasping the course of HPA-axis alterations during life in relation with psychiatric disease.

Although we still do not completely understand the HPA-axis in MDD, several studies already tried to influence the HPA-axis as a new antidepressant treatment mechanism. However, given the above described inconsistencies it is no wonder that therapeutic interventions directly aimed at modulating HPA-axis activity to treat MDD do not seem ready for clinical implementation yet. A relatively large trial on the effect of HPA-axis modulation in MDD observed no effect of add-on metyrapone (a cortisol synthesis inhibitor, i.e. an antiglucocorticoid) in treatment resistant MDD. Moreover, this lack of effect was independent of baseline HPA-axis activity. However, exemplary for the noted inconsistencies, the studied sample on average showed no baseline hypercortisolemia apart from slightly higher evening cortisol. The authors suggest that antiglucocorticoid treatment should still be further investigated in acutely depressed patients with actual HPA-axis hyperactivity.
As also shown in our studies, existing treatments can have an effect on the HPA-axis too. Our finding in the DELTA study that psychotherapy can influence cortisol is corroborated by several other studies, also in non-MDD samples.\textsuperscript{120,121} In the DELPHI study we also showed pharmacological effects on the HPA-axis. In brief, we observed that treatment with the selective serotonin reuptake inhibitor (SSRI) paroxetine resulted in a decreased HPA-axis setpoint with increased HPA-axis flexibility, which occurred especially in remitters.\textsuperscript{128}

The other way around, HPA-axis activity seems to influence the effects of existing treatments, which suggests that HPA-axis measures may be used to predict treatment outcomes and thereby personalize therapy. For example, we showed a worse clinical course after cognitive therapy treatment in patients with a higher cortisol/DHEAS-ratio, which was in line with other meta-analytic findings.\textsuperscript{122} In addition, it was previously shown that a persistently higher cortisol after antidepressant treatment predicted relapse.\textsuperscript{24}

The predictive effect of HPA-axis alterations on recurrence of MDD also remains a topic of investigation. While we observed no association between cortisol and recurrence during 2-years of follow-up in the DELTA-study, lower morning cortisol prospectively predicted recurrence during 5.5 years in the patients that did not receive the preventive cognitive therapy intervention.\textsuperscript{77} This may suggest that the observed overall trait of higher cortisol has partly adaptive effects. However, a similar investigation in the NESDA study, in contrast, showed that a higher morning cortisol awakening curve predicted recurrence in MDD.\textsuperscript{123} Nevertheless, another analysis in the NESDA study looking at trends across controls, subjects at risk for MDD and patients in different stages of the disease suggested that cortisol was involved in MDD etiology, but not disease progression.\textsuperscript{124} These inconsistencies may be explained by differences between samples (highly recurrent MDD versus MDD in general; specific comorbidity) or methodology (averaged morning values versus cortisol awakening curve), or analysis methods (direct prediction versus trends across disease stages). Moreover, that both low and high cortisol were associated with recurrence may point at an inverted-U shape of the prospective effects of HPA-axis activity on MDD-course.\textsuperscript{125}

DHEA(S) has so far received less attention.\textsuperscript{111} Interestingly, a recent study showed no overall differences between MDD-patients and healthy controls, but showed that higher DHEA(S) was associated with prospective remission during 8-weeks open label SSRI treatment, potentially providing an opportunity to personalize treatment. The authors even conclude with the suggestion that DHEA(S) may be used to augment SSRI efficacy.\textsuperscript{126} Nevertheless, several issues including carcinogenesis may withhold clinical implementation as discussed above in chapter 5. Another study investigated the steroid metabolome in men with mood and anxiety disorders and reported widespread differences in comparison with healthy controls and between mood and anxiety disorders,\textsuperscript{127} not only for DHEA but also for several other neuroactive steroids. This suggests that HPA-axis alterations in MDD are not limited to cortisol, and assessment of neurosteroids as DHEA(S) should be more routinely incorporated in HPA-axis studies in MDD. Finally, a recent pilot study showed a negative correlation between cortisol/DHEA(S)-ratio and hippocampal volume across MDD patients and controls, corroborating the suggested important role for DHEA(S) to counteract cortisol induced allostatic load.\textsuperscript{128}
Conclusion
Although the endocrinological stress-axis is one of the most extensively studied aspects in biological psychiatry in general and MDD in particular, we still do not have a definite concept of its role in the pathophysiology of MDD. The general picture suggests an endophenotypic HPA-axis hyperactivity trait in MDD patients, with increased cortisol and an increased cortisol/DHEA(S)-ratio. Inconsistencies in findings may be the reason that interventions targeted at the HPA-axis have not yet shown sufficiently convincing effects for clinical implementation, i.e. you cannot treat HPA-axis hyperactivity that is not there. In addition, alterations in the HPA-axis have been observed in almost every psychiatric disorder. These transdiagnostic similarities raise the question what the HPA-axis means for psychiatry in a broader context. A possible clinical application on a more short term may come from associations of HPA-axis measures with response to treatment. Although clinical usefulness seems still far away, this may point at interesting targets for attempts to personalize medicine.