Fatty acids in context
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Part III: Context - alterations in other pathophysiological aspects in MDD

This Part of the thesis is based on (or adapted from) the following publications:

Focus on fatty acids in the neurometabolic pathophysiology of psychiatric disorders. Mocking RJ, Assies J, Ruhé HG, Schene AH. J Inherit Metab Dis. Under Review.


INTRODUCTION

Given the involvement of fatty acids in the (patho)physiology of MDD as discussed in Part II, associations between fatty acid metabolism and other pathophysiological aspects in MDD can be expected, but remained largely uninvestigated. Preclinical data suggests relations with two of these aspects, namely neuroendocrinological stress and emotional processing. We will study these relations in Part IV, but to do so, we will first describe three studies on neuroendocrinological stress and emotional processing in this third Part. By investigating these aspects in the pathophysiology of MDD, we aim at further improving our understanding of MDD, and show ways to personalize treatment and prognosis.

First, in this third Part, we will provide a short introduction on neuroendocrinological stress. Subsequently, we will provide our own neuroendocrinological stress data on hypothalamic-pituitary-adrenal-axis activity in MDD for cortisol in chapter 4 and for dehydroepiandrosterone sulfate in chapter 5, respectively. We will then briefly discuss these findings in the context of related data by others and us. Subsequently, we will cover emotional processing, with a brief introduction followed by our data on brain activity during emotion regulation in MDD in chapter 6 and a short discussion. We finish this third Part with a brief overall discussion.

BRIEF INTRODUCTION OF NEUROENDOCRINOCLOGICAL STRESS

Stress is an important risk factor for MDD. The main endocrinological stress system is the hypothalamic-pituitary-adrenal-axis. This HPA-axis consists of the coordinated function of three structures: the hypothalamus, the anterior pituitary and the adrenal cortex. In response to triggers such as psychological stress, the hypothalamus produces corticotropin-releasing hormone (CRH), which stimulates the anterior pituitary to produce adrenocorticotropic hormone (ACTH). On its turn, ACTH boosts the adrenal cortex to produce the steroid end-hormones. Two main steroid hormones produced by the adrenal cortex are the glucocorticoid cortisol and the androgen dehydroepiandrosterone (DHEA) with its sulphate ester DHEAS, collectively called DHEA(S). The HPA-axis has inherent negative feedback loops, such that hypothalamic and anterior pituitary hormone secretion are reduced in response to cortisol.

Cortisol works mainly by binding to the nuclear glucocorticoid receptor (GR) to exert widespread and complex physiological effects, including (I) inducing a largely catabolic (i.e. "destructive") metabolic state and (II) modulating the immune system mostly leading to suppressed inflammation. In contrast, DHEA(S) seems to have anabolic and neuroprotective effects. Therefore, cortisol and DHEAS are thought to form a balance, that can be disturbed during disease.

HPA-axis activity can be measured in several ways. HPA-axis hormones can be measured in blood and cerebrospinal fluid, but also in saliva, urine, and more recently hair. Each method has its advantages and disadvantages in terms of precision, temporal effects, and convenience. In addition, the dynamics of the HPA-axis can be tested using suppression and/or stimulation tests.
Normally, HPA-axis activity follows a diurnal pattern with relatively high steroid concentrations early in the morning that decline during the day. A robust short-term HPA-axis response to acute stress may confer optimal physiological function and reflect adaptability or reactivity to environmental demands. However, more prolonged HPA-axis hyperactivity and non-suppression has been associated with MDD. One hypothesis is that this is caused by impaired GR-mediated feedback. Chronic high cortisol concentrations have potentially detrimental effects (termed allostatic load), e.g. they may lead to reduced hippocampal volumes and atherosclerosis. This allostatic load may be involved in MDD pathophysiology and could explain the high recurrence and cardiovascular comorbidity rates. While cortisol derived most attention in MDD, DHEA(S) is secreted more abundantly than cortisol. Although DHEA(S)’ precise role remains unclear, it is thought to counteract cortisol’s effects on allostatic load.

In the two chapters that follow, we describe longitudinal studies on cortisol and DHEAS in our DELTA-study.