# SLEEP-ENDOCRINE INTERACTIONS IN HEALTH AND DEPRESSIVE DISORDERS – A MODEL

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Melancholic depression is characterized by pronounced sleep disturbance, especially intermittent and early morning awakening, which is associated with high nocturnal ACTH and cortisol concentrations (Antonijevic *et al.* 2000). In melancholically depressed patients (Wong *et al.* 2000) CSF CRH, the trigger peptide for the HPA axis activity, has been demonstrated to be inappropriately high in relation to the elevated peripheral cortisol levels accompanied by a marked increase in CSF norepinephrine (NE), pointing to a close association between an inappropriately high CRH release and an increased NE release. The main reason for increased CRH activity may be a disturbance of the physiological negative feedback loop of the HPA axis, i.e. the ability of cortisol to suppress CRH and ACTH secretion, at the level of the hypothalamus. As a marker of a disturbance of the negative feedback of the HPA-axis, the ability of the synthetic glucocorticoid receptor (GR) agonist dexamethasone (dex) to suppress cortisol has been widely used. In accordance with the above dex-resistance was primarily described in melancholic depression (Carroll 1982;Holsboer *et al.* 1986).

Besides the negative feedback of cortisol via the hypothalamus a feedforward mechanism is established by the GR induced increase in the activity of the central nucleus of the amygdala (Schulkin *et al.* 1998;Shepard *et al.* 2000) and the amygdala activation induced HPA axis stimulation (Szafarczyk *et al.* 1986). In the hippocampus a concentration dependent effect of glucocorticoids is mediated via mineralocorticoid (MR) or glucocorticoid receptors (GR), which influences the HPA activity differentially (De Kloet *et al.* 1998). The prefrontal cortex mediates a negative feedback of GR on HPA axis activity (Boyle *et al.* 2005). On the other hand activation of specific parts of the brain are correlated with sleep-stages, i.e. amygdala activation with REM-sleep and frontal cortex deactivation with slow wave sleep (Maquet 2000). We hypothesize, that depression is characterized by specific changes in GR and MR sensitivity. Furthermore specific drugs might be able to modify these. For example EPA, an unsaturated fatty acid from the group of omega-3 fatty acids could have such an effect, as it has been demonstrated that EPA increase the sensitivity of human lymphocytes to cortisol (Klein *et al.* 1989). We propose a model to test for this hypothesis.