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Differential contribution of mineralocorticoid and glucocorticoid receptors to memory formation during sleep

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Summary Corticosteroids are known to modulate the consolidation of memories during sleep, specifically in the hippocampus-dependent declarative memory system. However, effects of the major human corticosteroid cortisol are conveyed via two different receptors, i.e., mineralocorticoid (MRs) and glucocorticoid receptors (GRs) whose specific contributions to memory consolidation are unclear. Whereas a shift in the balance between MR and GR activation toward predominant GR activation has been found to impair sleep-dependent consolidation of declarative memories, the effect of predominant MR activation is not well characterized. Here, we examined differential corticosteroid receptor contributions to memory consolidation during post-learning sleep in two placebo-controlled double-blind studies in humans, by comparing the effects of the selective MR agonist fludrocortisone (0.2 mg, orally, Study 1) and of hydrocortisone (22 mg, intravenously, Study 2) with strong binding affinity to both MR and GR. We hypothesized increased activation of MRs during sleep to enhance declarative memory consolidation, but the joint MR/GR activation to impair it. Participants (16 men in each study) learned a declarative (word pair associates) and a procedural task (mirror tracing) before a 7-h period of nocturnal retention sleep, with the substances administered before sleep (Study 1) and during sleep (Study 2), respectively. As hypothesized, retention of word pairs, but not of mirror tracing skill, was selectively enhanced by the MR agonist fludrocortisone. An impairing effect of hydrocortisone on word pair retention remained non-significant possibly reflecting that hydrocortisone administration failed to establish robust predominance of GR activation. Our results show that predominant MR activation benefits declarative memory consolidation presumably by enhancing the sleep-dependent reactivation of hippocampal memories and resultant synaptic plastic processes. The effect is counteracted by additional GR activation. Insufficient MR activation, like GR over-activation, might be a factor contributing to memory impairment in pathological conditions.

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1. Introduction

Sleep is known to facilitate the consolidation of memories (Stickgold, 2005; Diekelmann et al., 2009; Diekelmann and Born, 2010). In humans, in particular, the early hours of sleep which are dominated by slow-wave sleep (SWS) benefit the consolidation of declarative memory contents, i.e., memories for episodes and facts that rely on hippocampal and closely connected medial temporal lobe structures (Plihal and Born, 1997; Gais and Born, 2004). These early hours of nocturnal sleep are characterized by a strong suppression of the adrenal release of cortisol (the major corticosteroid in humans) reaching its 24-h nadir during this time, and it has been proposed that this suppression is an essential prerequisite for declarative memory consolidation (Born and Fehm, 1998). In fact administration of glucocorticoids, such as cortisol and dexamethasone, during this time period consistently impaired later retention performance (Plihal et al., 1999; Plihal and Born, 1999; Wilhelm et al., 2011). On the other hand, the complete suppression of cortisol release during sleep by the cortisol synthesis inhibitor methyrapone reduced declarative memory formation suggesting that a minimum of cortisol is necessary for declarative memory consolidation (Wagner et al., 2005). On the background of declarative memories benefitting from low levels of cortisol, but memory impairment as a consequence of complete absence as well as elevated cortisol, an inverted U-shape for corticosteroid effects on declarative memory consolidation has been proposed (Born and Fehm, 1998; see also Lupien and Lepage, 2001; Domes et al., 2005; Wagner and Born, 2008; Marin et al., 2011). Based on studies in rodents, this inverted U-shape has been considered to reflect the differential occupation of the two major receptor types binding cortisol (corticosterone in rats), i.e., mineralocorticoid receptors (MRs) and glucocorticoid receptors (GRs) (Oitzl et al., 2010). Due to their substantially higher affinity to cortisol, 70—90% of MRs, but only a small fraction of GRs, are occupied when endogenous cortisol levels are low, i.e., at the 24-h nadir which in humans occurs during the early hours of nocturnal sleep (Joëls and de Kloet, 1994; De Kloet et al., 1998). A more recent study in rats estimated the occupation of MRs around the time of glucocorticoid nadir concentration

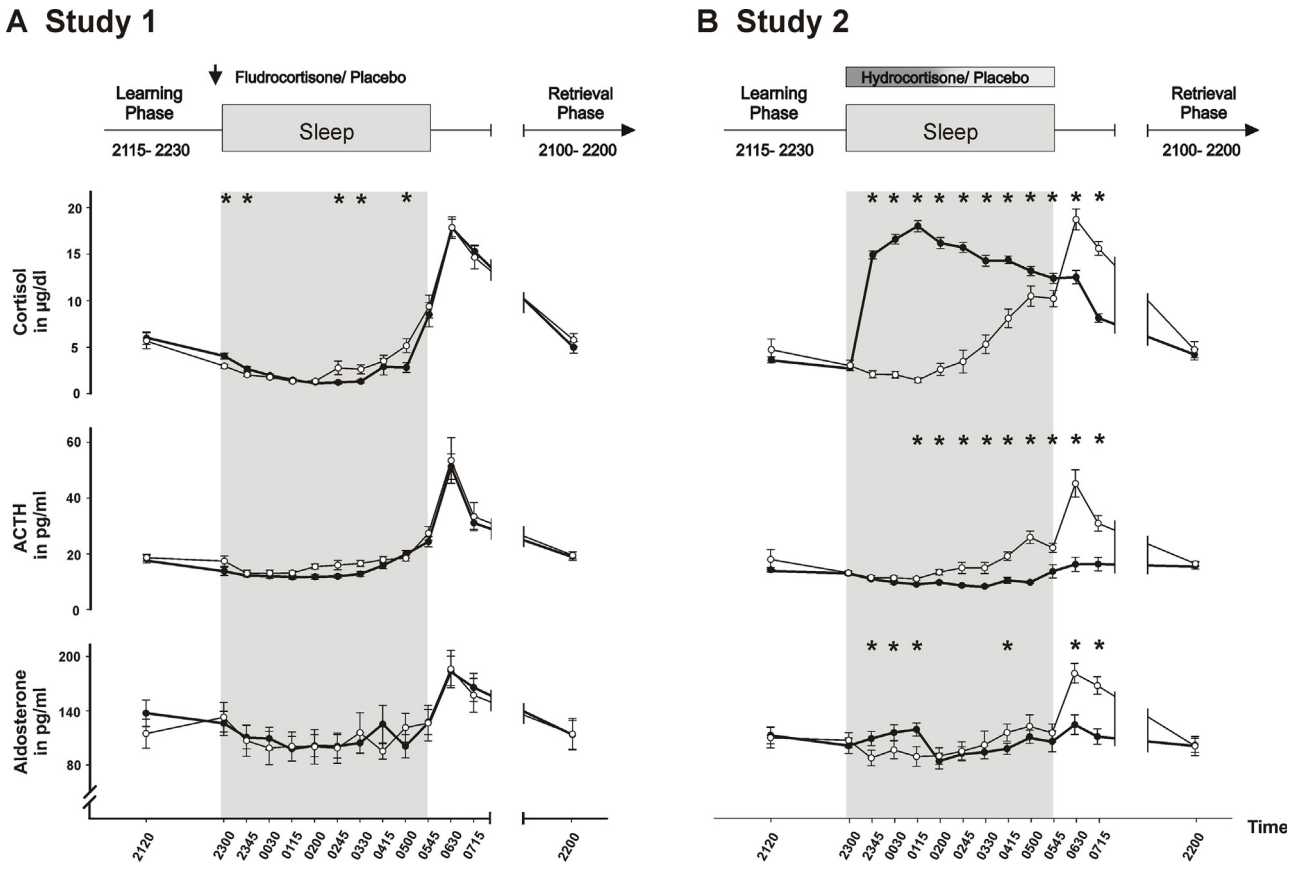

Figure 1 Study design. Subjects were tested on two conditions (A) fludrocortisone vs. placebo in Study 1, (B) hydrocortisone vs. placebo in Study 2, with the order balanced across subjects. The learning phase included a word pair associate learning task and a mirror tracing task which both were learnt up to a certain criterion. Learning was followed by a 7-h period of nocturnal retention sleep. The retrieval phase took place 24 h after learning and comprised cued recall of world pair memories and a retest on the mirror tracing task. Fludrocortisone (vs. placebo) in Study 1 was administered orally (200 mg) before lights off at 2300 h. Hydrocortisone (vs. placebo) in Study 2 was infused during the entire 7-h sleep period (total dose 22 mg), starting at 2300 h. Before learning and after retrieval as well as during retention sleep (starting with lights off) blood was sampled to assess concentrations of cortisol, ACTH and aldosterone. Bottom panels show mean (±SEM) concentrations for the active agent condition (black dots, thick lines) and respective placebo condition (empty dots, thin lines). $^{**}p < 0.01$, $^{*}p < 0.05$, for pairwise comparisons between treatment conditions.