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RAPID COMMUNICATION

Hippocampal Corticosterone Impairs Memory Consolidation During Sleep but Improves Consolidation in the Wake State

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ABSTRACT: We studied the interaction between glucocorticoid (GC) level and sleep/wake state during memory consolidation. Recent research has accumulated evidence that sleep supports memory consolidation in a unique physiological process, qualitatively distinct from consolidation occurring during wakefulness. This appears particularly true for memories that rely on the hippocampus, a region with abundant expression of GC receptors. Against this backdrop we hypothesized that GC effects on consolidation depend on the brain state, i.e., sleep and wakefulness. Following exploration of two objects in an open field, during 80 min retention periods rats received an intrahippocampal infusion of corticosterone (10 ng) or vehicle while asleep or awake. Then the memory was tested in the hippocampus-dependent object-place recognition paradigm. GCs impaired memory consolidation when administered during sleep but improved consolidation during the wake retention interval. Intrahippocampal infusion of GC or sleep/wake manipulations did not alter novel-object recognition performance that does not require the hippocampus. This work corroborates the notion of distinct consolidation processes occurring in sleep and wakefulnesss, and identifies GCs as a key player controlling distinct hippocampal memory consolidation processes in sleep and wake conditions. © 2014 The Authors. Hippocampus Published by Wiley Periodicals, Inc.

KEY WORDS: hippocampus; rats; glucocorticoids

Glucocorticoids (GCs) have strong influences on memory formation, and hippocampus-dependent memories are particularly sensitive to GC effects (Lupien and Lepage, 2001) consistent with abundant presence of GC and mineralocorticoid receptors in the hippocampus (Reul and deKloet, 1985; Joëls, 2008). In general, acute GC administration enhances encoding of such memories but impairs their retrieval, with the effects strongly dependent on the administered dose and emotionality of the stimulus materials (Kirschbaum et al., 1996; de Quervain et al., 2000; Maheu et al., 2004; de Quervain et al., 2009; Wolf, 2009; Rimmele et al., 2013). Previous studies reported enhancing effects of GCs on memory consolidation in the rodent hippocampus (Cottrell and Nakajima, 1977; Micheau et al., 1985; Roozendaal and McGaugh, 1997) as well as dorsal striatum (Medina et al., 2007; Lozano et al., 2013). However, most of the previous studies did not take into account possible differential effects of GCs on memory consolidation during sleep and wakefulness. In the studies where sleep state was controlled for and reported, a sleep-state dependent pattern of GC effects began emerging (Plihal and Born, 1999; Plihal et al., 1999; Born and Wagner, 2004; de Quervain et al., 2000). Directly comparing systemic administration of cortisol in humans during sleep and wakefulness, Wilhelm et al. (2011) revealed opposite effects depending on the brain state, i.e., consolidation of temporal order memory was impaired with the GC administered (intravenously) during a sleep retention interval, but enhanced with administration during a wake retention interval.

Memory consolidation refers to an offline process after acquisition, which turns initially unstable representations into more stable, long-term engrams (McGaugh, 2000). Consolidation of hippocampal memories is thought to originate from reactivations of the neuronal representation that can occur both during sleep, and here in particular during slow wave sleep (SWS), and during wakefulness (Pavlides and Winson, 1989; Wilson and McNaughton, 1994; Lee and Wilson, 2002; Foster and Wilson, 2006). However, memory reactivations during sleep induce processes qualitatively distinct from reactivations in wakefulness (Rasch and Born, 2007; Inostroza and Born, 2013). During sleep, reactivations exert an immediate strengthening effect on hippocampus-dependent memories as compared to reactivations in wakefulness, which invoke a transient labilization of the representation (Diekelmann et al., 2011). Considering growing evidence for substantial differences

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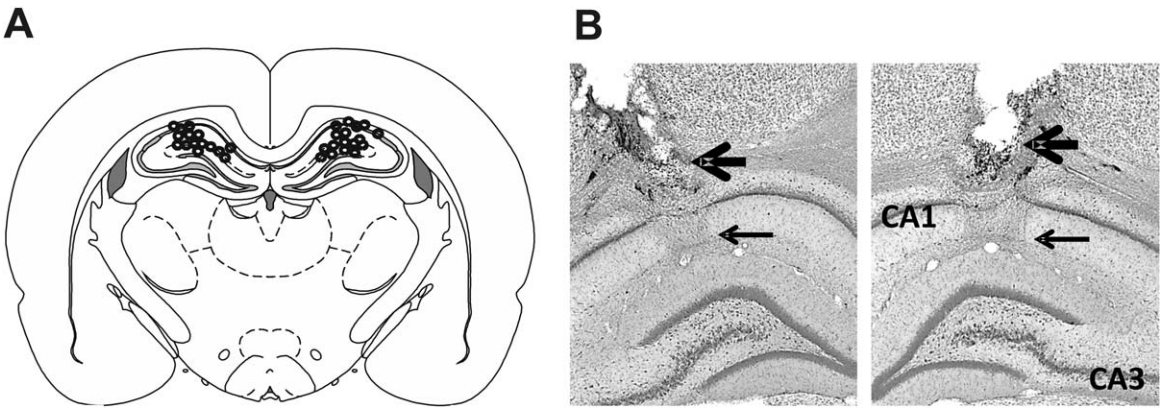

FIGURE 1. Overview of placements of the injection needle tips within the dorsal hippocampus (A) and example photomicrograph illustrating placement of the needle tips in one rat (B). Large arrows point to the cannula tips, and small arrows point to the injection needle tips. Diagram is redrawn from Paxinos and Watson (2007).

between consolidation processes in the sleep and wake states, here we followed the hypothesis that the effect of GC on such consolidation is brain-state dependent as well. In our experiments rats were exposed to two objects in an open field (sampling phase). Corticosterone, i.e. the major GC in rats, (vs. vehicle) was administered during the 80 min postlearning retention interval either during sleep or while the rats were awake. Afterwards the rats were tested either for a hippocampus-dependent object-place recognition memory or for a hippocampus-independent novel-object recognition memory (Binder et al., 2012; Inostroza et al., 2013). To specify the role of hippocampal circuitry in mediating these effects, we used intrahippocampal infusion of the substances.

Twenty adult male Long Evans rats were used. They were kept in a controlled 12 h light/12 h dark cycle with free access to food and water. The experiments were performed in the light part of the day and all procedures were approved by the Schleswig-Holstein state authority and were performed in accordance with the directive of the European Community Council (86/609/ECC). Injection cannulae aimed bilaterally at dorsal hippocampus were surgically implanted. (See online Supporting Information for details on experimental procedures.) After habituation to open field arena, testing of object-location memory and novel-object memory (Figs. 2A,B) was performed in pseudorandom order. For both tasks, the effects of sleep versus sleep deprivation and the effects of corticosterone (10 ng in 0.5 μl of saline) versus vehicle were tested, resulting in eight different experimental conditions. For each rat, each condition was tested on a separate day with at least 3 days in between subsequent conditions. Rats were tested only as long as no abnormality was detected during the infusion procedure. Thus, animals were not used further if fluid came out from the cannula or when the implant loosened. The final number of procedures (infusions and tasks) performed in each rat is presented in Table 1 of the Supporting Information. At the end of the experiments the animals were sacrificed and the locations of infusion sites were confirmed by histological analysis (Fig. 1). The total time spent exploring objects in the test phase or sample phase and the duration of the sample phase were comparable for the four different conditions (sleep/vehicle, sleep/corticosterone, wake/vehicle, wake/corticosterone) for both the object-place recognition task and the novel-object recognition task ($P > 0.24$, for all comparisons). During the retrieval phase the object-place memory was assessed using discrimination ratio, defined as the difference between exploration time of displaced and nondisplaced object divided by the sum of the two exploration times. Analysis of discrimination ratios on the object-place recognition task revealed a distinct sleep/wake × substance interaction ($F(1,29) = 11.09$, $P = 0.002$) in the absence of any main effect for the sleep/wake ($F(1,29) = 0.07$, $P = 0.80$) or substance factor ($F(1,29) = 0.01$, $P = 0.92$, Fig. 2C). Detailed comparisons confirmed differential effects of corticosterone during sleep and wake conditions: When sleep occurred during the retention interval, corticosterone decreased object-place recognition as compared to vehicle infusion ($t(15) = 2.32$, $P = 0.035$). The vehicle-injected rats that slept manifested significant memory for the task ($P = 0.007$), whereas performance in the corticosterone-injected rats, which had slept was not significantly different from chance ($P = 0.10$). By contrast, in the wake conditions corticosterone increased object-place recognition as compared to vehicle infusion ($t(14) = 2.39$, $P = 0.032$). In wake animals the corticosterone injection produced significant memory for the task ($P = 0.001$), whereas performance in the vehicle injected rats was not significantly different from chance ($P = 0.18$).

Retrieval of the novel-object recognition task was not significantly affected by either sleep ($F(1,35) = 0.61$, $P = 0.44$, for sleep/wake main effect) or corticosterone ($F(1,35) = 0.09$, $P = 0.77$, for substance main effect; $F(1,35) = 0.08$, $P = 0.78$, for sleep/wake × substance interaction, Fig. 2D). In each of the four experimental conditions, novel-object recognition was significantly above chance level (all P's < 0.01).

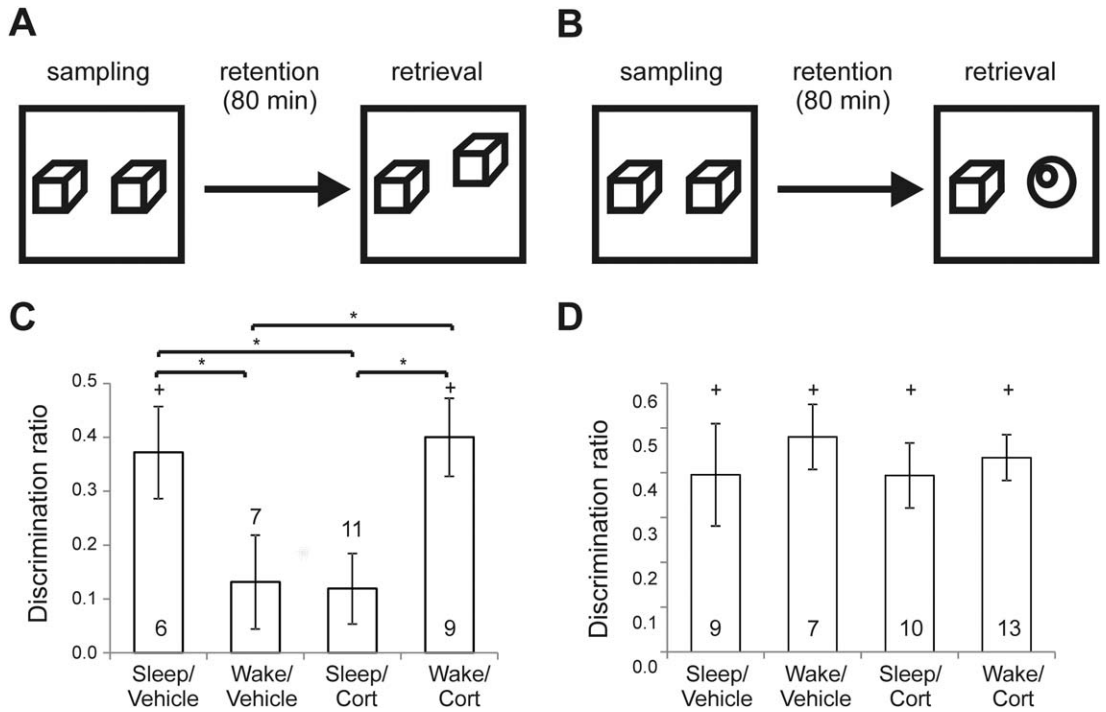

FIGURE 2. (A) Object-place recognition task. During the sampling phase the rats were exposed to an open field arena with two identical objects. During the 80 min retention phase the animals were either allowed to sleep or were sleep deprived. In the sleep conditions, the animals were infused with corticosterone or vehicle once they showed first signs of sleep; in the wake conditions, timing of the infusion was matched to that of the sleep conditions. During the retrieval phase the position of one of the objects was changed and the time spent exploring the two objects was assessed. Increased exploration time for the displaced object indicates memory for the location of the nondisplaced object. (B) Novel-object recognition task. The design of this task was identical to the object-place recognition task except for the retrieval phase when one of the familiar objects was replaced by a novel object. (C) Corticosterone effect on consolidation of object-place recognition task in sleep and wakefulness. $^{*}P < 0.05$ for difference between conditions, two-tailed, except for Sleep/Vehicle vs. Wake/Vehicle where directed one-tailed testing was used; $F(1,29) = 11.09$, $P = 0.002$, for sleep/wake × substance interaction; $+P < 0.05$ for significant difference from chance level. (D) There was no significant effect of sleep or intrahippocampal corticosterone infusion on novel-object recognition. Performance of all the groups during novel-object recognition test was above chance (+ for $P < 0.05$). Numbers in the bars indicate sample size (N).

Sleep during the sleep retention intervals did not differ between corticosterone and vehicle conditions for both tasks (vehicle vs. corticosterone: object-place recognition: sleep onset 39.29 ± 6.19 vs. 38.27 ± 3.51 min; $P = 0.89$; sleep duration 28.13 ± 3.12 vs. 24.12 ± 4.12 min, $P = 0.50$; novel-object recognition: sleep onset 40.67 ± 4.99 vs. 35.50 ± 3.87 min; $P = 0.42$; sleep duration 24.76 ± 3.12 vs. 29.32 ± 3.53 min, $P = 0.34$).

Individual differences in trait anxiety were assessed using the elevated plus maze. The tests indicated normal anxiety levels (proportion of time in the open arms 45.0 ± 3.1%, proportion of entrances to open arms 24.0 ± 2.1%; Hogg, 1996), which were not systematically correlated to performance in any of the memory tasks.

In summary, our results show that in vehicle-infused animals, sleep during the retention interval after encoding enhanced consolidation of hippocampus-dependent object-place recognition memory, as compared with a wake retention condition, which confirms previous studies (Binder et al., 2012; Inostroza et al., 2013). Intrahippocampal corticosterone impaired memory when infused during sleep retention, but improved memory when administered during a wake retention interval. Corticosterone had no effect on novel-object recognition memory that does not require the hippocampus (Bussey et al., 2000; Mumby et al., 2002). Although we did not observe effect of intrahippocampal corticosterone injection on novel object recognition, it is possible that corticosterone injection into different brain area (e.g., perirhinal cortex, Albasser et al., 2010) might be effective. This work extends our previous knowledge in two ways: First, we demonstrate distinct GC effects on memory consolidation dependent on the brain state, i.e., sleep and wakefulness, to our knowledge for the first time in an animal model. Furthermore, we show that this GC effect is localized to hippocampal networks. Our findings match nicely the results of Wilhelm et al. (2011), who showed in humans that cortisol when administered during sleep impaired temporal order (relational) memory considered hippocampus-dependent, but when administered during a wake retention interval it enhanced the memory.

In our study design, we took maximal care to minimize the potential confound of stress by using low-stress, unreinforced behavioral tasks and gentle handling procedure to keep rats

awake. Effects of sleep deprivation by "gentle handling" on corticosterone levels have been reported previously: Meerlo et al. (2002) did not observe increased corticosterone levels after 1 h of sleep deprivation, but did observe an increase after 6 h. Penalva et al. (2003) measured increased corticosterone levels (0.3–0.4 μg/dl) in hippocampal dialysate within an hour of sleep deprivation, while Zant et al. (2011) report no significant corticosterone increase in basal forebrain during the first 3 h of sleep deprivation. Although unlikely, we cannot entirely rule out that a slight increase in endogenous corticosterone occurred during sleep deprivation; however, this increase would be negligible as compared to the dose of corticosterone injected to the hippocampus and would not be expected to be of any behavioral relevance. While our experiments clearly show corticosterone interacting with sleep/wake effects on memory consolidation, we are aware of potential corticosterone effects on memory retrieval (e.g., de Quervain et al., 2000, Roozendaal et al., 2004, reviewed in Roozendaal et al., 2006a, 2006b), because we tested the behavior shortly after the retention period. Yet, such confounding influence would not explain the present findings. While GCs have been consistently shown to impair retrieval (de Quervain et al., 2000, 2009; Wolf, 2009) we observed either enhancing or impairing effects depending on whether animals were asleep or awake during the retention interval. In the two GC-infused groups (sleep group and wake group) memory was tested in entirely identical retrieval conditions. Hence, the observed difference in retrieval performance between the two groups must be attributed to the difference during prior consolidation (retention) period. Yet, the speculation that sleep/wake during retention interval somehow interacts with corticosterone level during retrieval might suggest an intriguing direction for future studies.

Although some effect of the corticosterone on structures outside the hippocampus cannot be fully excluded, the most parsimonious explanation of the observed corticosterone effects in our study refers to the hippocampus. First, histological analysis confirmed that the injection locations were in the hippocampus. Furthermore, in a study by Medina et al. (2007) corticosterone applied at the identical dose and in the same way as in the present study did not spread to nearby structures. In that study corticosterone injected into parietal cortex did not spread effectively into dorsal striatum. Third, the hippocampus has an abundance of GC receptors as compared to adjacent structures (Reul and de Kloet, 1985). All these lines of evidence make the hippocampus the most likely site of corticosterone effect, even if some of the corticosterone leaked.

Our results demonstrate an important role of GC receptors in controlling memory consolidation in sleep and wakefulness. However, while conveying strong GC receptor activation in local hippocampal circuitry, the injection of corticosterone directly into the hippocampus is obviously a nonphysiological intervention. Thus, our results also stimulate future experiments that would study effects of lower and more physiological increases in hippocampal corticosterone levels on memory consolidation in sleep and wake.

The mechanisms mediating opposing GC influences on hippocampal memory consolidation during sleep and wakefulness remain obscure. Corticosterone binds to two types of receptors. High affinity mineralocorticoid receptors are preferentially activated in basal conditions when GC levels are low, i.e., during sleep. Low affinity GC receptors become additionally activated when GC levels are elevated, i.e., during wakefulness and stress (Born and Fehm, 1998; de Kloet et al., 1998, 2005; Joëls, 2008). However, although owing to the lower basal GC levels corticosterone infused during sleep might have occupied mineralocorticoid receptors to a greater extent than during wakefulness, high local hippocampal GC concentrations after infusion are expected to activate GC receptors. Accordingly, effects of intrahippocampal infusion of corticosterone are likely mediated via predominant GC receptor activation in both the sleep and wake retention condition. Because of the relatively short latency of the memory effects observed here, in addition to genomic actions, nongenomic actions of the receptor might have been involved (Chen et al., 2012).

Rather than reflecting differential activation of GC receptors, opposing effects of GC on memory consolidation during sleep and wakefulness might result from brain state-dependent interactions with neurotransmitter activity, such as noradrenaline (Joëls et al., 2011) or acetylcholine. When compared with wakefulness, noradrenergic, and acetylcholinergic activity is diminished during sleep. In fact, minimal levels of acetylcholine, which are reached during SWS have been considered to facilitate sleep associated memory reactivations in hippocampal networks and resultant redistribution of representations towards extrahippocampal networks (Gais and Born, 2004; Hasselmo, 2006; Rasch et al., 2009). By contrast, during wakefulness high acetylcholine levels suppress the information transfer from hippocampal towards extrahippocampal circuitry. GCs might act in parallel with acetylcholine to support sleep and wake modes of memory consolidation (Born and Wagner, 2004). There is only limited information about how GCs affect reactivation of hippocampal neuronal activity. To our knowledge the only study investigating this issue in mouse hippocampal slices showed that the incidence of hippocampal sharp waves, which coincide with replay events, is increased at low and decreased at high corticosterone concentration (Weiss et al., 2008). Also, evidence from rat studies suggests that high GC levels via resultant predominant activation of GC receptors suppress excitatory hippocampal output from the CA1 region as well as long-term potentiation and primed burst potentiation in hippocampal networks, and stimulate long-term synaptic depression and depotentiation (e.g., Pavlides et al., 1996; Coussens et al., 1997; Alfarez et al., 2002; Korz and Frey, 2003; Yang et al., 2004; Avital et al., 2006; Dumas et al., 2010). Such effects could well explain impairing effects of GCs on consolidation occurring during sleep (Born and Wagner, 2004). For the opposing effects GCs exert on wake consolidation, increased noradrenergic activity hallmarking the wake state might be of particular relevance, as the enhancing effect of GCs on encoding is known to require additional noradrenergic activation (Roozendaal 2003; Roozendaal et al., 2006a, 2006b). In the presence of high noradrenaline levels, corticosterone might

boost process of re-encoding induced by reactivations during waking (although reactivations *per se* occur at a lower rate), and such effect might underlie the strengthening effects of GC on hippocampal memory consolidation if administered during wakefulness. However, although plausible, these explanations as to the neuronal mechanisms of GC effects on memory consolidation remain speculative, inasmuch as none of the relevant studies accounted for a possible brain-state dependency of the effects. Extensive future research may be required to investigate the mechanism behind the corticosterone effect on memory consolidation in sleep and wake. Our results show that for solving the conundrum of GC effects on memory consolidation, sleep, and wakefulness need to be considered as crucial determinants.

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