Signs of enhanced sleep and sleep-associated memory processing following the anti-inflammatory antibiotic minocycline in men

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**Abstract**

**Study Objectives:**

Pro-inflammatory cytokines can promote sleep and neuronal processes underlying memory formation. However, this has mainly been revealed in animal studies. Here, we examined how changes in the balance between pro- and anti-inflammatory signaling affect sleep and sleep-associated memory consolidation in humans.

**Design:**

Experimental study in a placebo-controlled, double-blind within-subject crossover design.

**Setting:**

Sleep laboratory.

**Participants:**

Healthy young men (n = 21, age: 23.39±3.56 years) without any signs of sleep disturbances.

**Measurements and Results:**

After learning of declarative memory tasks (word pairs, texts) and a procedural memory task (finger tapping) in the evening, participants orally received either 200 mg of the anti-inflammatory antibiotic minocycline or placebo shortly before nocturnal sleep. Sleep was allowed between 23:00 and 7:00 h and recorded polysomnographically. Retrieval of memories was tested 2 days later. Rather than weakening sleep as expected based on the animal studies, the anti-inflammatory agent promoted sleep and memory consolidation. Specifically, minocycline increased slow-wave activity (SWA, 0.68-4.0 Hz) during non-rapid eye movement (NonREM) sleep stage 2 and selectively enhanced episodic aspects in memory, i.e., memory for the temporal order of events in the texts.

**Conclusions:**

In combination with previous results, our findings indicate that, in humans, prevailing anti-inflammatory, rather than pro-inflammatory, signaling acts towards enhancing NonREM sleep and its memory forming efficacy.

Key words: Minocycline, memory consolidation, sleep, slow-wave activity, neuroinflammation

**1. Introduction**

Although originally discovered as mediators in the immune system, cytokines are strong modulators of central nervous processes, including sleep and memory formation. The pro-inflammatory cytokines interleukin-1β (IL-1) and tumor necrosis factor (TNF) play a major role in this context. These substances are crucial for neuronal plasticity underlying memory formation1,2 and promote synaptic long-term potentiation (LTP), i.e., a neural correlate of memory consolidation3–7. IL-1 and TNF are also sleep-regulatory substances. Accumulation of these pro-inflammatory cytokines during waking drives the homeostatic regulation of non-rapid eye movement (NonREM) sleep8. Injection of IL-1 and TNF consistently enhanced the duration of NonREM sleep and increased slow-wave activity (SWA) in rodents and rabbits9, whereas blocking these cytokines reduced NonREM sleep10.

In humans, cytokine effects on sleep are less clear. In disease conditions with elevated cytokine levels (e.g., in patients with rheumatoid arthritis) blocking IL-1 and TNF signaling decreased excessive daytime sleepiness and subjective fatigue11–13. However, polysomnography in such patients did not reveal any change in NonREM sleep following treatment with the TNF antagonist etanercept12,14. In healthy humans, an early study reported a decrease in slow wave sleep (SWS) following administration of a single dose of the anti-inflammatory antibiotic minocycline15, whereas in a recent study the IL-1 receptor antagonist anakinra increased SWA16.

In light of the mixed picture of effects in humans, here we re-investigated the effects of minocycline on sleep in healthy humans and also assessed sleep-associated memory consolidation. The broad-spectrum tetracycline antibiotic minocycline is particularly suited for examining the role of inflammatory signaling on brain processes in humans, because it readily crosses the blood-brain barrier and exerts its anti-inflammatory effects directly in the brain by suppressing microglial activation and pro-inflammatory cytokine production17.

**2. Material and Methods**

*2.1. Subjects*

Subjects were 21 healthy men (mean ± SEM age: 23.39 ± 3.56 years, range 18 - 33 years). Women were not included in the study because of known interactions between sleep and the menstrual cycle (e.g.,18). The participants were non-smokers presenting a normal nocturnal sleep pattern and did not take any medication at the time of the experiments. Acute and chronic illness was excluded by medical history, physical examination, and clinical routine laboratory investigation. Participants were adapted to the sleep laboratory by spending one adaptation night prior to the experiments proper in the lab (which included polysomnographic recordings and blood sampling). Written informed consent was obtained from each participant, and the study was approved by the local ethics committee.

*2.2. Experimental design and procedure*

The experiments were conducted in the sleep laboratories of the University Hospital Schleswig-Holstein, Campus Luebeck, Germany, according to a placebo-controlled within-subject crossover design. Each subject participated in two experimental conditions. In one condition, 200 mg minocycline (Skid®, Zentiva Pharma GmbH, Frankfurt, Germany, half-life in plasma 12 hours) was orally administered at 22:30 h; in the other condition subjects received placebo. Both sessions for each subject were separated by an interval of at least 14 days. On experimental nights, after preparations for polysomnographic recordings, participants performed (between 21:00 and 22:30 h) on a word pair associates learning task, a text learning task, and a finger tapping task with a 10-min break between the tasks. Subjects were awakened at 7:00 h and then left the lab. During the following 2 days participants engaged in their usual activities. After 48 hours (i.e., in the evening of day 2) retrieval of the memory tasks was tested, in reverse order of learning.

 The experimental night also included repeated blood samplings via an intravenous catheter, which were performed from an adjacent room without disturbing the subject’s sleep in order to assess the release of SWS-associated hormones (prolactin, growth hormone, cortisol). Minocycline did not systematically affect any of these measures which, hence, are not reported here in detail.

*2.3. Polysomnography, sleep analyses, and subjective sleepiness*

Standard polysomnographic recordings were obtained including electro­ence­phalo­graphic (EEG) recordings from electrodes attached at C3 and C4 (according to the international 10–20 system) as well as electro­oculo­graphic and electromyographic recordings. Signals were amplified (Brain Amp, Brain Products, Germany) and digitized, with the EEG sampled at a rate of 200 Hz and filtered between 0.16 and 70 Hz. Sleep stages were determined off-line for subsequent 30-sec recording epochs following standard criteria19. For a more fine-grained analysis of NonREM sleep, EEG power spectra were calculated applying Fast Fourier Transformation (FFT; Vision Analyzer, Brain Products, Germany) on succeeding 10.24-s (2048 data points) epochs of NonREM sleep stage 2 and across S3 and S4 (SWS). Mean power density was determined for the 0.68 - 4 Hz (slow wave activity) and the 12 - 15 Hz (spindle) frequency bands. Sleep stages and mean power density were determined for the whole night and separately for the first and second night-half. Subjective sleepiness was assessed with the Stanford Sleepiness Scale in the evening before and in the morning after the experimental night and again at retrieval testing.

*2.4. Memory tests*

A declarative verbal paired-associates task was applied that required learning a list of 40 pairs of semantically related words (e.g., clock–church). The word pairs were consecutively presented on a screen (presentation time 3 sec, interstimulus interval 500 msec), and the subject was instructed to memorize the pairs. Immediately after learning, baseline memory performance was assessed using a cued recall procedure, i.e., the first word (cue) of each pair was presented and the subject had to name the associated second word (response). The correct response word was then presented as a feedback for 2 sec, regardless of whether the response was correct or not, to allow re-encoding of the correct word pair. The recall procedure was repeated until the criterion of 60% correct responses was reached. Delayed recall (48 hours later) was tested using the same cued recall procedure as during the learning phase, except that no feedback of the correct response word was given and each word pair was tested only once. Different lists of word pairs were used on the subject's two experimental nights. The number of word pairs recalled at retrieval testing, relative to immediate recall performance (absolute difference and percent), served as a measure of 48-hour retention.

In addition, a text learning task was applied. Two standardized neutral German texts which were validated in previous studies20 were used on the subject's two experimental nights. The subject had 4 min to read and memorize the text. For testing immediate recall and delayed recall (48 hours later) the subject was instructed to write down everything he could remember of the texts including details. The number of correct content words recalled at retrieval testing, relative to immediate recall performance (absolute difference and percent), served as a measure of retention. At retrieval testing, in addition to free recall, recognition memory and memory for the temporal order of content words in the texts was assessed. In this test, 12 pairs of words were presented with one word of each pair representing a content word of the text and the other one a synonym. Subjects were required to select the correct content words (recognition) and to bring these words into the sequential order in which they occurred in the text (temporal order). Recall of sequential order was determined by a deviation score, i.e., the distance of the remembered sequence position for a content word (or synonym) from its actual position in the story21.

Subjects also performed on a procedural learning task (finger tapping). They were instructed to tap a repeating five-element sequence as fast and accurately as possible. The task was conducted as described in22. Performance was determined as the number of correctly completed sequences per 30-sec block and performance improvement was assessed as the percent difference between test performance and learning performance All memory tasks had proven to be sensitive to the benefiting effects of sleep in previous studies e.g.,21–24.

*2.7. Statistical analyses*

Statistical analysis was based on analysis of variance (ANOVA), including repeated-measures factors representing the administered substance (minocycline vs. placebo) and (regarding the sleep analyses) the night-half (1st vs. 2nd). There were no drop outs, i.e., all 21 subjects completed both conditions. However, sample size was reduced to *n* = 15-19 for the analyses of sleep stages, EEG power, and memory performance due to artifacts, technical failures or because of outliers (> 2 standard deviations from the mean). Because three subjects did not enter SWS in the 2nd night-half, for the respective analyses of SWS-associated SWA and spindle activity *n* = 14. Degrees of freedom were corrected using the Greenhouse-Geisser procedure. Post-hoc t-tests were used to specify significant ANOVA effects. A *p* –value < 0.05 was considered significant. Data are presented as means ± SEM.

**3. Results**

*3.1. Polysomnography,sleep analyses, and subjective sleepiness*

Minocycline did not change absolute or percent time spent in the different sleep stages or subjective sleepiness (Table 1). Analysis of EEG power spectra indicated that minocycline enhanced slow-wave activity (SWA: 0.68 – 4 Hz) in NonREM sleep stage 2 (*p* = 0.041 for main effect of condition, *n* = 17) with this effect being most prominent during the first night-half (*p* = 0.028; Figure 1). There were no significant changes in spindle activity.

*3.2. Memory tests*

Minocycline did not influence delayed recall of word pairs (absolute numbers) or retention of word pairs (i.e., absolute and percent change of retrieved words at the 48-hour interval relative to immediate recall performance) on the word pair associates task (all *p* > 0.7, *n* = 17). Also, recall and retention of the texts as well as recognition of content words remained unaffected by minocycline (all *p* > 0.4, *n* = 17). However, minocycline significantly decreased the deviation score assessing memory for the temporal order in the content words of the texts (*p* = 0.023, *n* = 16), reflecting an enhancement in aspects of episodic memory performance (Figure 2). Subjects showed normal overnight gains on the finger tapping task (averaging 18.9 % improvement). However, there was no effect of minocycline (*p* > 0.7, *n* = 15).

**4. Discussion**

Investigations in rabbits and rodents provided consistent evidence that pro-inflammatory cytokines like TNF and IL-1 promote sleep, particularly NonREM sleep, and enhance SWA9,10. Physiological levels of IL-1 and TNF also support hippocampus-dependent memory formation and synaptic LTP4,6,7,25–27. Here, we used the anti-inflammatory agent minocycline to clarify how the balance in inflammatory signaling affects sleep and sleep-dependent memory consolidation in humans. Given the pro-inflammatory actions observed in animals we expected that shifting signaling towards predominant anti-inflammatory signaling would weaken sleep and associated memory formation. Contrary to this expectation, after minocycline administration we found signs of deepened sleep, i.e., enhanced SWA during NonREM stage 2 sleep, and of a concurrently enhanced episodic memory processing during sleep.

The changes in sleep observed here in humans following the anti-inflammatory treatment with minocycline do not only contrast with the sleep-promoting influence observed following pro-inflammatory cytokine administration in animals, but also with findings after minocycline administration in mice28 and humans15. In those studies acute administration of the substance decreased time in NonREM sleep and SWS, respectively. These discrepancies are difficult to explain, particularly considereing that dosing and route of minocycline administration were identical in the present and previous human study. Curiously, in both studies minocycline-induced effects on NonREM sleep, though in the opposite direction, appeared to concentrate on the first hours of the nocturnal sleep period, suggesting an action on processes of homeostatic sleep regulation. Thus, it could be speculated that sleep promoting effects of minocycline emerge only in conditions of diminished homeostatic sleep drive, considering that our subjects were on average older and showed less SWS than the subjects of the Nonaka et al. study. This view would concur also with the present observation that increases in SWA after minocycline were most robust during lighter stage 2 NonREM sleep, although the anti-inflammatory agent, on a descriptive level, likewise enhanced SWA during SWS epochs in the early night. On the other hand, conditions of already strong SWS, as present in the Nonaka et al. study, might prevent the emergence of additional deepening influences on NonREM sleep and, instead, sleep disrupting effects may prevail as a result of any other of the multiple effects of the drug29. This explanation would also agree with the overall moderate size of the NonREM sleep promoting effect of minocycline observed here.

Minocycline also improved signs of episodic memory consolidation in our study, which might be a direct consequence of the increase in SWA as this parameter is known to be crucially linked to hippocampus-dependent memory processing during sleep30,31. Fitting our memory results, there is first evidence of a memory improving effect of minocycline also from studies in rodents32–34 and in schizophrenic patients35,36. However, the underlying processes affected in those studies might be different37.

Our present data corroborate a previous study of ours in healthy humans which revealed a similar increase in SWA following administration of another anti-inflammatory agent, i.e., the IL-1 receptor antagonist anakinra16. Although any conclusions remain tentative in light of conflicting results, those and the present findings in combination support the view that, different from various animal species, in humans changes in the balance of inflammatory signaling towards prevailing ant-inflammatory activity favor the expression of NonREM sleep.

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**Legends**

**Figure 1. SWA and spindle activity during SWS and stage 2 (S2) NonREM sleep after administration of minocycline vs. placebo.**

Slow wave activity (SWA, power density in µV2/Hz) and spindle activity (12-15 Hz) during periods of SWS (left panel) and NonREM S2 sleep (right) following administration of minocycline (black bars) and placebo (white bars) for the whole night as well as for the first and second night-half. Means ± SEM are indicated, *n* = 17-18, \* *p* < 0.05 for pairwise comparisons between substance conditions.

**Figure 2. Memory performance after administration of minocycline vs. placebo.**

Retention of word pairs (A) and content words of the texts (B) as well as recognition of content words (C) and deviation scores indicating memory for the temporal order of content words in the texts (D) for the minocycline (mino, black bars) and placebo (plac, white bars) conditions. Retention of word pairs and of content words is expressed as recall performance at 48-hours retrieval relative to immediate recall performance (i.e. Δ from baseline). Means ± SEM are indicated, *n* = 16-17, \* *p* < 0.05 for pairwise comparisons between substance conditions.

**Tables**

**Table 1.** Sleep stages and subjective sleepiness.

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Minocycline** | **Placebo** |  |
|  | **Means** | **SEM** | **Means** | **SEM** | ***p*-values** |
| **In minutes** |  |  |  |  |  |
|  |  |  |  |  |  |
| **TST** | 428.97 | 7.30 | 415.76 | 7.92 | 0.12 |
| **Wake** | 23.00 | 7.50 | 20.24 | 5.65 | 0.67 |
| **S1** | 47.32 | 2.94 | 50.87 | 5.15 | 0.51 |
| **S2** | 233.61 | 7.69 | 229.21 | 10.22 | 0.68 |
| **S3** | 31.61 | 2.27 | 27.74 | 2.17 | 0.22 |
| **S4** | 30.87 | 4.41 | 31.58 | 5.39 | 0.88 |
| **SWS** | 62.47 | 6.17 | 59.32 | 6.32 | 0.62 |
| **REM** | 62.58 | 5.46 | 56.08 | 6.15 | 0.26 |
| **Sleep onset latency** | 25.89 | 5.08 | 25.55 | 4.53 | 0.94 |
| **SWS latency** | 16.92 | 1.65 | 17.42 | 2.04 | 0.81 |
| **REM latency** | 118.56 | 10.72 | 113.87 | 12.67 | 0.89 |
|  |  |  |  |  |  |
|  |  |  |  |  |  |
| **In %** |  |  |  |  |  |
|  |  |  |  |  |  |
| **Wake** | 5.48 | 1.79 | 4.94 | 1.34 | 0.73 |
| **S1**  | 10.99 | 0.60 | 12.27 | 1.24 | 0.33 |
| **S2** | 54.74 | 2.06 | 55.18 | 2.33 | 0.83 |
| **S3** | 7.33 | 0.49 | 6.67 | 0.53 | 0.37 |
| **S4** | 7.10 | 1.00 | 7.69 | 1.37 | 0.60 |
| **SWS** | 14.43 | 1.36 | 14.36 | 1.61 | 0.97 |
| **REM** | 14.35 | 1.11 | 13.23 | 1.36 | 0.36 |
|  |  |  |  |  |  |
| **Subjective sleepiness** | 3.73 | 0.43 | 3.88 | 0.32 | 0.83 |

Absolute duration and percentage of total sleep time (TST) spent awake (W) and in sleep stages 1 – 4 (S1 – S4), slow-wave sleep (SWS, i.e. the sum of S3 and S4), and rapid eye movement (REM) sleep as well as subjective sleepiness (1 – 7, ‘feeling active, vital, alert, or wide awake’ to ‘no longer fighting sleep, sleep onset soon, having dream-like thoughts’), in the morning after the experimental night. Means (± SEM) are given for the minocycline and placebo conditions. There were no significant differences between conditions (*n* = 19).

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