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Promote Sleep in Rats

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ABSTRACT: We previously showed that inhibition of brain NO production suppresses sleep in rats and rabbits. In the preaent experiments we studied the effects of stimulation of NO-receptive brain mechanisms on sleep. Male rats were injected intracerebroventricularly with the NO donor S-nitroso-N-acetylpenicillamine (SNAP, 400 μg) or molsidomine (SIN-1, 7 and 70 μg). Seven micrograms of SIN-1 did not affect sleep, but increased the delta wave activity of the electroencephalogram (EEG) during nonrapid-eye-movement sleep (NREMS) and suppressed EEG alpha and beta activities in NREMS and delta, theta, and beta activities during wakefulness. Seventy micrograms of SIN-1 significantly increased NREMS after a latency of -9 h. EEG power was suppressed in each frequency band during rapid-eye-movement sleep (REMS) and wakefulness, whereas during NREMS, delta activities were increased after the injection of 7 μg SIN-1, and higher frequencies were suppressed after both doses. On the recovery day sleep remained elevated, but EEG power returned to baseline. The effects of SNAP on NREMS were similar to those of SIN-1, but REMS was decreased and slight increases in brain temperature accompanied the sleep changes. The EEG theta, alpha, and beta activities were suppressed in both wakefulness and REMS. Collectively, these results are consistent with the hypothesis that NO plays a role in the regulation of vigilance.

KEY WORDS: Electroencephalogram, EEG power spectrum, NREMS, REMS, Brain temperature.

INTRODUCTION

Nitric oxide (NO) is involved in a variety of elementary neural functions such as regulation of transmitter release and synaptic efficacy [31,32]. The regulation of complex neural functions such as development of neural networks [9], memory [13], sexual behavior [24], and eating [26] are also influenced by NO. Substantial indirect evidence indicates that NO has a crucial role in the function of brain mechanisms in physiological sleep regulation. NO synthase (NOS) is localized in central nervous system (CNS) structures, which are important in sleep regulation, e.g., basal forebrain and brainstem [36]. NOS activities of the hypothalamus, brainstem, cerebellum, and hippocampus show pronounced diurnal variation [1]. Inhibition of NO synthesis results in sleep loss in rabbits [21] and rats [16], and interferes with the somnogenic actions of interleukin 1 (IL-1) in rabbits [21]. Intracerebroventricular (ICV) injections [21], or brain stem microinjections [18] of N^{ω}-nitro-L-arginine methyl ester (L-NAME), a NOS inhibitor, suppress nonrapid-eye-movement sleep (NREMS). From these data it is logical to hypothesize that stimulation of NO-receptive mechanisms in the brain should enhance NREMS. To test this hypothesis the effects of NO donor substances, which spontaneously release NO in vivo [8], on sleep were tested. Both NO donors used, S-nitroso-N-acetylpenicillamine

Recordings

EEG, brain temperature (T_{br}), and motor activity, detected by an ultrasonic sensor, were recorded by computer. The results of the motor activity served as an aid for determining the vigilance states [16] and were not further quantified. EEG was filtered below 0.1 and above 40 Hz. The amplified signals were digitized at the frequency of 128 Hz for EEG, and at 2 Hz for motor activity and T_{br}. Single T_{br} samples were saved on the hard disc in 10-s intervals. On-line fast Fourier analysis of the EEG was also performed in 10-s intervals on 2-s segments of the EEG in 0.5 Hz bands of the 0.5–30 Hz frequency range. The vigilance states were determined offline in 10-s epochs. EEG, T_{br}, and the motor activity were displayed on the computer monitor in 10-s epochs, and also simultaneously in a more condensed form, in 12-min

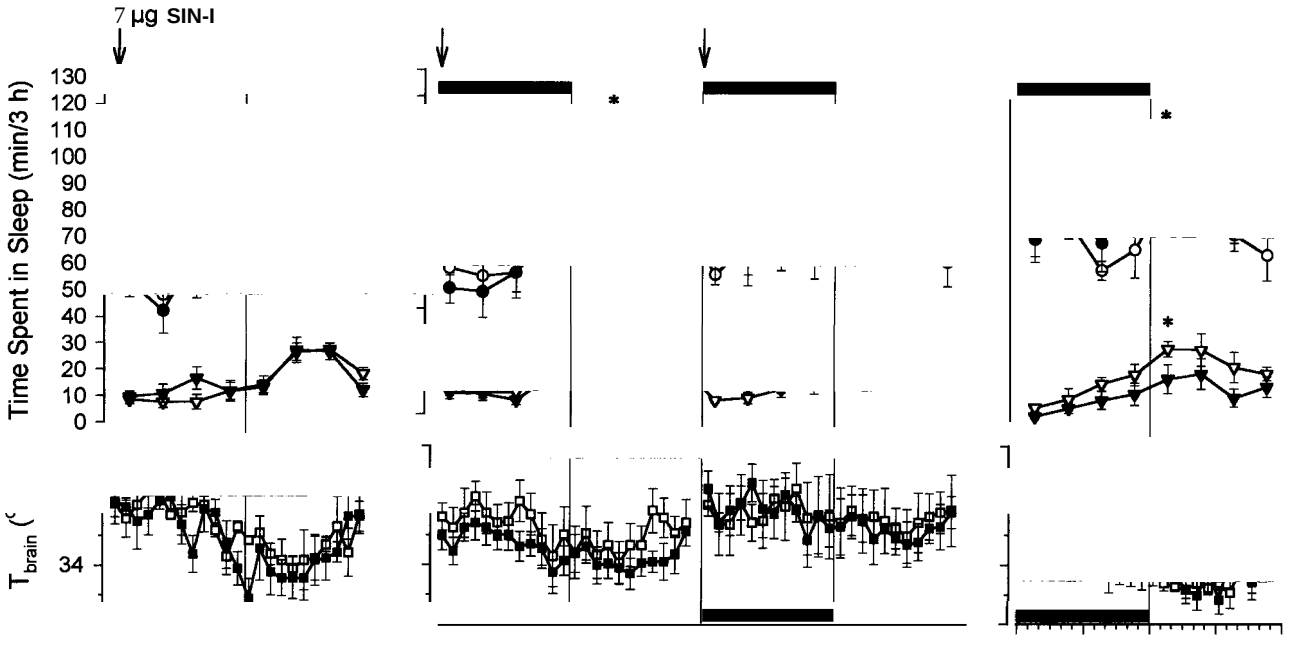
7 µg SIN-I
Time Spent in Sleep (min/3 h)
130
120
110
100
90
80
70
60
50
40
30
20
10
0
T_{brain} (°
34
*
*
*

TABLE 1

THE EFFECTS OF NITRIC OXIDE DONORS ON THE AMOUNT OF SLEEP AND ON BRAIN TEMPERATURE: STATISTICAL RESULTS

	NREMS			REMS			T_{br}
	1–23 h[a]	1–Y h[b]	10–23 h[c]	1–23 h[a]	1-9 h[b]	10–23 h[c]	1–23 h[d]
7 μg SIN-t	$F(1, 6) = 0.90$ NS						
70 μg SIN-1	$F(1, 7) =$						

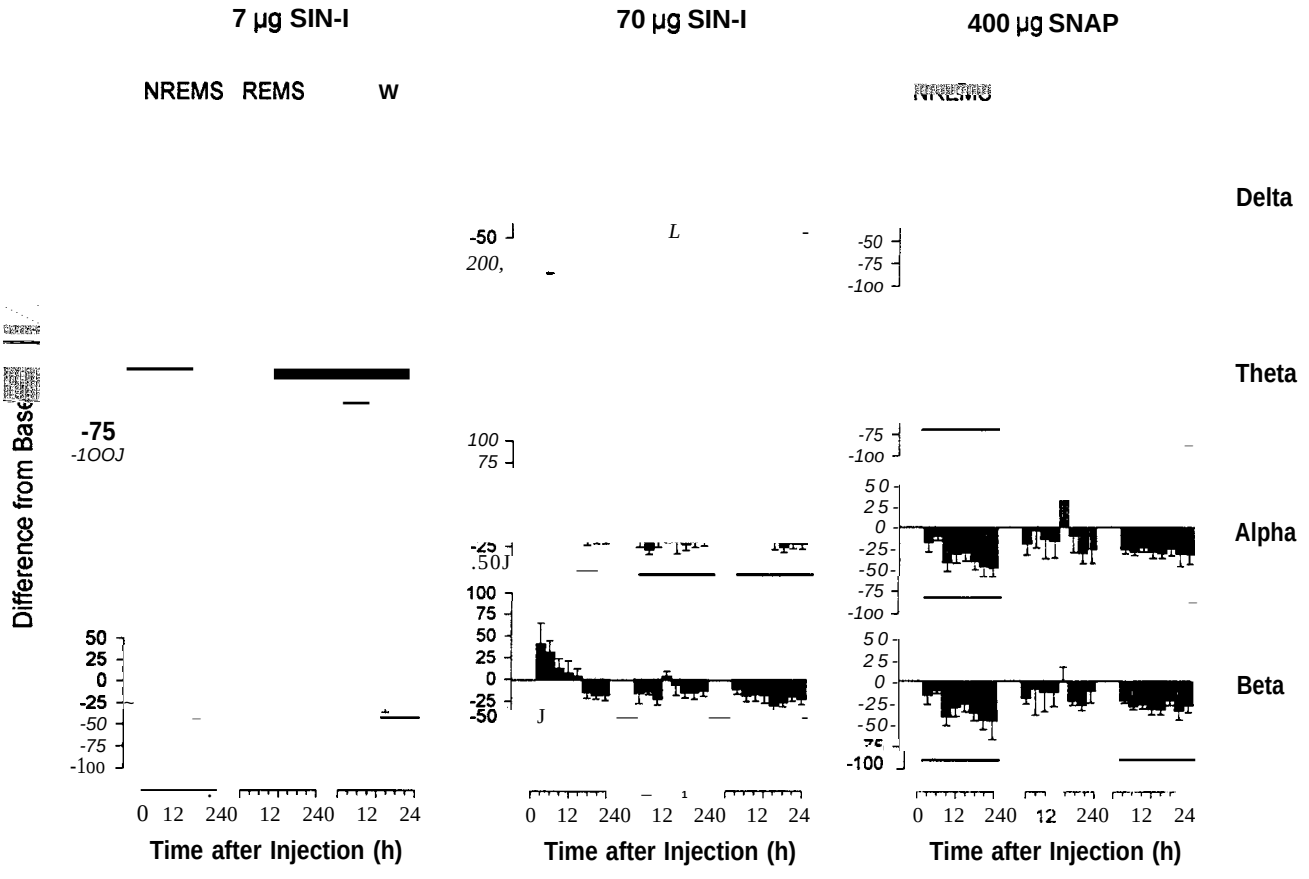

FIG. 2. The effects of SIN-1 and SNAP on EEG power spectra. EEG power values were averaged in 3-h time blocks from h 1 to 21 and from h 25 to 45 and in 2-h time blocks from h 22 to 23 and h 46 to 47. The effects of NO donors are expressed as percent change from the baseline ± SE (baseline: 100%). Upper row: delta activity, second row from the top: theta activity, second row from the bottom: alpha activity, bottom row: beta activity; W: wakefulness. For statistics, the EEG

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