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Sawtooth waves during REM sleep after administration of haloperidol combined with total sleep deprivation in healthy young subjects

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Abstract

We sought to examine the possible participation of dopaminergic receptors in the phasic events that occur during rapid eye movement (REM) sleep, known as sawtooth waves (STW). These phasic phenomena of REM sleep exhibit a unique morphology and, although they represent a characteristic feature of REM sleep, little is known about the mechanisms which generate them and which are apparently different from rapid eye movements. STW behavior was studied in 10 male volunteers aged 20 to 35 years, who were submitted to polysomnographic monitoring (PSG). On the adaptation night they were submitted to the first PSG and on the second night, to the basal PSG. On the third night the volunteers received placebo or haloperidol and spent the whole night awake. On the fourth night they were submitted to the third PSG. After a 15-day rest period, the volunteers returned to the sleep laboratory and, according to a double-blind crossover randomized design, received haloperidol or placebo and spent the whole night awake, after which they were submitted to the fourth PSG. The volunteers who were given haloperidol combined with sleep deprivation exhibited an elevation of the duration and density of the STW, without significant alterations of the other REM sleep phasic phenomena such as rapid eye movement. These findings suggest that sawtooth waves must have their own generating mechanisms and that the dopaminergic receptors must exert a modulating role since REM sleep deprivation, as well as administration of neuroleptics, produces supersensitivity of dopaminergic receptors.

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Key words
- Sawtooth waves
- REM sleep
- Sleep deprivation
- Dopaminergic receptors
- Rapid eye movements
- Haloperidol

Introduction

The electroencephalographic pattern known as sawtooth waves (STW) exhibits a unique morphology and represent a typical element of rapid eye movement (REM) sleep. These waves were first reported by Schwartz and Fischgold (1) in 1960. In the same year, Jouvet et al. (2) named them sawtooth waves due to their characteristic morphology, defining them as slow waves, with a frequency of 2 to 3 Hz, projecting mainly to the anterior areas of the scalp. Sawtooth waves appear in a wide area of the

scalp, with maximum amplitude in the central region (3,4).

The mechanisms and neurotransmitters involved in STW genesis are not completely known. However, some experiments suggest that REM sleep and STW genesis could be related to dopaminergic receptors. The effects of neuroleptics on REM sleep have been described, but the results are controversial and depend on the dose administered (5,6). Animal experiments demonstrate that neuroleptic administration produces supersensitivity of dopaminergic receptors (6-10). In the rat the same is observed after sleep deprivation, and particularly after the combination of neuroleptic administration and sleep deprivation (11,12).

On the basis of these considerations, we examined rapid eye movements and STW, events that occur during REM sleep, after haloperidol administration combined with sleep deprivation in normal volunteers.

Subjects and Methods

Healthy young adult men were recruited by advertisement. Exclusion criteria were sleep complaints, abnormal sleep/wake schedule, medication and drug intake, including alcohol, and an abnormal amount of caffeine intake (up to 50 mg/day). Ten male volunteers ranging in age from 20 to 35 years (mean: 27.5 ± 5.0 years) participated in the study, which was approved by the Ethics Committee of São Paulo Federal University and written informed consent was obtained from all volunteers.

Each subject was asked to arrive in the laboratory at 9:00 pm and was prepared for polysomnographic monitoring (PSG). The volunteers spent six nights in the laboratory: the first one was the adaptation night (first PSG) and the second was the baseline night (second or basal PSG). On the third night the volunteers received placebo or haloperidol (5 mg at 10 pm) and spent the whole night and the following day awake in the laboratory. On the fourth night they were submitted to the third PSG (placebo/haloperidol PSG). After a 15-day rest period, the volunteers returned to the sleep laboratory and, according to a double-blind crossover randomized design, received haloperidol or placebo and spent the whole night and the following day awake in the laboratory, after which they were submitted to the fourth PSG (haloperidol/placebo PSG).

The following recordings were obtained systematically: electroencephalogram (C3/A2 and C4/A1), right and left electrooculograms, and chin and right and left leg electromyograms. The Medilog SAC system (Oxford, UK) was used and recordings were scored using an automatic analysis program with visual corrections. Sleep stages, including REM sleep, were identified and quantified according to criteria established by Rechtschaffen and Kales (13). Wake-up time was not fixed and was decided by the subjects.

All recordings were scored by the same investigator, blind to the experimental conditions. Each STW burst was identified. The following parameters were calculated for each burst: frequency, amplitude and hemispheric symmetry of the STW; the relationship between the period of REM sleep and STW; total number and duration (in seconds) of the bursts during each period, and total REM sleep period. STW density was calculated as the percentage of STW time during total REM sleep time. Density of rapid eye movements during REM sleep was calculated for total REM sleep and for each REM sleep period (number of eye movements/total REM sleep time).

Statistical analysis was performed by two-way ANOVA for repeated measures with sleep condition (basal, sleep deprivation) and treatment (placebo, haloperidol) as main factors. The sleep condition sum of square with two degrees of freedom was split into two orthogonal contrasts. The first one compared basal with placebo conditions and the

second one compared haloperidol with the other two sleep conditions. The values are reported as the mean ± SD and the level of significance was set at $P<0.05$.

Results

The data for the normal pattern of STW obtained on the baseline recording night indicated that visually identified STW had a mean frequency of 2.7 ± 0.2 Hz, with a mean amplitude of 66.9 ± 12.8 μV, a mean density of 3.8 ± 2.9%, and a mean total duration of 178.3 ± 148.6 s during total sleep time (Table 1). All STW projected symmetrically in both hemispheres (as seen in C3 and C4). There was no set pattern of occurrence of STW, i.e., they did not seem to correlate with rapid eye movements and exhibited a variable timing during a given REM sleep period.

Mean values during the three sleep conditions (basal, placebo and haloperidol nights) tested by analysis of variance were different for STW duration ($F_{2,18} = 8.385$, $P = 0.003$) and for density ($F_{2,18} = 4.069$, $P = 0.03$). The equality of means for the first two sleep conditions, basal and placebo tested by orthogonal contrast was not rejected for STW duration ($F_{1,18} = 1.039$, $P = 0.320$) and for density ($F_{1,18} = 1.759$, $P = 0.201$), while the haloperidol condition was considered to be significantly different from the other two for STW duration ($F_{1,18} = 15.730$, $P = 0.0009$) and for density ($F_{1,18} = 6.366$, $P = 0.021$) (Table 2; Figures 1 and 2). No changes in total REM sleep time or density of rapid eye movements were detected in any of the conditions (Table 2).

Discussion

Normal pattern of sawtooth waves and its relationship to REM sleep

The frequency of STW observed in our healthy volunteers (2.7 Hz) was similar to that reported by Jouvet et al. (2), i.e., 2 to 3 Hz. The mean amplitude of the waves was

Table 1. Sawtooth wave duration and density observed in 10 volunteers during the basal night.

	Total REM sleep	REM 1	REM 2	REM 3	REM 4	REM 5
Duration (s)	178.3 ± 148.6	34.6 ± 46.2	41.7 ± 46.2	24.8 ± 17.7	38.3 ± 44.9	59.9 ± 91.8
Density (%)	3.8 ± 2.9	4.5 ± 2.4	4.1 ± 5.1	1.8 ± 0.9	3.8 ± 2.9	6.4 ± 11.6

Each parameter is represented for total rapid eye movement (REM) sleep time and for each REM sleep period during the recording night. Data are reported as means ± SD.

Table 2. Sawtooth wave (STW) duration and density, rapid eye movement (REM) sleep time and REM sleep density observed in 10 volunteers during the basal night and the subsequent recording night after placebo and haloperidol administration before one night of sleep deprivation.

	Basal	Placebo	Haloperidol
STW duration (s)	178.3 ± 148.6	255.5 ± 167.2	476.9 ± 373.4*
STW density (%)	3.8 ± 2.9	5.9 ± 3.5	8.4 ± 6.5*
REM sleep time (min)	97.5 ± 13.8	91.6 ± 22.2	100.5 ± 15.9
REM density	1.9 ± 1.1	1.3 ± 0.6	1.1 ± 0.6

Data are reported as means ± SD.
*P<0.05 compared to basal and placebo administration (two-way ANOVA, followed by a test of orthogonal contrast).

66.9 μV in the central areas, comparable to the 50.0 μV value reported by Yasoshima et al. (4).

Some studies have suggested independent generating mechanisms between STW and the rapid eye movements. Geisler and colleagues (14) examined the density of STW in patients taking narcoleptics and healthy volunteers and found increased density of rapid eye movements in narcoleptic patients, without alterations of STW, indicating that these events are regulated by independent mechanisms. In a previous study we observed that visually handicapped subjects presented increased STW density during REM sleep, concomitantly with a reduction of rapid eye movements (15). The present results suggest the same, insofar as sleep deprivation in association with haloperidol administration increased the total time and density of STW with a reduction of rapid eye movement density. Sato and co-workers (16) suggested that a predictable sequence of muscle tone reduction, followed by STW and then rapid eye movements precedes the generally accepted onset of REM sleep and may have implications for the determination of physiological REM sleep onset.

The fact that STW could be observed in sleep phases other than REM sleep was interpreted by Schwartz (3) as a transition from vertex sharp waves to REM sleep. In a comparison between STW and vertex sharp waves, Yasoshima et al. (4) described STW with lower voltage than vertex sharp waves. Sawtooth waves exhibit a positive component of prolonged duration (approximately 252 ms), longer than vertex sharp waves. The authors hypothesized that since these two transitory elements show opposite polarities, i.e., STW are negative, whereas vertex sharp waves are positive, they could be generated by different neuronal populations from the same cortical area, or they may originate from different segments of the same cortical neurons.

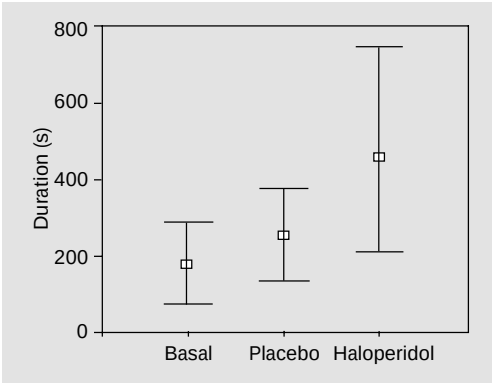

Figure 1. Sawtooth wave duration. Data are reported as seconds (means ± SD), in the EEG of 10 healthy young subjects during a basal night of sleep and during a sleep-deprived night combined with administration of placebo or haloperidol.

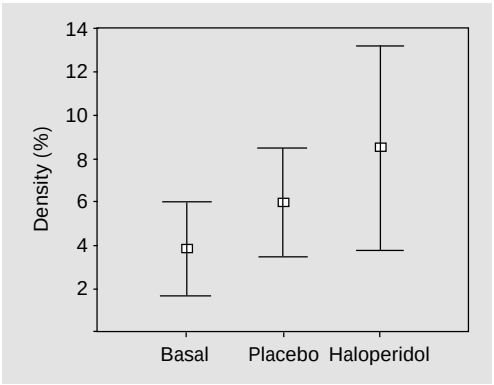

Figure 2. Sawtooth wave density. Data are reported as means ± SD in the EEG of 10 healthy young subjects during a basal night of sleep and during a sleep-deprived night combined with administration of placebo or haloperidol.

The effects of haloperidol and sleep deprivation on sawtooth waves

Although we did not observe significant differences between sleep deprivation subjects treated with placebo or haloperidol, analysis of the data suggested that a combination of sleep deprivation and haloperidol produces an increase in STW, since this group was statistically different from the other two groups pooled together. This result suggests that the dopaminergic system may play a role in certain REM sleep phenomena. The effects of neuroleptics on paradoxical sleep are controversial. Lewis and Evans (5) administered two distinct doses of chlorpromazine (25 and 100 mg) to healthy volunteers and found that the lower one produced an increase in REM sleep, whereas the higher one resulted in decreased paradoxical sleep. Okuma and co-workers (17) compared the effects of several drugs on the

sleep of healthy volunteers and observed that low doses of chlorpromazine produced a slight increase in percentage of REM sleep, with no change in the density of rapid eye movements. Contradictory results were also obtained by Nakazawa et al. (18) who administered 1.5 mg haloperidol to healthy volunteers and examined REM sleep after sleep deprivation. The authors observed that subjects who presented the smallest paradoxical sleep rebound following REM sleep deprivation also presented reduction of REM sleep after drug administration. On the contrary, those volunteers who exhibited significant REM sleep rebound following sleep deprivation presented an equivalent increase of REM sleep after haloperidol ingestion.

A supersensitivity of dopaminergic receptors after neuroleptic administration and sleep deprivation has been described. Christensen et al. (8) observed supersensitivity of dopaminergic receptors after receptor blockade induced by a single dose of neuroleptics. This is a dynamic phenomenon and the degree and duration of supersensitivity are related to the degree and duration of the preceding receptor blockade.

A study by Tufik and colleagues (12) showed that REM sleep-deprived rats are more responsive to apomorphine, indicating that this manipulation induces up-regulation of dopaminergic receptors. An alternative explanation given by Tufik and colleagues involves increased dopaminergic activity at the presynaptic level. Using an autoradiographic technique, Nunes Jr. et al. (19) showed that REM sleep deprivation resulted in an augmented population of D2 receptors in rats. The association of REM sleep deprivation with an injection of haloperidol 24 h before apomorphine administration induced an even higher level of aggressive behavior than that of rats submitted only to sleep deprivation. It has been claimed that 24 h after haloperidol administration is the necessary period for a state of supersensitivity to dopamine agonists to occur in the brain (20). The studies on sleep deprivation and administration of neuroleptics and their effects do not refer to STW; however, their increase as reported here could be related to a supersensitivity of dopaminergic receptors. In a recent study on humans, we were not able to demonstrate the participation of dopamine in STW (21).

The physiological meaning of STW is still more unclear. Recently Mann et al. (22) reported a slow rhythm (delta) in the limbic areas, and Hobson et al. (23) suggested a relationship of these waves with dreams. Since it is known that STW occur in delta frequency and the mesolimbic path is modulated by the dopaminergic system, we could establish an association between STW, dopaminergic system, limbic regions, and consequently, oniric activity.

Our results showed that STW occur at an average frequency of 2.7 Hz, with a total duration of 178.3 s and a density of 3.8% in healthy young subjects. These waves may precede REM sleep or occur after the end of this sleep phase. The combination of haloperidol and total sleep deprivation resulted in increased total time and density of STW during sleep during the subsequent night, without changes in other REM sleep parameters. These results, taken together with literature data, suggest that STW seem to be a phenomenon independent of other REM sleep events, with exclusive generating mechanisms in which the dopaminergic system might play a modulatory role.

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