Adenosine is currently being investigated as a possible mediator of a homeostatic sleep need. Reports from different laboratories suggest that both adenosine A1 agonists and selective serotonin reuptake inhibitors (SSRI) increase deep slow wave sleep (SWS-2) after an interval. In this study, the sleep-wake effects of the adenosine A1 agonist N6-cyclopentyladenosine (CPA) and the SSRI zimeldine are directly compared in the same animals. Since the SWS-2 increase following SSRIs may be secondary to increased adenosine levels during the initially increased waking, it was also investigated whether the adenosine A1 antagonist 8-cyclopentyltheophylline (CPT) would inhibit the SWS-2 increase following the serotonin reuptake inhibitor. Both the adenosine A1 agonist CPA and the SSRI zimeldine increased SWS-2 after an interval. Both drugs increased slow wave activity and decreased 9-20 Hz activity during SWS-2. Both the adenosine A1 antagonist CPA, zimeldine and the two drugs combined initially increased waking and subsequently increased SWS-2 after 2 or 4 h. All treatments increased 2-6 Hz activity in SWS-2 after 2 h. Thus, CPT did not antagonize the SWS-2 increase of zimeldine. Based on the sleep and power spectral effects it is suggested that the adenosine A1 antagonist potentiated the zimeldine effect, possibly due to antagonism of adenosine A1 inhibition of serotonin release. The data indicate that the delayed SWS-2 and slow wave activity increases following zimeldine are not due to increased stimulation of adenosine A1 receptors following the initial sleep loss.

CURRENT CLAIM: The adenosine A1 antagonist 8-cyclopentyltheophylline potentiates the sleep-wake and slow wave activity effects of the SSRI zimeldine.
In rats, CPT (10-20 mg/kg i.p.) increased waking and reduced SWS-2 (Virus et al., 1990). Thus, CPT should be able to block the zimeldine induced SWS-2 increase, if this is a consequence of increased extracellular adenosine and increased adenosine A₁ stimulation.

**METHODS**

**Ethical evaluation**

The experiment described in this article has been approved by the local responsible laboratory animal science specialist under the surveillance of the Norwegian Animal Research Authority and registered by the Authority. Norway has signed and ratified The European Convention for the protection of Vertebrate Animals used for Experimental and other Scientific Purposes of March 18, 1986.

**Animals**

Twenty-three male Mol/WIST rats (Møllegaard, Copenhagen, Denmark) weighing 250-300 g were used. The animals were housed individually in conventional macrolone cages. They were kept on a controlled 12-hour light/12-hour dark schedule with lights on at 0600 hours, and ambient temperature at 22°C ± 1°C. The animals had access to food (RM1.(E)., SDS, England) and water ad libitum, also during the actual recording. During surgery animals were anesthetized with a mixture containing 0.05 mg/ml fentanyl, 2.5 mg/ml fluanizone and 1.25 mg/ml midazolam, 3 ml/kg s.c. The rats were implanted with stainless steel screw electrodes epidurally for bilateral fronto-frontal and fronto-parietal EEG recording (Ursin and Larsen, 1983). Silver wires were inserted in the neck muscle for electromyographic (EMG) recording. Temgesic (1 ml/kg s.c.) was given as a postoperative analgesic.

**Drugs**

Zimeldine 20 mg/kg (Astra Läkemedel AB, Sweden) was dissolved in 0.9% NaCl and injected intraperitoneally (i.p.).

N⁶-cyclopentyladenosine (CPA) (RBI, USA) was dissolved in the vehicle dimethyl sulfoxide (DMSO) and injected i.p. in doses of 0.5 mg/kg (n=3) or 1 mg/kg (n=3).

8-cyclopentyltheofylline RBI (CPT) was dissolved in DMSO and injected i.p. in doses of 5 mg/kg (n=9) or 10 mg/kg (n=8). Injected volume was 1.5 ml/kg (ca. 0.5 ml per animal) for all injections.

**Experimental design**

Three weeks were allowed following surgery for recovery and adaptation prior to the experiments. The animals were adapted to the recording environment during the last week before the experiments started, with cables attached for at least three days, several hours per day.

**CPA compared with zimeldine:** A baseline recording was followed by recordings following 20 mg/kg zimeldine, or CPA 0.5 mg/kg (n=3) or 1 mg/kg (n=3), or vehicle alone, in a balanced order design.

**CPT plus zimeldine:** Each of the 17 rats went through four
Figure 2. EEG power densities (means) in 2-h periods in SWS-2 following vehicle (○), CPA (0.5 or 1 mg/kg (∆) and zimeldine 20 mg/kg (■)). Symbols above the x-axis indicate significant differences from control (p< 0.05, Wilcoxon signed ranks test). ● indicate significant difference zimeldine vs zimeldine + CPT.
experimental conditions, with two i.p. injections given 15 min apart, in a balanced order design: Saline + vehicle; zimeldine + vehicle; saline + CPT 5 mg/kg (n=9) or 10 mg/kg (n=8); and zimeldine + CPT (5 or 10 mg/kg). Six rats were recorded for 6 h. Since many effects were still present in the 6th hour following drug administration, 11 rats were recorded for 8 h to study effects 7-8 h following drug administration.

**Recording and sleep scoring**

The animals in their home cages (Gabbia Plastic Cage, Tecniplast, Italy, measuring 425 x 266 x 150 mm), with water and food ad libitum, were placed into sound-attenuated recording chambers (430 x 280 x 620 mm) with light (15-W electric bulb) and ventilation. Ambient temperature was 24-28°C during recording. Free movement was permitted due to a flexible recording cable and a rotating connector fixed to a moveable arm outside the chamber. Recording started at 08.30 h ± 15 minutes.

Fronto-frontal (FF) and fronto-parietal (FP) EEG and EMG signals were recorded with paper velocity 10 mm/second. FF EEG was high-pass filtered with a 3 Hz half-amplitude filter (6 dB/octave) and low-pass filtered with a 35 Hz half-amplitude filter (12 dB/octave), and FP EEG was high-pass filtered with a 1 Hz half-amplitude filter (6 dB/octave) and low-pass filtered with a 35 Hz half-amplitude filter (12 dB/octave). The difference in filter characteristics was chosen to facilitate visual-spindle detection in the FF lead. EEG sensitivities ranged from 50-150 µV/cm (FF) and 100-300 µV/cm (FP). The amplifiers had a 50 Hz notch filter to eliminate influence from the AC frequency. EEG and EMG signals were also digitized on-line with a sampling frequency of 128 samples per second, A/D converted (12-bit Keithley 575 A/D converter) and stored.

Off-line the two EEG signals were subjected to a fast Fourier transform (FFT) using 2-sec epochs, giving half-Hz bins from 0-64 Hz. Each bin was named after its lower limit. The 0 Hz and 60.5-64.0 Hz bins were discarded. The bins from 20.5-60.0 Hz were collapsed into a single High bin. EMG was analyzed off-line to obtain total variance.

Sleep and waking were scored in 10-sec epochs following a semiautomatic procedure employing EEG power spectral values in the delta, theta and sigma (11-16 Hz) bands and EMG variance (Neckelmann et al., 1994), based on earlier published criteria (Ursin and Larsen, 1983; Neckelmann and Ursin, 1993), and validated against visual scoring (Neckelmann et al., 1994). Stages scored were waking, slow wave sleep-1 (SWS-1) with spindles, slow wave sleep-2 (SWS-2) with spindles and delta activity, and REM sleep. Spindle and delta thresholds were determined in the baseline recording and remained the same for scoring of the drug condition records. Scoring epoch length was 10 sec, which means five 2-sec FFT epochs within each scoring epoch. This was done to take into account the

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**Figure 3.** Waking and sleep per 2-h recording (means + SEM) following i.p. administration of saline + vehicle (DMSO) ( ), saline + CPT 5 or 10 mg/kg ( ), zimeldine 20 mg/kg + vehicle ( ), and zimeldine + CPT ( ). The two injections were given 15 min apart. N=17 for the first three 2-h periods. Values for the fourth 2-h period are from 11 rats. Significance levels for post hoc t-tests: *** p < 0.001; ** p < 0.01; * p < 0.05.
Figure 4. EEG power densities (means) in 2-h periods in SWS-2 following i.p. administration of saline + vehicle (DMSO)(O), saline + CPT (▲), zimeldine + vehicle (■), and zimeldine + CPT (▼). Symbols above the x-axis indicate significant differences from control (p< 0.05, Wilcoxon signed ranks test). ● indicate significant difference zimeldine vs zimeldine + CPT.
temporal aspect important in visual EEG scoring, and was performed following a set of hierarchical rules as described by Neckelmann et al. (1994).

**EEG power spectral analysis**

Power spectra were computed for the six rats in the CPA and zimeldine experiment and for the 17 rats in the CPT plus zimeldine experiment for 6 hours of recording.

A computer program selected all 2-sec FFT data from waking, SWS-1 and SWS-2. Artifact epochs were excluded from the analysis. The selected FFT data were averaged in 2-hour periods for each stage separately. Since REM sleep was almost absent following zimeldine administration, spectral values from this stage were not investigated.

**Statistics**

Data were analyzed with Statsoft Statistica, using ANOVA for overall comparison. Significant effects were further evaluated with ANOVAs and t-tests. Dose, treatment, stage and 2-h period were entered in the overall analyses. Significance was accepted at \( p < 0.05 \).

In the analysis of the power spectral data, absolute power densities are not very suitable for visualization of drug effects, because the interindividual variation is considerable and the absolute values of the lower frequencies are several orders of magnitude higher than those of the higher frequencies. For each rat, the power values of the drug conditions were therefore expressed relative to control. These relative values were log-transformed prior to the statistical analysis to reduce the effects of non-gaussian distribution. The interindividual averages of the log-transformed relative power densities were retransformed before plotting to give a linear axis (Bjørvatn and Ursin, 1994; Dijk et al., 1989). The non-parametric Wilcoxon signed rank test was used for the analysis of these data.

**RESULTS**

**CPA compared with zimeldine**

Sleep and waking stages. There was no significant difference between baseline and vehicle experiments (MANOVA, Rao’s R (3,3) = 0.62, \( p = 0.64 \)) and the rest of the statistics were run with the vehicle experiment as control.

Overall ANOVA showed no effect of CPA dose (F (1,4) = 0.76, \( p = 0.43 \)). There was no overall effect of treatment (F (2,8) = 2.97, \( p = 0.11 \)), but there was a significant interaction between treatment, stage and 2-h period (F (12,48) = 9.41, \( p < 0.0001 \)). Since there was no effect of CPA dose, data from the two groups were pooled for the post hoc analyses. Post hoc t-tests indicated sleep-wake changes as illustrated in Fig. 1. Waking was increased and sleep decreased in the first 2-h period following administration of both zimeldine and CPA. SWS-2 was increased in the second 2-h period following zimeldine. The values following CPA in the second and third 2-h period did not reach significance (\( p < 0.06 \)), however SWS-2 added over the two 2-h periods was significantly increased (\( p < 0.05 \)). The two treatments had significantly different effects only on REM sleep (F (1.5) = 9.88, \( p < 0.05 \)). REM sleep was reduced following zimeldine throughout the recording, following CPA only in the first 2-h period (Fig. 1).

EEG power spectrum. Fig. 2 shows fronto-parietal EEG power spectrum in SWS-2. Following CPA there was an increase in slow wave activity (0.5-2.5) Hz during the first and second 2-h period, following zimeldine the increase was in the 3-4.5 Hz range and particularly in the second 2-h period. Following zimeldine there was also a reduction of frequencies above 7 Hz; this was present but less conspicuous following CPA.

**CPT and zimeldine combined**

Sleep and waking stages. Overall ANOVA showed no effect of CPT dose (F (1,15) = 0.02, \( p = 0.96 \)). There was an overall effect of treatment (F (3,45) = 19.95, \( p < 0.0001 \)) and an effect of sleep stage (\( p < 0.0001 \)). Since there was no effect of CPT dose, data from the two groups were pooled for the post hoc analyses and figures. The sleep and waking stages for the 17 rats recorded for 6 h are shown in Fig. 3. Eleven of the animals were recorded for 8 h, data from hours 7-8 in these animals are also shown in Fig. 3.

There was an effect of CPT treatment (F (2,32) = 19.3, \( p < 0.0001 \)) and an interaction of treatment, stage and 2-h period (F (12,192) = 35.5, \( p < 0.0001 \)). There was also effect of zimeldine treatment (F (2,32) = 21.3, \( p < 0.0001 \)) and an interaction between treatment, stage and 2-h period (F (12,192) = 41.7, \( p < 0.0001 \)). A comparison of CPT versus CPT plus zimeldine effects showed a significant difference between these treatments (F (1,16)= 19.5, \( p < 0.001 \)). The difference between zimeldine recordings and zimeldine plus CPT recordings did not reach significance (\( p = 0.06 \)) but there was a significant interaction between treatment, stage and 2-h period (F (6,96) = 26.7, \( p < 0.0001 \)).

Waking. Both zimeldine, CPT and the combination zimeldine + CPT induced a large increase of waking during hours 1-2 following injections (Fig. 3). During hours 3-4 waking was increased by over 100% by the combination, less, but still significantly increased by zimeldine alone and CPT alone.

Slow wave sleep. There was a decrease of SWS-1 in the first and second 2-h periods (hours 1-4) following all treatments, particularly following the combination zimeldine plus CPT. During the third 2-h period there was still a large decrement following the drug combination, and a smaller decrease following CPT. In the fourth 2-h period the values were back to control level (Fig. 3). SWS-2 values were considerably reduced during the first 2-h period by all treatments (Fig. 3). However, in the second 2-h period there was a significant increase following zimeldine alone, while SWS-2 following CPT and zimeldine plus CPT was not different from control level. In the third 2-h period, the CPT treatment gave a small but significant increase (\( p < 0.01 \)), while the combination zimeldine plus CPT gave a 100% increase in SWS-2 compared to control level (\( p < 0.0001 \)), and an almost 50% increase in the CPT-alone condition (\( p < 0.0001 \)). The difference between the combination and zimeldine alone was also significant in the third 2-h period (\( p < 0.0001 \)). During the fourth 2-h period there was still a slight elevation of SWS-2 following the
combination, while levels following zimeldine and CPT alone were back to control level (Fig. 3).

Corresponding to the changes in SWS-1 and SWS-2, total SWS was reduced in the first 2-h period following all treatments. In the second 2-h period, only the zimeldine-CPT combination reduced total SWS. In the third 2-h period there were small but significant increases following all three treatments, in the fourth 2-h period only following the combination (Fig. 3).

REM sleep was almost abolished during the first 2-h period following both zimeldine, CPT and combination treatments (Fig. 3). In the second, third and fourth 2-h period values were still very low following zimeldine and the combination. REM sleep following CPT was slightly but significantly reduced in the second 2-h period, in the third and fourth 2-h period it was not different from control value.

EEG power spectrum. Both zimeldine and CPT increased slow wave activity in SWS-2 in the 2.5-6 Hz range (Fig. 4). While zimeldine decreased 9-20 Hz activity, this was not seen following CPT, rather, there was a slight increase in some bins. The most conspicuous finding was the power increase in the 2-6 Hz bins following the combination CPT plus zimeldine, particularly in the second 2-h period, but also in the third 2-h period and in the total 6-h period (Fig. 4). Following the combination there was less reduction of 9-20 Hz activity than following zimeldine alone.

DISCUSSION

Zimeldine and the adenosine A<sub>1</sub> agonist CPA both increased waking and subsequently increased SWS-2. Both compounds reduced REM sleep, however, zimeldine considerably more than CPA, and this was the only clear difference between the sleep/wake effects of the two drugs. Following both compounds EEG slow wave activity increased particularly in the second 2-h period, the frequencies following zimeldine being higher (3-4.5 Hz) than following CPA (0.5-2.5 Hz). Decrease in the power of frequencies between 8-9 Hz and 20 Hz was present following both treatments. It has been argued (Benington et al., 1995; Schwierin et al., 1996) that CPA effects on sleep mimic effects of sleep deprivation, with an increase of slow wave activity below 4-5 Hz and a decrease of frequencies above 10 Hz (Tobler and Borbely, 1990). In the present study both CPA and zimeldine seemed to have such effects, although the frequency spectrum of the increased slow wave activity was slightly different for the two compounds.

For CPA, it has been demonstrated that the initial waking effect may be secondary to a reduction in body temperature (Benington et al., 1995). When this effect was eliminated by warming the animal, the slow wave increase appeared earlier (Schwierin et al., 1996). There is no temperature change following zimeldine (Bjorvatn et al., 1996). The initial waking following zimeldine administration may be a consequence of other serotonergic effects incompatible with sleep (see Bjorvatn and Ursin, 1990), e.g., a direct serotonergic effect on the thalamus, reducing spindle oscillations and thereby sleep (Lee and McCormick, 1996). According to Benington and Heller (1995), adenosine operates as a feedback signal in sleep homeostasis, stimulated by depletion of cerebral glycogen reserves. The manifestation of the sleep need is postulated to appear as increased EEG slow wave activity following stimulation of the adenosine A<sub>1</sub> receptor. It has been demonstrated that prolonged wakefulness increases extracellular adenosine in the basal forebrain of cats, the values declining towards baseline during 3-h recovery sleep (Porkka-Heiskanen et al., 1997). Also, during spontaneous sleep-wake cycles these authors found lower adenosine levels in SWS than during waking. Adenosine increases in the hippocampus towards the end of the dark period in rats (Huston et al., 1996). The mechanism by which adenosine may affect sleep is not clear. Adenosine perfusion both into the basal forebrain and the lateral dorsal tegmental nucleus decreases waking (Portas et al., 1997). Adenosine sleep effects may be direct on central nervous system neurons or may be mediated via effects on neurotransmitter release (see Brundege and Dunwiddie, 1997) or via receptor effects (Ferré et al., 1996).

The background for the SWS-2 and slow wave activity increases following zimeldine and other serotonin uptake inhibitors (Ursin et al., 1989; Sommerfelt and Ursin, 1991; Olsen et al., 1994; Lelkes et al., 1994; Maudhuit et al., 1994) is not clear. The similar effects of zimeldine and CPA in the present study may indeed suggest that the SWS-2 increase following zimeldine is a consequence of increased adenosine levels during the initial sleep loss (Porkka-Heiskanen et al., 1997) and therefore increased adenosine A<sub>1</sub> receptor stimulation (Benington et al., 1995). If so, it should be eliminated by an adenosine A<sub>1</sub> antagonist.

When zimeldine was administered in combination with the A<sub>1</sub> antagonist CPT, however, the increase of SWS-2 was still present, only postponed to the third 2-h period following administration (Fig. 3). There was also increased slow wave activity in SWS-2 in the second and third 2-h period (Fig. 4) following the combination. Thus the zimeldine-induced SWS-2 and slow wave activity increases were not blocked by the A<sub>1</sub> antagonist, the sleep increase was postponed and the slow wave activity increased. The present data, then, do not support the idea that the zimeldine SWS-2 and slow wave activity effect were a consequence of increased extracellular adenosine and A<sub>1</sub> receptor stimulation following the initial waking increase.

The adenosine A<sub>1</sub> antagonist CPT administered alone increased waking during the first two 2-h periods following administration. This indicates a biological effect of CPT over at least 4 hours, in agreement with Virus et al. (1990), who reported increased waking over a 6-h period following 10 mg/kg CPT. SWS-1 and REM sleep were still reduced during the second 2-h period while SWS-2 was similar to control. In the second 2-h period there was an increase of EEG slow wave activity in SWS-2 (Fig. 4). This finding is consistent with the data of Schwierin et al. (1996). They employed a high dose of the A<sub>1</sub> antagonist caffeine and reported an initial sleep decrease succeeded by increased slow wave activity in the second 2-h period following administration. Thus, in theirs as well as in our study, slow
wave activity following the adenosine A<sub>1</sub> antagonist was increased while sleep was still decreased. The findings of increased slow wave activity 2-4 h following A<sub>1</sub> antagonists, while there is still a drug-induced sleep reduction, are surprising. The findings might be due to a buildup of sleep drive during the preceding waking period. However, the effect came too soon and following a too small sleep loss to be a compensatory response. Tobler and Borbely (1990) found no significant increase of slow wave activity after a 3-h total sleep deprivation. It is possible that adenosine A<sub>1</sub> antagonists may increase the rate of buildup of sleep drive during the drug-induced waking. However, Schwierin et al. (1996) found a smaller rise of EEG power density following caffeine-induced waking than following the same length of non-drug sleep deprivation. Also, the frequency distribution of the slow wave activity following CPT (2.5-6 Hz) was different from the frequency spectrum of the slow wave activity following sleep deprivation (Tobler and Borbely, 1990; Franken et al., 1991). In any case, if the manifestation of increased sleep drive is mediated through adenosine A<sub>1</sub> receptors, one should have expected the A<sub>1</sub> antagonists to block this manifestation.

The sleep-wake effects of CPT and zimeldine were surprisingly similar, as were the changes in EEG slow wave activity following their administration. The combination of zimeldine and the A<sub>1</sub> receptor antagonist seemed to accentuate the zimeldine effects, both the initial waking and the delayed SWS-2 increase. Also, the combination augmented the slow wave activity effects of zimeldine, with a 2-6 Hz increase following zimeldine and a 2-7 Hz increase following the combination.

A prominent effect of adenosine in the brain is its ability to inhibit the release of neurotransmitters. These effects are reported to be mediated by presynaptic A<sub>1</sub> receptors in most systems and may be due to inhibition of calcium entry into nerve terminals (see Brundege and Dunwiddie, 1997). Both adenosine and the A<sub>1</sub> agonist CPA perfused into the dorsal hippocampus of rats decrease extracellular 5-HT levels, while CPT and caffeine increase hippocampal extracellular 5-HT (Okada et al., 1997). A possible explanation for the similarities between the A<sub>1</sub> receptor antagonist CPT and zimeldine, and the potentiation of effects by the combination of the drugs, may be that the A<sub>1</sub> antagonist blocks an adenosine inhibitory effect on 5-HT release, leading to increased release. Another possibility is blockade of the inhibition of raphe cells mediated via A<sub>1</sub> receptors. An adenosine transporter blocker infused into the dorsal raphe nucleus increased REM sleep (Strecker et al., 1997), possibly because of inhibition of serotonergic cells, thereby disinhibiting REM sleep-generating mechanisms (McCarley et al., 1995).

Both caffeine (Schwierin et al., 1996) and CPT tended to increase 8-20 Hz activity, and the combination zimeldine-CPT reduced these frequencies less than zimeldine alone. Activity in these frequencies tends to be low in the beginning of the light period and are high in the dark (Trachsel et al., 1988). As rats are nocturnal animals this effect of the drugs suggests a tendency towards increased activation, which would be expected.

The effects of zimeldine as a selective serotonin reuptake inhibitor are considered mainly due to increased serotonin at serotonergic nerve terminals and are thus dependent on the physiological activity of the serotonergic neurons. Zimeldine has no pharmacological receptor effects on its own (Hall and Ögren, 1981). It is thus likely that the zimeldine effects on slow wave activity and SWS-2 are related to increased serotonergic transmission. In the thalamus, modulation by serotonin in vitro may increase the frequency of intrinsic oscillations in thalamocortical neurons, and also tend to reduce the cells’ ability to oscillate (see McCormick and Bal, 1997). However, 5-HT<sub>1A</sub> receptor stimulation may under certain conditions increase SWS-2 and slow wave activity. Systemic administration of the 5-HT<sub>1A</sub> receptor agonist 8-OH-DPAT produces a delayed SWS-2 increase too large to reflect a rebound after the initial waking period following this drug (Bjorvatn et al., 1997). In vitro stimulation of 5-HT<sub>1A</sub> receptors on basal forebrain cholinergic neurons increases rhythmic burst activity mediated by low-threshold calcium spikes (Khateb et al., 1993), and microinjection of serotonin into the nucleus basalis in vivo in rats increases slow wave activity (Cape and Jones, 1998). Jouvet (1995) has suggested that release of serotonin during waking may initiate a cascade of genomic events in hypnogenic neurons in the preoptic area, thus linking serotonin to a homeostatic regulation of slow wave sleep.

Adenosine A<sub>1</sub> receptor modulating drugs may also interact with dopamine D<sub>1</sub> receptor function both in the basal ganglia, the medial prefrontal cortex and in the nucleus accumbens (Ferré et al., 1996). Dopamine release in the nucleus accumbens is in part regulated by serotonergic neurotransmission (Yoshimoto and McBride, 1992). Firing rate in the nucleus accumbens is associated with the level of cortical arousal, being higher in waking and REM sleep than in NREM sleep (Callaway and Henriksen, 1992). Thus the effects on waking and on the higher EEG frequencies by CPT and its potentiation by zimeldine may possibly be mediated via increased dopaminergic activity in the nucleus accumbens.

In conclusion, the present data indicate that the delayed SWS-2 and slow wave activity increases following zimeldine are not due to increased stimulation of adenosine A<sub>1</sub> receptors following the initial sleep loss. Instead, the data suggest that the observed potentiation of the zimeldine sleep/waking and slow wave effects by the adenosine A<sub>1</sub> antagonist CPT may be due to antagonism of adenosine’s ability to inhibit serotonin release, and/or to interactions with dopaminergic activity.

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