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Slow Wave Sleep Elevations After Body Heating: Proximity to Sleep and Effects of Aspirin

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Summary: On three different occasions, six healthy young adult subjects had their body temperatures raised by an average of 2.0°C for 30 min while sitting in baths of warm water. This was done once at 1700 h and on two occasions at 2100 h, once after the subjects had taken aspirin and once after a placebo. Nighttime sleep was recorded after each experimental condition and for baseline nights following nil heating. Records were scored both visually and by an automated sleep stager. Electroencephalographic (EEG) power was computed over the night. Results from the automated scoring were very similar to those of the visual method. While the early bath caused no changes in sleep, the late bath + placebo resulted in significant rises in stage 4 sleep and slow wave sleep (SWS) and significant falls in sleep onset and in REM sleep. Aspirin mostly counteracted these effects and, in particular, left stage 4 sleep and SWS at baseline levels. EEG power was significantly increased only after the late bath plus placebo, supporting the SWS outcome. These findings were assessed in light of other comparable results from our laboratory. It seems that as the time of the day of heating recedes from nighttime sleep, a larger "dose" of heating is required to produce the same effect. **Key Words:** Body heating—Slow wave sleep—Aspirin.

We previously found that artificially raising body temperature during the daytime either actively by exercise or passively by sitting in a warm bath leads to increased stages 3 + 4 sleep [slow wave sleep (SWS)] in the subsequent night (1–3). However, physically untrained ("unfit") subjects cannot sustain exercise long enough to get sufficiently hot the active way, which is probably why they fail to show SWS rises after exercise (4). But like "fit" subjects they can easily be heated up passively, and then both types of individuals show similar SWS elevations (1,3). SWS does not rise when fit subjects are force cooled during exercise to reduce the core temperature increase (2). Earlier studies of passive heating, through sauna (5) or Turkish bath (6), have reported increases in SWS. Another effect of heating on subsequent sleep is a reduction

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in the first REM sleep period, probably as a consequence of the apparent increase in SWS "pressure" (1,3).

The reasons for SWS changes after this heating are not known, although such changes are likely to be due to an increase in brain temperature [tympanic temperature rises also (2)]. Brain metabolism also rises, and, for example, so does the activity in wakefulness of neurophysiological processes and biochemical substrates underlying sleep and SWS.

Our studies (1–3) all involved 80 or 90 min of heating via exercise or bath ~8 h before bedtime (between 1400 and 1700 h). It is not known if the effect on SWS decays over interim wakefulness, with some form of heat "dose × delay" interaction. For example, would a smaller dose of heating given nearer bedtime produce the same SWS rise? In a recent study by Bunnell and Horvath (7), subjects were awakened after the second REM period, when most of the night's SWS had been taken. They were then passively heated for only 20 min by water immersion to produce an average tympanic temperature rise of ~1.4°C and allowed to return to sleep. The main finding was an increase in SWS and non-REM sleep in the second non-REM sleep cycle following the new sleep onset. These results also suggest that some time (~2 h) has to elapse before body heating affects SWS.

There was a secondary theme we wanted to pursue. Earlier work (8) has shown that 600 mg aspirin t.i.d significantly lowers SWS, with few other significant effects on sleep. Does pretreatment with aspirin reduce heating effects on SWS?

The main aim of the present study was to supplement our previous work by comparing the effects of a fixed dose of body heating given either ~2 h before sleep or 8 h beforehand. The latter condition was given with and without aspirin pretreatment. The volunteers were from the same subject pool as that of our other studies.

METHOD

Pilot study

As we previously had used 80- or 90-min periods of passive heating in the afternoon (1,3), we considered using this dose again. However, there was concern over whether such a long session just prior to bedtime might be counterproductive. A pilot study was run to evaluate this and also to determine whether a shorter heating session might be more suitable. Our usual method for passive heating was retained (see below). Two subjects participated in the pilot study. Following baseline nights each underwent 1.5 and 0.5 h of this heating between 2000 and 2200 h on separate occasions. Bedtime was at 2345 h. For both subjects 1.5 h heating produced long sleep onset delays, major sleep disturbances, and frequent awakenings. This dose of heating was abandoned for nighttime use, being too much, too near to bedtime. However, 0.5 h of heating produced obvious increases in SWS with no sleep disruptions, and it was adopted for the main study.

Subjects

Six healthy subjects, three men and three women, aged between 21 and 33 years, good sleepers, and moderately physically trained (i.e., neither fit nor unfit), were selected from volunteers among the campus population. They were given modest payment for their services.

Experimental conditions and design

There were three experimental conditions, all incorporating 0.5 h of passive heating. Additionally, there were baselines of sleep recording following no heating. For one experimental condition, heating was given at 1700 h while for the other two it was given at 2100 h. Three times (after meals) over each experimental day, subjects took 2 × 300-mg tablets of placebo or aspirin. However, aspirin was given only once, for one of the 2100-h bath sessions. Placebos were taken on the other experimental days. Subjects knew that they would be taking either placebo or aspirin, but were "blind" to this. Insoluble aspirin (acetylsalicyclic acid) tablets were used, and had to be taken with a glass of water. The placebos tasted like aspirin and were supplied by a local pharmaceutical company.

Heating followed our normal procedure of sitting subjects comfortably up to mid-thorax in a bathtub of water maintained at 41 ± 1°C, to produce an average body temperature rise of 2.0°C. The surface of the water was covered with foam produced by a "bubble bath" solution, which acted as an excellent heat insulator for the water underneath. This allows the upper trunk and head to "feel cooler" and makes the procedure quite acceptable to subjects. Although they were free to get out of the water whenever they wished during the immersion period, none did so. An experimenter remained with each subject throughout this time. We find a bathtub much more suitable for the subject than an immersion tank, as the latter can cause distress owing to greater confinement and poorer comfort.

For subject convenience, this time we used oral temperature as the index of body temperature rather than rectal temperature. We have found that rectal and oral temperatures show similar changes over time under these circumstances, although, of course, absolute temperature levels differ between the two methods. Oral temperatures were taken every 5 min by a calibrated digital thermometer, with the mouth firmly shut and the probe right under the tongue. Recordings were not made until the probe had been in the mouth for 2 min and the temperature measurement had stabilized. Little heat rose from the bath, and so oral temperature was not affected by extraneous heat. Group mean oral temperature changes over the 30 min of immersion are given in Fig. 1. As each subject's oral temperature rise was identical for each experimental condition, the values for the three conditions have been averaged. The mean temperature rise over the set of measurement intervals during the immersion was 2.0°C. Circadian differences in body temperature between the start of the early and late bath sessions were very small, being in the range of 0–0.2°C. It should be noted that for all subjects, oral temperatures returned to normal values within 0.5 h of ending the heating.

The experiment lasted for 2 weeks, with subjects taken in pairs at a time. The first night was for adaptation, with subjects wired up for the standard method (9) of sleep electroencephalogram (EEG) recording. The experiment was run in 2-day blocks, each containing an experimental day and a baseline day. At least 3 "rest" days separated the blocks to allow "washout" of the aspirin. The order of the experimental conditions was different for each subject. On experimental and baseline days, subjects had to refrain from baths, exercise, and other activities that would raise body temperature. Also on these days they abstained from alcohol, kept coffee to a minimum, and maintained the same feeding habits.

During the periods between heating and bedtime, subjects relaxed through reading and watching TV. Electrodes were attached at 2300 h and subjects retired at 2330.

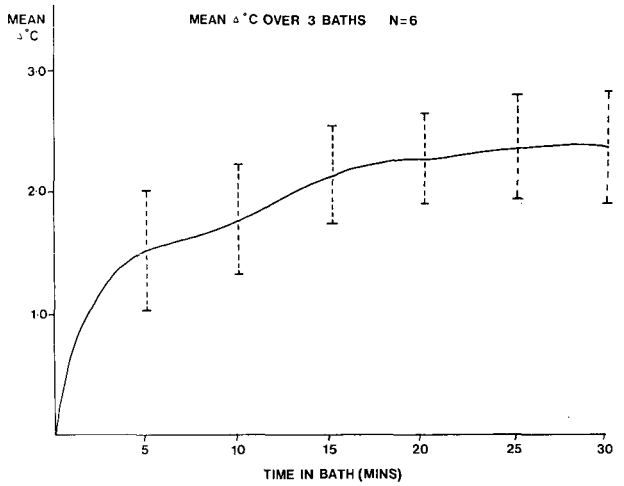

FIG. 1. Oral temperature changes from baseline during 30 min in bath. Average for all subjects over the three experimental conditions. Standard deviations shown as bars. Temperatures returned to normal within 30 min of termination of heating.

"Lights out" was at 2345 h, following completion of the Stanford Sleepiness Scale. This was completed again, a half-hour after morning arising. Subjects were allowed their usual amounts of sleep.

Data analyses

For the following analyses, the first 420 min of sleep from sleep onset was taken as the period for assessment. This was the highest common denominator across subjects. Sleep onset is defined below. Three types of EEG assessment were carried out:

(a) Visual scoring. Two experienced scorers assessed paper write-outs "blind" in 1-min epochs. The 5% epochs where there was disagreement were resolved by discussion.

(b) Microprocessor scoring. This study also provided an opportunity to use the new Oxford Medical Systems "Medilog" sleep stager, particularly as a quantifier of stages 3 and 4 sleep. This microprocessor scores sleep according to the standard criteria (9), at 20 × real time, in real-time epochs of either 20 or 30 s (we used the latter). The usual four channels of data are used: one channel of EEG (A1–C3), two channels of (left and right) electrooculogram, and one channel of submental electromyogram. Tape-recorded whole-night records are fed into the stager at 20 × real time.

(c) Root mean square of the EEG. We were interested in total power across all EEG frequencies, although, given that EEG power is inversely proportional to frequency, this technique was primarily quantifying delta activity. The EEG was assessed as follows. After A-D conversion and high-frequency filtering at >25 Hz real time to remove muscle and other artifacts, the EEG voltage was sampled at 10 Hz for 30-s epochs by an Apple E2 microcomputer, with the root-mean-square (RMS) calculation done on the 300 samples. This value was stored for later use and the process repeated for 420 min of sleep.

These analyses were performed on separate occasions. Although it is desirable to compare the Medilog sleep stager output epoch by epoch with visual scoring epochs, precise synchrony to, say, within 30 s for the two methods over the entire night was not

possible, as some "drifting" is inevitable. The automated stager was thought to be potentially useful for objective within-subject comparisons across conditions, particularly for SWS. Our preliminary findings show that it had a good test/retest reliability of 92–96% for sleep stage analysis.

For the visual scoring, whole-night data were collated in the way shown by the column headings of Table 2 and Fig. 2. Data from the relevant baseline nights were subtracted from each experimental condition, giving changes from baseline. This was done for each subject and variable. Statistical analyses were then performed using two-way analysis of variance. Of interest to us were the following comparisons (see introductory section): (a) early versus late bath plus placebo and (b) late bath plus placebo versus late bath plus aspirin. There was no a priori reason for comparing early versus late bath plus aspirin. An overall F value was first obtained across all conditions, and the treatment effects were compared using standard errors estimated for all 18 values (6 subjects × 3 conditions). Estimates for the two treatment comparisons were divided by their appropriate standard error and the t statistic applied having 10 degrees of freedom. Two-tailed significance values were used, with $p < 0.05$ set as the criterion level. Because results determined from the sleep stager were so similar to those from visual analysis, it was decided not to replicate these statistical analyses, but to use only the visual scorings for this purpose.

Definitions

The following definitions were used: sleep onset, the beginning of the first period of 15 min of continuous stage 2 sleep or "deeper"; sleep period, the time from sleep onset to final awakening; sleep time, sleep period minus interim wakefulness; REM latency, time from sleep onset to the beginning of the first REM sleep period of >1 min.

RESULTS

Figure 2 gives the all-night sleep stage changes from baseline for both visual and automated methods. Statistically significant differences are presented only for the visual scoring. Average baseline values for these parameters are shown in Table 1. From Fig. 2 it can be seen that the two scoring methods produce similar results. A half-hour of heating at 1700 h leads to no obvious change from baseline with any sleep parameter for either method of sleep staging. However, when early bath was compared with late bath plus placebo, significant increases were found in the later condition for SWS ($t = 3.89$, $df = 10$, $p < 0.02$) and stage 4 sleep ($t = 4.78$, $df = 10$, $p < 0.002$). Visual scoring showed that SWS rose from the baseline by an average of 23 min and stage 4 sleep by 17 min. Total minutes of REM sleep was reduced significantly following the late bath plus placebo ($t = 2.43$, $df = 10$, $p < 0.05$), and so was sleep onset latency ($t = 2.85$, $df = 10$, $p < 0.02$). There was a strong but nonsignificant tendency for REM sleep latency to be longer during the late bath plus placebo condition and the first REM sleep period to be shorter. The value given in Table 2 under this condition includes one subject with an unusually long REM sleep latency, with the first REM sleep period seemingly "missed." A value of zero is included in the group average for this first REM sleep period.

Aspirin seemed to reduce most of these late bath effects. Comparisons between the two bath conditions produced significant differences for SWS ($t = 4.32$, $df = 10$, $p < 0.002$) and for stage 4 sleep ($t = 4.17$, $df = 10$, $p < 0.002$). Although REM sleep latency, length of the first REM sleep period, and total REM sleep were lower fol-

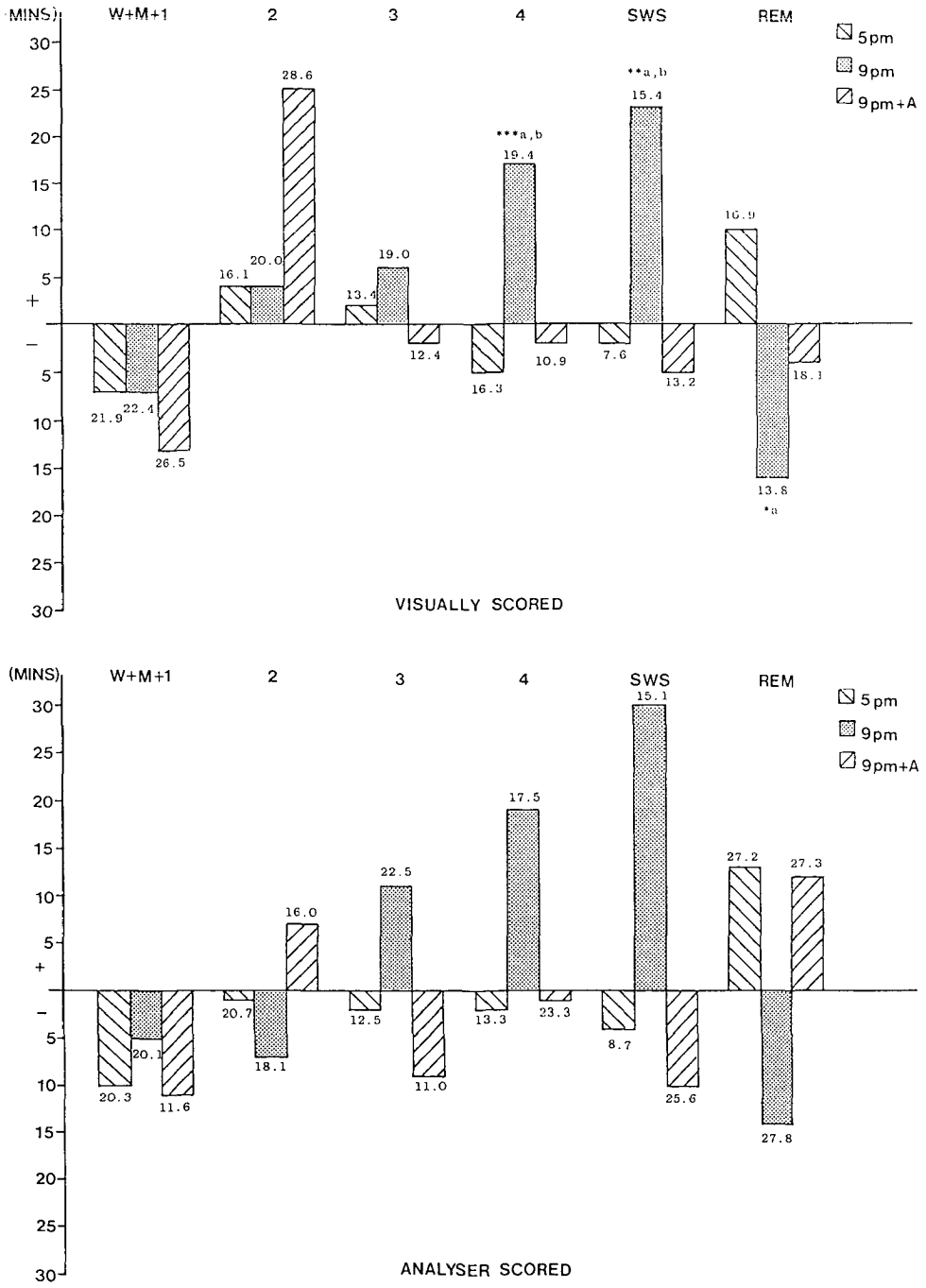

FIG. 2. Sleep stage changes from baseline for the three experimental conditions. All values for 420 min of sleep. **Top:** Based on visual scoring; **bottom:** based on automated scoring. Standard deviations given as numbers for visual scoring only. Note that statistical comparisons (see text for details) were done for early versus late plus placebo and late plus aspirin versus late plus placebo. SWS, slow wave sleep. *Significant at $p < 0.05$; **significant at $p < 0.02$; [a]significantly different from early; [b]significantly different from late plus aspirin.

TABLE 1. *Group mean baseline levels of sleep stages over the first 420 min of sleep, averaged over baseline nights, for both visual and automated scoring*

	Minutes						
	Wake plus movement	Stage 1	Stage 2	Stage 3	Stage 4	Slow wave sleep	REM
Visual	20.1	29.1	211.5	41.1	32.2	73.3	86.7
	(14.2)	(8.0)	(21.7)	(13.2)	(13.6)	(15.5)	(12.1)
Automated	27.2	22.2	214.7	54.7	17.0	71.7	85.0
	(21.6)	(10.2)	(29.6)	(16.0)	(14.3)	(19.0)	(7.1)

Standard deviations in parentheses.

lowing the aspirin condition when compared with placebo, and sleep onset latency longer, none of these reached significance. EEG RMS power for each of the three experimental conditions is shown in Fig. 3 as the cumulative difference from the relevant baseline. That is, each point has had its corresponding baseline value subtracted and the result added to that of the previous point. Average power values for the whole night are given in Table 2. However, there were statistically significant differences between early and late bath plus placebo ($t = 2.89$, $df = 10$, $p < 0.02$) and between the two late bath conditions ($t = 2.95$, $df = 10$, $p < 0.02$). It can be seen that although the

TABLE 2. *Other sleep parameters for average baseline and the three experimental conditions, using the visual scoring method only, where appropriate*

	Baseline	Early	Late	Late + aspirin
Sleep onset (min)	16.6	20.5	11.3[a,b]	15.1
	(8.9)	(14.4)	(8.9)	(12.7)
Sleep period (min)	451.5	448.0	455.6	454.5
	(12.0)	(15.6)	(13.8)	(14.0)
Sleep time (min)	432.0	443.2	437.8	444.7
	(11.9)	(17.4)	(16.4)	(13.8)
REM latency (min)	89.0	64.7	113.8[d]	87.0
	(15.2)	(14.4)	(35.4)	(28.9)
Length 1st REM period (min)	6.2	5.3	3.0[e]	3.3
	(2.8)	(5.2)	(4.1)	(4.0)
SSS score—bedtime	3.8	4.3	3.3	4.8
	(1.3)	(1.8)	(1.6)	(2.1)
SSS score—arising	2.4	2.8	3.0	3.0
	(1.5)	(0.9)	(0.8)	(1.6)
EEG power (RMS V., average over night)	1.29	1.32	1.49[a,b,c]	1.32
	(0.13)	(0.17)	(0.13)	(0.17)

Values are means (standard deviations) with significance values. Note that statistical comparisons were performed on differences from the respective baselines for (a) early versus late bath plus placebo and (b) late bath plus placebo versus late bath plus aspirin (see text).

[a] Significant at $p < 0.02$.

[b] Significantly different from early.

[c] Significantly different from late plus aspirin.

[d] Includes one subject with a "missed" first REM sleep period (see text).

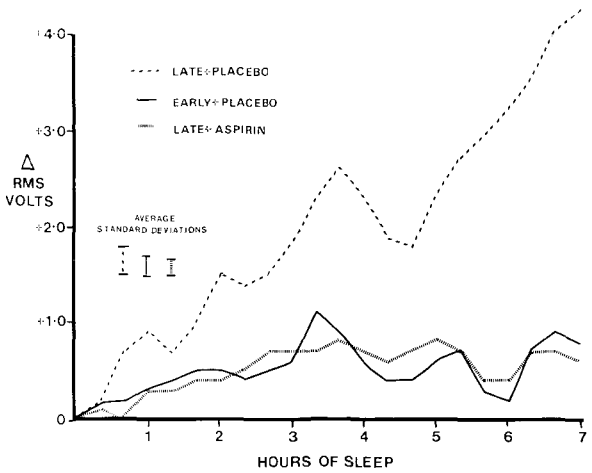

FIG. 3. Electroencephalographic power: cumulative changes from baseline levels over 7 h of sleep, averaged across subjects for each experimental condition. Whole-night means and standard deviations given in Table 2. RMS, root-mean-square.

cumulative graphs in Fig. 3 for both aspirin and early bath conditions are somewhat higher than the baseline, there is a decline in the second half of sleep.

These findings with EEG power support the outcome from the sleep stage analyses. For the late bath plus placebo condition, the increase in power is sustained throughout most of the night (Fig. 3), particularly during SWS episodes (shown by the peaks). It should be remembered that the apparent surge in the last 2 h of the night is relative to the baseline levels, which are low. That is, the usual fall is not so great following late bath plus placebo. Interestingly, though, visual and automated sleep stagings show little increase in total stage 3 sleep for the last two non-REM periods here (there was virtually no stage 4 sleep), with average values for baseline, early bath, late bath plus placebo, and late bath plus aspirin being, respectively, 11, 9, 15, and 8 min. However, if the EEG amplitude criterion for SWS of 75 μV is lowered to 50 μV, as can be done with the stager, then more "SWS" is revealed during this latter part of sleep.

While epoch-by-epoch comparisons of the two methods for sleep staging were not possible (see Data analyses), the automated stager produced results similar to those of visual analysis. As a rough guide, for every subject night, the minutes of each stage visually scored was taken as the "standard," and the difference between this value and that of the sleep stager was expressed as a percentage of the "standard." So, for example, if the visual assessment produced 200 min of stage 2 and the automated stager 220 min, then the result was 10%. Of course, this index is not a true measure of agreement between the two systems, and also does not take into consideration the direction (±) of the difference. However, the average values for 48 subject nights for stages 1, 2, 3, and 4, REM, and SWS, were 30, 7, 23, 24, 13, and 16%, respectively. Visual analysis produced a different cutoff between stage 3 and 4 sleep than the automated stager, but the two methods seemed to be in fairly close agreement for SWS as a whole. We believe that the stager is more accurate with this cutoff than is the human observer. The greatest disagreement lay over stage 1 sleep, but as this constitutes only 20–30 min of the night, the 30% "difference" is small in absolute terms. It should be remem-

bered that we adopted the analyzer mainly for within-subject comparisons, particularly to give more objectivity for measuring SWS changes over conditions.

DISCUSSION

A half-hour of heating given 7–8 h before sleep has little effect on sleep. But when administered 2–3 h beforehand (without aspirin), SWS, especially stage 4 sleep, rises significantly and REM sleep falls. Of further interest is that although the late bath plus placebo significantly reduced sleep onset time, subjects did not report being sleepier at bedtime. It seems that the elapsed time between heating and sleep is the key to whether these sleep stages change—the longer the time, the less the effect. Alternatively, one could argue that there is a circadian effect, with heating given during the late afternoon being less "potent" than that later at night. The 1700-h bath is on the incline of the circadian metabolic and behavioral arousal rhythm, whereas the 2100-h bath is on the circadian decline.

These findings must be viewed as a supplement to our earlier work. Unfortunately, we were unable to continue the study with permutations of different lengths of heating and proximities to sleep. However, we have data from two earlier studies (1,3) for a total of 14 fit and unfit subjects, taken from the same subject pool as that of the present study. This information can be used as a guide to the interpretation of the present findings. In the earlier studies, subjects were given 80–90 min of heating ending at 1700 h, under near-identical conditions to those used here. Those fit and unfit subjects showed similar and significant SWS rises of 19 (1) and 21 (3) min above respective baselines of 75 and 62 min of SWS. In both cases the main effect of heating was with stage 4 sleep. This rose significantly by an average of 15 min for the two groups from an average baseline value of 37 min. These figures are similar to those of the present study for the late bath condition, where a 22-min rise in SWS from baseline (visual scoring) was observed, encompassing a 17-min rise in stage 4. Comparing the present with the past figures, it seems that three times the dose of heating is required ~7.5 h before sleep to produce the same effect on SWS as that when given 2.5 h beforehand (i.e., approximately one-third the time). While this suggests a dose × time effect, this is not the only interpretation of such results, and does not take into consideration circadian effects.

Aspirin given in the dose used here seems to counterbalance potential changes to sleep produced by heating. We appreciate the dangers of describing a nil effect in terms of two opposing processes. However, some relevant points can be made. It should be remembered that aspirin is antipyretic only in febrile states and does not affect normal thermoregulation. Also, there was no difference between aspirin and placebo conditions in the body temperature rise during heating. Reasons why aspirin should negate a potential SWS increase are not really understood. We do not know whether the mechanisms underlying the SWS increase following heating are the same or different from those affected by aspirin.

It should be borne in mind, though, that one of the most potent effects of aspirin is to suppress prostaglandin (PG) synthesis. There are strong indications that enhancement of brain levels of PGD_2 in rodents increases non-REM sleep (10). Tissue warming increases PG turnover, and one possible reason for the present findings is that brain warming through body heating increases brain PG levels, with this action blocked by aspirin. We have also shown in another study on similar subjects (8), investigating the

effects on sleep of aspirin (acetylsalicylic acid) without heating, that aspirin reduces baseline levels of SWS and stage 4 sleep by ~15 and 12%, respectively, within subjects. This effect could have contributed to the present findings, as aspirin may well have depressed baseline SWS values during the heating condition. Ideally, in the present study we would have liked to have given an aspirin-only condition to clarify this point further.

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