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Nonsteroidal Anti-Inflammatory Drugs Alter Body Temperature and Suppress Melatonin in Humans

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MURPHY, P. J., B. L. MYERS AND P. BADIA. *Nonsteroidal anti-inflammatory drugs alter body temperature and suppress melatonin in humans.* PHYSIOL BEHAV **59**(1) 133–139, 1996.—Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit prostaglandin synthesis in humans. Prostaglandins are involved in thermoregulation, melatonin synthesis, and sleep. To determine effects of NSAIDs on body temperature (BT) and melatonin synthesis (MT) in humans, and to elucidate mechanisms by which NSAIDs may alter sleep patterns, a series of experiments using the NSAIDs aspirin and ibuprofen was conducted. Seventy-five subjects were tested under several experimental protocols. BT after NSAID or placebo was assessed in both between- and within-subjects designs at night and during the day. MT levels were assessed after NSAID or placebo at night in a within-subjects design. The normal nocturnal BT decrease was attenuated and MT was suppressed after NSAID relative to after placebo administration. Lower MT levels were associated with a relative flattening of BT. Daytime BT was not affected by NSAIDs. These results are compatible with the hypothesis that some of the behavioral changes associated with NSAIDs, including changes in sleep, are due to changes in BT and MT. We speculate that NSAID effects on sleep and BT are related to prostaglandin synthesis inhibition and/or suppression of MT.

Nonsteroidal anti-inflammatory drugs Aspirin Ibuprofen Humans Body temperature
Thermoregulation Melatonin Seasonal depression Prostaglandins Sleep

NONSTEROIDAL anti-inflammatory drugs (NSAIDs) include the substances aspirin and ibuprofen. These drugs are thought to exert most of their physiological effects via prostaglandin synthesis inhibition (10,34). Prostaglandins are ubiquitous intracellular substances which directly affect sleep and body temperature (12,13,16). Prostaglandins also markedly enhance the synthesis of the pineal hormone melatonin during the nighttime hours (4,5,30,35). Given that the circadian rhythms of sleep, body temperature, and melatonin are used as primary markers of the output of the circadian system, determining potential effects of commonly used NSAIDs on these markers is important. We have previously determined that the NSAIDs aspirin and ibuprofen can change normal sleep patterns in healthy humans (17,18). In an attempt to further elucidate the physiological effects of commonly used NSAIDs on humans and investigate possible mechanisms of NSAID effects on sleep, we conducted a series of experiments to ascertain whether NSAIDs alter body temperature and melatonin synthesis.

Other researchers have examined NSAID effects on body temperature in humans, but results are contradictory (see 6, for a review). Most of these studies have been conducted in subjects who are febrile or in pain, in whom an immune response has most likely been initiated (10). Furthermore, NSAID type and dose level varied widely. Finally, most investigations of NSAID effects on body temperature have not evaluated time-of-day (circadian) effects. It is reasonable to predict differential circadian effects of NSAIDs on body temperature as there is a circadian rhythm in the synthesis of certain prostaglandins (13,21,28). A study that investigated whether NSAIDs alter melatonin levels in humans (33) determined that a 400 mg dose of ibuprofen suppressed melatonin release by approximately 75% during the nighttime hours. However, the investigation was limited to a small number of subjects ($N = 4$) and to males only.

Systematic studies of NSAID effects on normal body temperature and melatonin synthesis in humans with time-of-day as a factor have not been completed. Thus, the present experiments assessed how the NSAIDs aspirin and ibuprofen affect diurnal and nocturnal body temperature and nocturnal melatonin synthesis. We hypothesized that inhibiting prostaglandin synthesis by administration of aspirin and ibuprofen would attenuate the noc-

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turnal decrease in body temperature and result in antagonism of nighttime melatonin synthesis. In addition, given recent reviews which illustrate the important role of melatonin in thermoregulatory processes (2,3,8,31,32), we hypothesized that body temperature and melatonin changes following NSAID administration during the nighttime hours would be inversely related. Specifically, we predicted that greater suppression of nighttime melatonin levels would be associated with a smaller decrease in body temperature across the experimental period.

METHOD

General information

All subjects were screened via a phone interview for a history of reactions to anti-inflammatory drugs, and for conditions that could predispose them to adverse reactions including ulcers, asthma, nasal polyps, gastritis, and gout. All subjects were medication-free (including NSAIDs) for a minimum 72-h period prior to each experimental session. In addition, no caffeine was permitted for 6 h before NSAID administration. Subjects were also screened for regular sleep/wake schedules, napping habits, and any activities at or around time of participation that could alter their sleep patterns. Females were scheduled to participate between the second and eighth day following menses (i.e., early follicular phase) to control for differential melatonin and body temperature levels across menstrual cycle phases (20,36). Subjects arrived at the laboratory 2 h prior to the first temperature measurement. After giving informed consent and completing questionnaires concerning medical history and morningness/eveningness (14) , all were required to remain seated in a comfortable chair in a dimly lit room ($\leq$ 100 lx) during the entire experimental period. Activity was restricted to reading, and social interaction was limited to necessary exchanges with the experimenter. Figure 1 depicts the protocol for each of the studies described below. The initial 2 h served as a body temperature unmasking period, during which subjects sat quietly and no measurements were obtained. Our laboratory has shown this amount of time to be sufficient for stabilizing body temperature (19). At 2300 h (nighttime studies) or 1500 h (daytime study), baseline tympanic temperature was measured and a standard NSAID dose (650 mg aspirin, 400 mg ibuprofen; equal to manufacturer's recommended dosage) or placebo was administered with water and a small snack. The 2300 h time of administration was chosen to occur well within the nighttime melatonin period (previous data from our laboratory has shown that melatonin onset occurs at approximately 2100–2200 h in this population); the 1500 h time of administration was chosen to occur well outside the melatonin period and several hours from normal mealtimes. Both NSAID and placebo were administered in a double-blind manner in unmarked gelatin capsules. Thereafter, tympanic temperature was assessed every 15 min until 0100 h (nighttime studies) or 1700 h (daytime study).

NSAIDs and BT Studies

Nighttime/Between subjects study. Assignment to drug group was random. Each subject received a dose of aspirin, ibuprofen, or placebo. A total of 54 subjects were tested in this protocol (21 placebo [10M,11F], 13 aspirin [6M,7F], 20 ibuprofen [10M,10F]). Nighttime/Within subjects study. This experiment used only ibuprofen, given results from the between subjects study suggesting that ibuprofen had a larger effect than aspirin (along with data showing significant disruption of sleep after ibuprofen administration; 18). A total of 11 subjects were tested in this protocol (placebo/ibuprofen [10M,1F]). The sessions were separated by a minimum 3-day washout period and a maximum of 7 days, and drug or placebo was administered in a counterbalanced order. Daytime/between subjects study. Another 17 subjects (9 placebo, 8 ibuprofen; all M) were tested during the daytime hours.

NSAIDs and Melatonin Study with Body Temperature Replication

The procedure for this study was similar to that for the nighttime studies described above. However, the experimental period was extended until 0300 h, tympanic temperature was assessed every 30 min, and saliva samples (approximately 1200

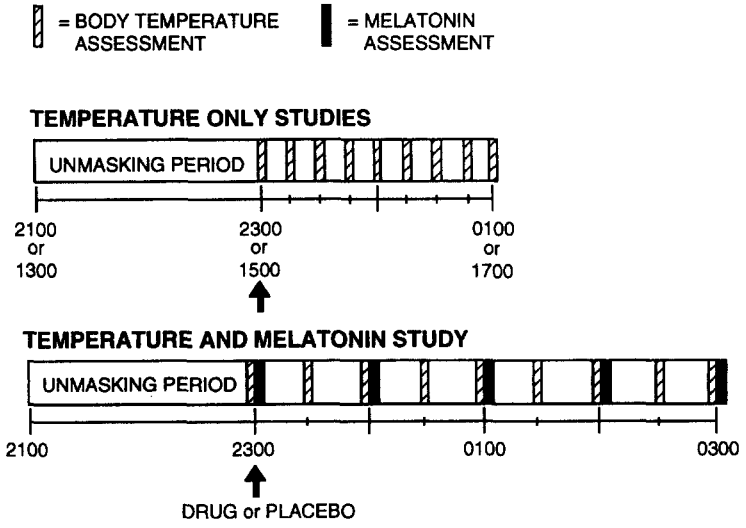

FIG. 1. Schematic representation of experimental protocols. For studies in which only temperature was assessed, drug or placebo was administered at 1500 h (daytime study) or 2300 h (nighttime studies), and tympanic temperature was assessed every 15 min for 2 h. For study in which both temperature and melatonin levels were assessed, drug or placebo was administered at 2300 h, tympanic temperature was assessed every 30 min, and saliva samples were collected every 60 min.

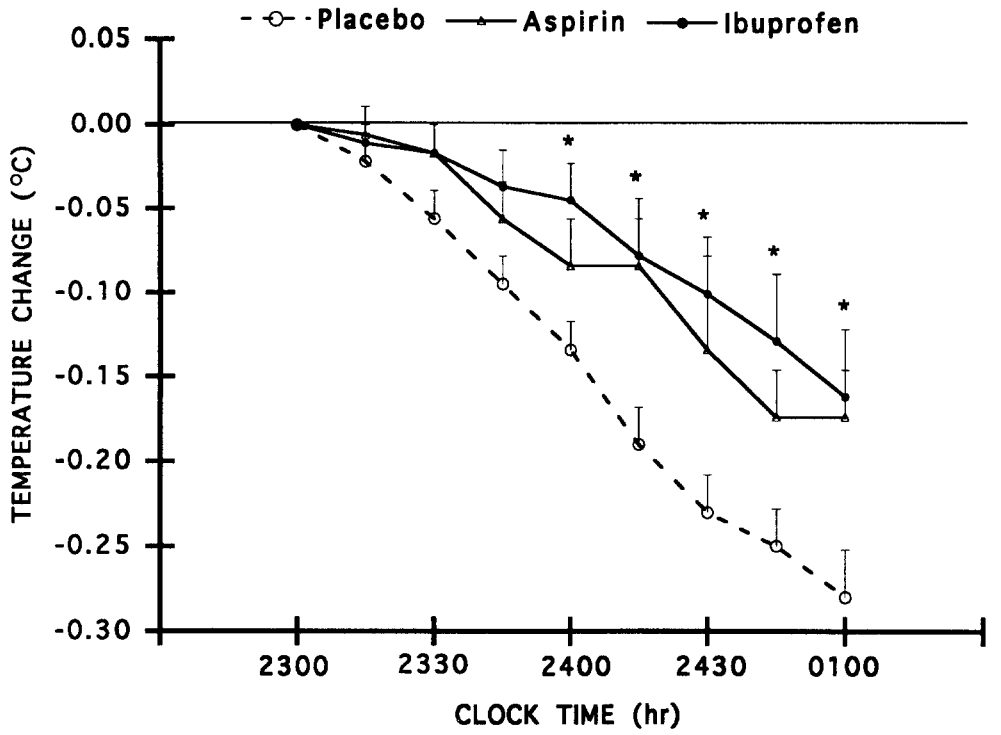

FIG. 2. Body temperature change scores (±SEM), calculated as difference from baseline measurement at 2300 h for placebo (○---○), aspirin (▽—▽), and ibuprofen (●—●). *denotes both aspirin and ibuprofen different from placebo, $p < .05$. A total of 54 subjects were tested on one occasion from 2300–0100 h. Each subject received 650 mg aspirin, 400 mg ibuprofen, or placebo.

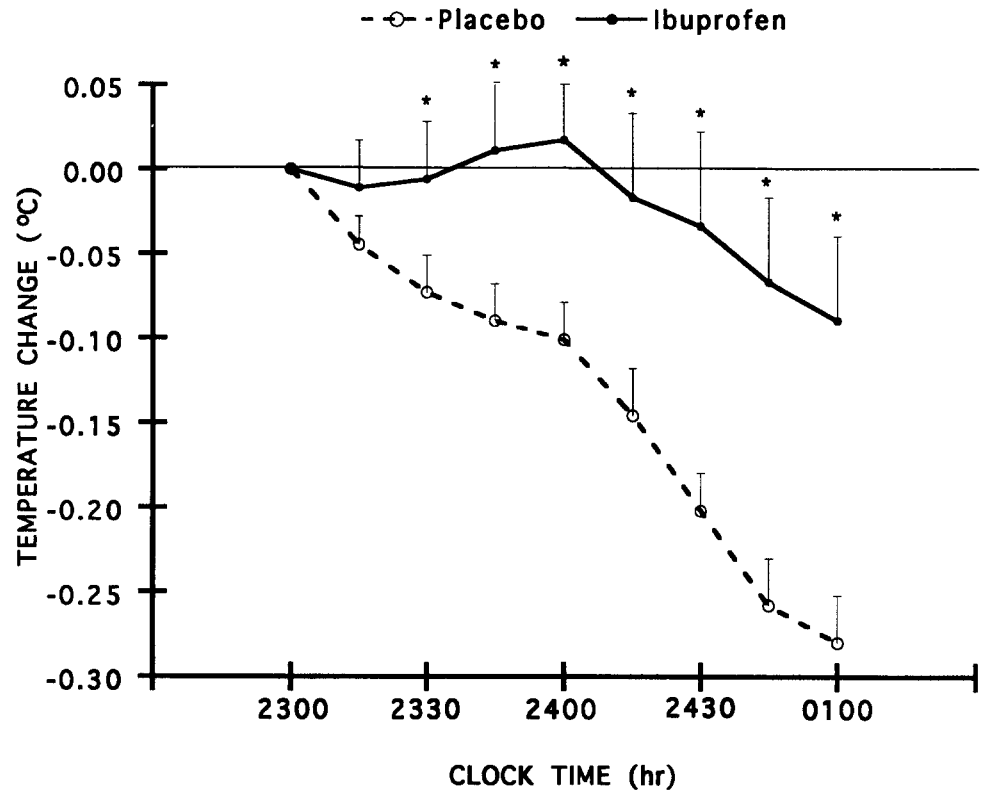

FIG. 3. Body temperature change scores (±SEM), calculated as difference from baseline measurement at 2300 h, for placebo (○---○) and ibuprofen (●—●). *denotes different from placebo, $p < .05$. A total of 11 subjects were tested on two occasions from 2300-0100 h. Each subject received 400 mg ibuprofen at one session, and placebo at the other, in a counterbalanced order.

μl unstimulated) were collected every 60 min for purposes of radioimmunoassay of salivary melatonin levels. All subjects (N = 10; 3M,7F) participated for two sessions, separated by a minimum 3-day washout period and a maximum of 7 days. Each subject received aspirin or ibuprofen at one session, and placebo at the other session in a counterbalanced order. Saliva samples were centrifuged at 2500 rpm immediately after collection, then frozen at −20°C until assayed.

Tympanic temperature was recorded using the Firsttemp system (Clinical Technologies, Calabasas, CA). This system averages an error of ±.056°C; a minimum of two consecutive measurements differing by less than or equal to this error was required at each assessment. Saliva samples were assayed for melatonin concentration using a radioimmunoassay procedure (Elias usa, inc., Osceola, WI).

Statistical Analysis

Difference scores were used to reduce the influence of interindividual differences in absolute body temperature and melatonin levels, as well as to emphasize the change in body temperature or melatonin following NSAID administration. The necessity of using difference scores is illustrated by considering that in the nighttime melatonin and body temperature experiment there was a range in baseline body temperature of 36.3–37.6°C, and a range in baseline melatonin levels of 1–36 pg/ml. Difference scores were calculated as the change from baseline just prior to NSAID administration. For example, the body temperature difference score at 2400 h is the average difference between the body temperature levels at 2400 h and the 2300 h values.

Statistical tests included either repeated measures ANOVA or mixed design ANOVA (SuperANOVA v1.11) depending upon the experimental protocol. Greenhouse-Geisser corrections (which adjust the numerator and denominator degrees of freedom in repeated measures designs to reduce the likelihood of a Type 1 Error; 11), were applied to all analyses given that body temperature was assessed multiple times in each experimental period within the same subject. Probability values stated include the Greenhouse-Geisser correction.

RESULTS

NSAIDs and BT studies

Nighttime / between subjects design. Body temperature changes from baseline at 2300 h for each NSAID compared to placebo are shown in Fig. 2. As predicted, the decrease in body temperature was attenuated for both NSAID groups relative to the placebo group. There were large interindividual differences in body temperature changes, but the subjects in the placebo group generally showed a normal decline (> .4°C) in body temperature across the testing period. The average difference in body temperature at 0100 h between the placebo group and NSAID groups was 0.11°C. A two-way ANOVA for repeated measures (Condition × Time of Night) revealed main effects for both Condition [$F(2, 51) = 3.34$, $p < .05$] and Time of Night [$F(8, 408) = 62.48$, $p < .001$]. Pairwise comparisons confirmed that aspirin and ibuprofen did not differ from each other, but both groups differed from placebo at every temperature assessment from 2400–0100 h There was also an interaction between Condition and Time of Night [$F(16, 408) = 2.64$, $p < .05$], further illustrating that body temperature for the NSAID groups was attenuated across the

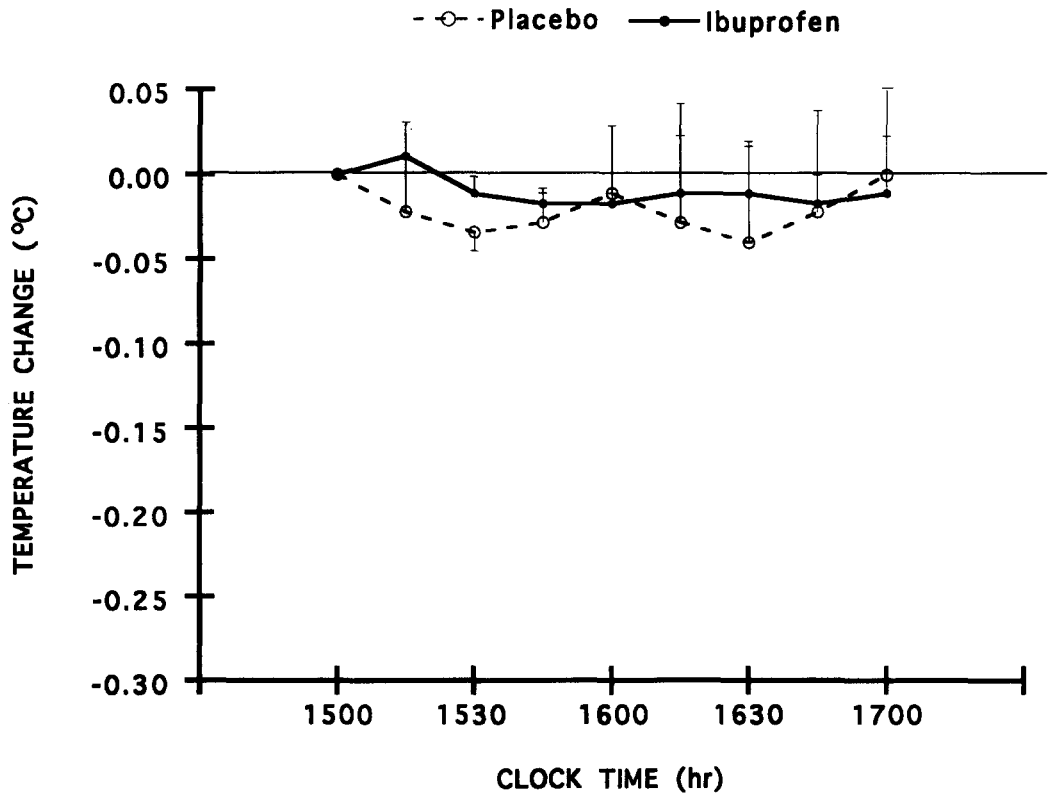

FIG. 4. Body temperature change scores (± SEM), calculated as difference from baseline at 1500 h for placebo (○---○) and ibuprofen (●—●). A total of 17 subjects were tested on one occasion from 1500–1700 h. Each subject received 400 mg ibuprofen or placebo.

experimental period relative to body temperature in the placebo group. Within subjects design. Body temperature changes from baseline at 2300 h after NSAID administration compared to after placebo administration are shown in Fig. 3. The difference between NSAID and placebo body temperature was most evident when compared within the same individual. The average difference in body temperature at 0100 h between the placebo group and NSAID group was .19°C. A two-way ANOVA for repeated measures (Condition × Time of Night) revealed main effects for both Condition [$F(1, 12) = 7.88$, $p < .05$] and Time of Night [$F(8, 80) = 20.16$, $p < .001$; Greenhouse-Geisser $p < .001$]. Pairwise comparisons revealed that body temperature differed significantly between NSAID and placebo at every time point after drug administration. As expected, there was also an interaction between Condition and Time of Night [$F(8, 80) = 7.12$, $p < .001$].

Daytime / between subjects design. Administration of an NSAID had no effect on body temperature during the daytime hours as shown in Fig. 4. That is, when subjects were tested between 1500–1700 h, body temperature was not different for the placebo vs. the NSAID groups. Body temperature was relatively flat across the experimental period for all subjects, although some subjects in both groups showed a slight increase in temperature between 1500–1700 h, as would be expected at this time of day when temperature is nearing its circadian peak.

NSAIDs and Melatonin Study with Body Temperature Replication

Body temperature. Figure 5 shows body temperature difference scores as a function of clock time after NSAID administration compared to after placebo administration. This study replicated previous findings concerning NSAID effects on body temperature as described above. All subjects exhibited the normal nighttime decrease in body temperature under the placebo condition, although some subjects showed a greater decrease in temperature from 2300–0300 h.

NSAID treatment attenuated the nighttime decrease in body temperature. There were no differences between aspirin and ibuprofen on body temperature changes; both NSAIDs maintained body temperature relative to placebo to a similar degree. The average change in body temperature after NSAID treatment was +.028, −.006, −.050, −.118, −.134, −.151, −.213, and −.207°C at 2330, 2400, 2430, 0100, 0130, 0200, 0230, and 0300 h, respectively. In comparison, the average change in body temperature after placebo was −.028, −.056, −.129, −.202, −.286, −.353, and −.403°C at the same times. Thus, the average difference in body temperature at 0300 h between the placebo groups and NSAID groups was .196°C.

An initial 3-way ANOVA confirmed that there was no effect of NSAID type (aspirin vs. ibuprofen). Subsequently, a 2-way ANOVA for repeated measures (Condition × Time of Night) was performed to determine (a) whether NSAIDs maintained body temperature at a higher level than placebo; and (b) whether body temperature levels within subjects changed across the night (i.e., exhibited a circadian rhythm). This analysis confirmed that body temperature differed significantly between the NSAID and placebo conditions [$F(1, 9) = 18.87$, $p < .01$]. Pairwise comparison at each time point established that body temperature was significantly higher after NSAID relative to placebo at 0030 h

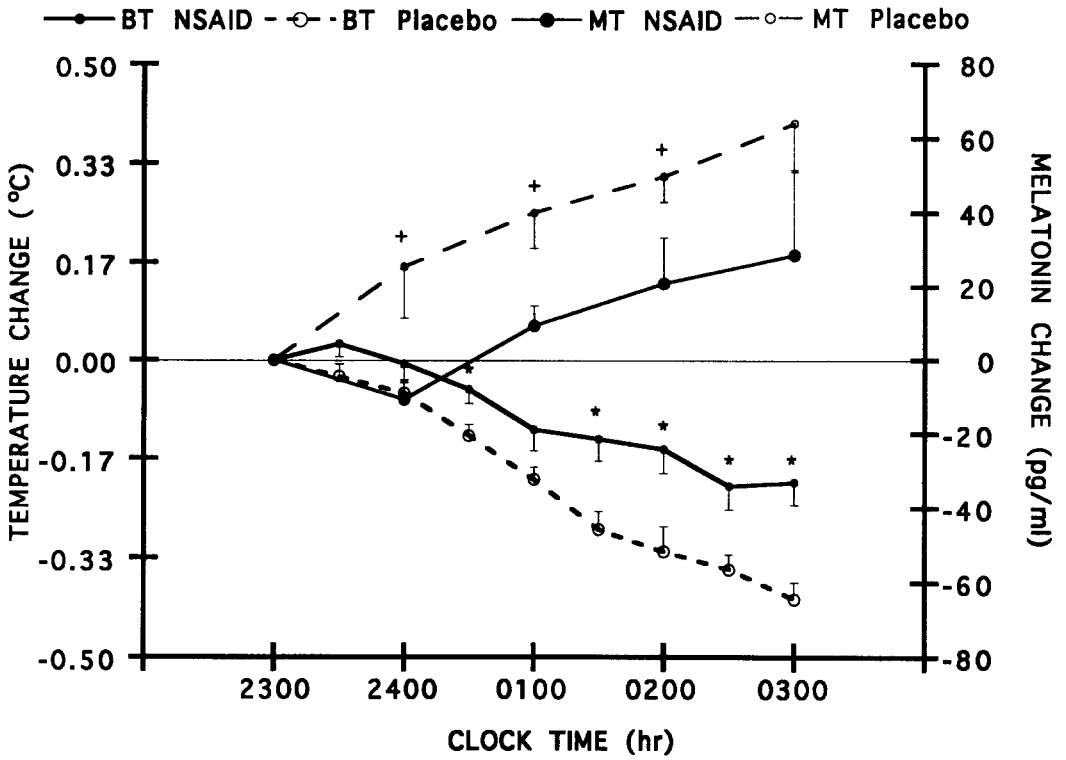

FIG. 5. Body temperature and melatonin change scores (±SEM), calculated as difference from baseline at 2300 h for placebo (O---O) and ibuprofen (●—●). +denotes body temperature different from placebo, $p < .05$. *denotes melatonin different from placebo, $p < .05$. A total of 10 subjects were tested on two occasions from 2300-0300 h. Each subject received 650 mg or 400 mg ibuprofen at one session, and placebo at the other, in a counterbalanced order.

and every 30 min from 0130–0300 h ($p < .05$). There was a main effect for Time of Night as well [$F(8, 72) = 41.77$, $p < .01$], confirming that body temperature did decline across the experimental period as expected. The presence of a significant Condition × Time of Night interaction [$F(8, 72) = 2.74$, $p < .05$] revealed furthermore that body temperature did not decline to the same degree after NSAID administration as after placebo administration.

Melatonin. Changes in melatonin levels as a function of clock time for NSAIDs compared to placebo are also shown in Fig. 5. All subjects exhibited the normal nighttime circadian increase in melatonin levels during the nighttime hours under the placebo condition, although in some subjects it appeared that melatonin levels peaked by 0200 h and lower levels were observed at 0300 h. There were the normally observed large interindividual differences in absolute melatonin levels, but intraindividual levels of melatonin between placebo and drug nights were stable at the pretreatment baseline measure (i.e., 2300 h).NSAID treatment suppressed melatonin levels relative to placebo treatment. As with body temperature, there was no significant difference in amount of melatonin suppression between aspirin and ibuprofen; both NSAIDs reduced melatonin levels by approximately 75% at 2400 h. As depicted in Fig. 5, the average change in melatonin levels after NSAID administration (relative to baseline measurement of 21.5 pg/ml) was −10.7, 9.3, 20.8, and 28.6 pg/ml at 2400, 0100, 0200, and 0300 h, respectively. In comparison, the average change in melatonin levels after placebo administration (relative to basline measurement of 21.6 pg/ml) was 25.4, 40.0, 49.8, and 64.0 pg/ml at the same times.

An initial 3-way ANOVA confirmed that there was no effect of NSAID type (aspirin vs. ibuprofen). Subsequently, a 2-way ANOVA for repeated measures (Condition × Time of Night) was performed to determine (a) whether melatonin levels after NSAID administration differed significantly from levels after placebo administration; and (b) whether melatonin levels within a subject changed across the night (i.e., exhibited a circadian rhythm). This analysis confirmed that melatonin levels differed significantly between the NSAID and placebo conditions [$F(1, 9) = 18.07$, $p < .01$]. Paired-comparisons analyses established that melatonin levels were significantly lower after NSAID than after placebo at 2400, 0100, and 0200 h ($p < .05$), but were not different at 2300 h (baseline) or 0300 h. As expected, there was a main effect for Time of Night [$F(4, 36) = 5.64$, $p < .01$), with melatonin levels increasing significantly every hour ($p < .05$). The Condition × Time interaction was not significant ($p > .05$), indicating that a circadian rhythm was exhibited under both the placebo and NSAID conditions, although the amplitude of the rhythm was lower after NSAID administration.

DISCUSSION

The primary purposes of these studies were to determine whether body temperature and melatonin levels are altered by the administration of a single dose of the NSAIDs aspirin and ibuprofen in humans. The normal circadian decrease in body temperature during the nighttime hours was attenuated by the administration of aspirin or ibuprofen, but daytime body temperature was not affected by NSAID administration. In addition, it was demonstrated that melatonin was suppressed by the administration of these NSAIDs during the nighttime hours, confirming previous reports that NSAIDs can suppress melatonin synthesis in animals (27,29) and in humans (33). These results are compatible with the hypothesis that some of the behavioral changes associated with NSAID administration, including changes in sleep (18), may be due to melatonin suppression and relatively higher body temperature. The lack of effects on daytime body temperature are also compatible with this hypothesis given that melatonin levels are very low during the diurnal hours. Further support for this argument is that NSAIDs had no effect on daytime naps relative to a placebo control condition (17).

It should be noted that salivary melatonin levels observed in this experiment were relatively higher than those reported in the literature. The reasons for this are not known, but the radioimmunoassay used has since been shown to be reliable and to produce values within the typically expected range (e.g., 22). Additionally, each subject's placebo and NSAID saliva samples were assayed simultaneously, and the differences between NSAID and placebo melatonin levels were consistent.

Differences in body temperature between NSAID and placebo were apparent within 30 min after NSAID administration (i.e., 2330 h); these differences continued and increased for up to 4 h after administration (Figs. 2–5). NSAID suppression of melatonin synthesis was apparent within 1 h of administration, but in contrast to NSAID effects on body temperature, the difference in melatonin levels between NSAID and placebo became smaller across the next 4 h (Fig. 5). This time course for initial body temperature changes and melatonin suppression is in accord with evidence that prostaglandin inhibition in the peripheral nervous system begins almost immediately after administration of an NSAID (10,34). The fact that there was not a one-to-one correspondence between body temperature and melatonin changes throughout the experimental period indicates that neither prostaglandin suppression nor melatonin suppression are sole determinants of body temperature changes after NSAID administration. It may be that a combination of prostaglandin and melatonin suppression by NSAID resulted in the observed pattern of body temperature changes in this experiment. An alternate hypothesis is that the abrupt suppression of melatonin synthesis (i.e., within 1 h) after NSAID administration in effect signaled the circadian timing mechanism, presumably at the level of the suprachiasmatic nuclei, that it was "no longer nighttime," and body temperature subsequently resembled a more diurnal pattern. This speculation cannot be confirmed by the present study, but it is in accord with theories suggesting that the role of endogenous melatonin is as a chemical signal of time (e.g., 2,8,25,26). Another explanation of how NSAIDs affect body temperature and other circadian rhythms is that NSAID administration may have simply delayed the onset of melatonin rhythm, essentially shifting the rhythm to a later clock time.

There were large interindividual differences in responsivity to the drug as manifested by the extent of change in melatonin and body temperature levels across subjects. This individual responsivity was evident especially in subjects who received both NSAID and placebo on separate occasions. The basis for such individual responsivity is not understood, but may include the influence of genetic variability and gender-related factors (24) or absorption and excretion rates (23).

The present study indicates that NSAIDs can significantly alter both melatonin and body temperature during the nighttime hours. The circadian rhythms of melatonin and body temperature are thought to be primary markers of the output of the circadian system. Research in circadian rhythms has shown that by attenuating (i.e., squashing) the amplitude of melatonin and body temperature (for example, with exposure to bright light), phase shifting and reentrainment of circadian rhythms is achieved relatively easily (e.g., 7,9,15), and acute enhancement of nighttime performance and alertness levels occurs (1). In relation to the present study, the speculation is that judicious administration of NSAIDs might be used to facilitate phase shifts of human circadian rhythms or enhance nighttime performance and alert-

ness in a way which is similar to but more convenient than bright light exposure. Beneficial effects of such phase shifting and reentrainment of circadian rhythms could include alleviation of symptoms of jet lag, seasonal depression, and other circadian rhythm disorders.

ACKNOWLEDGEMENTS

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