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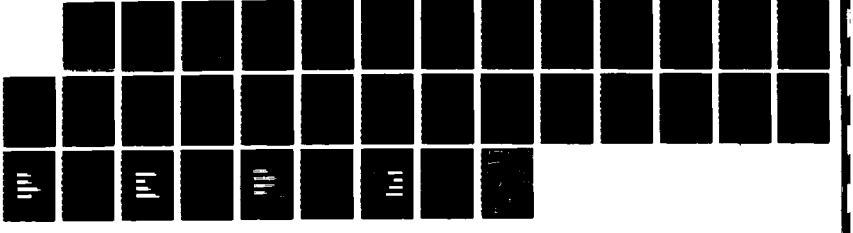
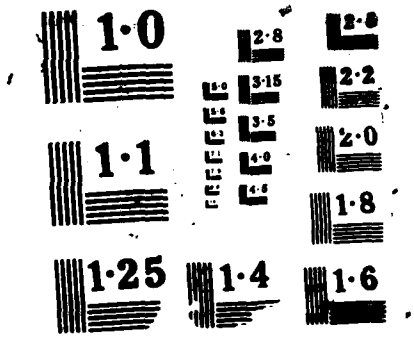
UNCLASSIFIED N00014-85-K-0027 F/G 6/15 NL

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THE EFFECT OF ANTIPYRETIC DRUGS ON THE CIRCADIAN RHYTHM IN BODY TEMPERATURE OF RATS

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Running Head: Antipyretic drugs and body temperature of rats

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Research Supported by ONR Contract N00014-85-K-0027

ABSTRACT

In many species, including the laboratory rat, body temperature varies on a circadian (24 hour) basis. There is considerable evidence that the circadian rise in body temperature is attributable to an elevation in thermoregulatory set-point. We hypothesized that this rise in set-point may be mediated by prostaglandins. If this hypothesis is correct, then it should be possible to block or reduce the nighttime rise in body temperature by the administration of prostaglandin synthesis inhibitors. Rats were injected with the prostaglandin synthesis inibitors sodium salicylate, acetylsalicylic acid and indomethacin at 5:00pm and at 9:00am. Administration of these drugs had little effect on body temperature during the day, but caused a significant fall in body temperature at night when temperature is normally in the rising or plateau phase of the cycle. We conclude that prostaglandin synthesis is an important component of the circadian rise in body temperature in the rat. In addition, evidence is presented that there exists a cryogenic factor that opposes the nighttime prostaglandin mediated rise in body temperature.

KEYWORDS: Sodium salicylate, acetylsalicylic acid, indomethacin, prostaglandins, body temperature

INTRODUCTION

A circadian rhythm in the body temperature of many laboratory animals and man has been well documented (25). This rhythm has been shown to be independent of activity patterns and food intake, although the magnitude of the changes in temperature are smaller during sleep deprivation and bed rest (2).

Several investigators have presented data indicating that the circadian rhythm in body temperature is due to a change in the thermoregulatory "set-point." Wenger et al. (37) and Stephenson et al. (31) investigated the thresholds for sweating and vasodilation of human subjects during exercise at night and during the day. Reduced thresholds for sweating and forearm blood flow were noted at 4:00am as compared to the late afternoon or early evening. Timbal et al. (35) have also shown that the latent period for the onset of sweating during exposure to elevated ambient temperatures is reduced at night compared to the daytime thresholds. Cabanac et al. (8) have examined the set-point for core temperature in humans based upon behavioral responses to immersion in water baths at 40°C and 30°C at different times of the day. These experiments also support the concept of an elevation in thermoregulatory set-point in the late afternoon or early evening as compared to the night or just prior to waking. Terai et al. (34) found that the preferred environmental temperature in human volunteers was elevated during the rising phase of the temperature cycle as compared to the falling phase of the circadian cycle. These data suggest that body temperature in human beings is regulated around a lower set-point at night than during the day.

If a circadian variation in thermoregulatory set-point exists, then it is possible that this set-point change may be mediated by prostaglandins, in a manner similar to the elevation in thermoregulatory set-point that occurs during most fevers (6,14,32). If the circadian change in temperature set-point were mediated by prostaglandins, then it should be possible to block or reduce the circadian rise in body temperature by the administration of a prostaglandin synthesis inhibitor (i.e. an antipyretic drug). A number of studies have investigated the effects of antipyretic drugs on the normal body temperature of a variety of species in their respective thermoneutral zones (5, and review in 36). Many of these studies failed to show an effect of antipyretic drugs on normal body temperature. However, a few studies have demonstrated a reduction in the rectal temperature of afebrile rats following the injection of antipyretic drugs, particularly when the animals are maintained at cold ambient temperatures (28,30). In general, studies investigating the effect of antipyretic drugs on normal body temperature have not addressed the effect of such drugs with respect to the circadian rhythm in body temperature.

In the rat, a nocturnal animal, body temperature is highest at night and lowest during the day (27,33). In this study, we have tested the hypothesis that the circadian rise in body temperature in the rat is consistent with an elevation in thermoregulatory set-point, mediated by prostaglandins. We administered the prostaglandin synthesis inhibitors sodium salicylate, acetylsalicylic acid and indomethacin at 5:00pm (during the rising phase of the circadian temperature rhythm) and at 9:00am (when body temperature is low and relatively stable) and monitored the 24 hour rhythms in body temperature and activity.

MATERIALS AND METHODS

Animals. Male Sprague-Dawley rats (Rattus norvegicus), 250-400 grams, obtained from Charles River Laboratories, Portage, MI, were housed individually in polycarbonate cages. The animals were maintained on a 12:12 light/dark cycle (lights on 6:00am to 6:00pm, lights off 6:00pm to 6:00am) in a temperature controlled chamber at 26± 1°C. Food (Purina rat chow) and water were provided ad libitum.

Temperature Measurement. Body temperature was measured using battery-operated biotelemetry devices (Mini-mitter, Inc., Sunriver, OR) implanted intraperitoneally. Output (frequency in Hz) was monitored by a mounted antenna (receiver board) placed under each animal's cage and fed into a peripheral processor (Dataquest III, Data Sciences, Inc.) connected to an IBM-PC. Each rat was surgically implanted intraabdominally with a telemetry device (model VMFH) and allowed to recover at least 1 week prior to experimentation. For all experiments, body temperature was monitored at 30 minute intervals for at least 24 hours prior to injection to obtain stable baseline temperatures. Normalization of the temperature data to a given time interval provided compensation for animal-to-animal variation in 'baseline' temperatures. The calculation of "change in temperature" was determined in the following manner. The average temperature for the interval between 12:00pm and 4:30pm was calculated for each rat on the control day (no injection). This mean value was then subtracted from each temperature value at a given time point on subsequent days for the determination of change in temperature relative to the control day.

Activity. The measurement of activity was also via biotelemetry and the Dataquest System. Activity measurement is based upon the principle that as the orientation of the telemetry device (implanted in the rat) changes over the receiver card, the transition results in a change in the signal strength as detected by the receiver card, and hence a "pulse" of activity is recorded. This "pulse" of activity is recorded and increments the counter associated with a specific channel. Each input is compared with the state recorded on the previous sample, and as a result if the animal has not moved from its previous location, activity will not be incremented. Because the transmitters are not calibrated for activity as for temperature, it was useful to calculate "relative activity" by normalizing each animal to a given time interval on the control day. This facilitated analysis of the activity for multiple animals, and provided a means to compare groups. In a manner similar to the determination of change in temperature, "relative activity" was determined by normalizing the activity value for each 30 minute interval to the mean activity between 12:00pm and 4:30pm on the control day.

Injections. All injections were made intraperitoneally. Sodium salicylate (The University of Michigan Hospital Pharmacy) was prepared in pyrogen-free 0.9% sodium chloride and injected at a dose of 300mg/kg. Acetylsalicylic acid (Sigma Chemical) was dissolved in a basic NaOH solution resulting in a final pH of approximately 8-9 and injected at a dose of 300mg/kg. Indomethacin (kindly provided by Merck Sharp & Dohme Research Laboratories) was prepared in a sodium carbonate solution (1.14mg/ml) and injected at doses of 5, 7.5, 10, 15 and 20mg/kg. Control injections for each antipyretic drug consisted of the appropriate

vehicle. All solutions were filter sterilized (0.22um filters, Millipore) prior to injection. The doses of the salicylates used for these experiments were antipyretic for endotoxin-induced fevers in rats. For the indomethacin experiments, the 10, 15 and 20mg/kg doses were antipyretic for endotoxin-induced fevers in rats. Doses of 5 and 7.5mg/kg indomethacin were not effective at blocking endotoxin fevers.

Statistics. All data for these experiments were analyzed using the computer services of the Michigan Terminal System. The programs implemented for the statistical analysis of the data included Student's T-Test (Michigan Interactive Data Analysis System), and Repeated measures analysis of variance (BMDP Statistical Software, UCLA). Student's T-test was used for making comparisons between groups and days for the mean temperatures of a given time interval. Repeated measures analysis of variance was used to analyze sequential points within a given time interval for group and time effects.

RESULTS

A. Normal Rhythm in Body Temperature and Activity

When maintained on a 24 hour light/dark cycle the circadian rhythm in body temperature of the rat may be arbitrarily divided into 4 phases. These include: 1) a daytime phase in which body temperature is low and relatively stable, (average body temperature during this time: 37.31 $\pm$ .04°C, N=64); 2) a rising phase which begins gradually around 4:00pm, with the steepest increase between 5:30pm-7:00pm; 3) a plateau phase between 7:00pm-5:00am during which temperature is elevated (average body temperature during this time: 38.05 $\pm$ .05°C, N=64); and 4) a rapid

falling phase in which temperature falls below the average afternoon temperature, and then gradually returns to daytime values. Not surprisingly, a rhythm in activity parallels the rhythm in body temperature (Fig. 1).

B. Salicylate Experiments

Intraperitoneal injection of sodium salicylate (300mg/kg) and acetylsalicylic acid (300mg/kg) at 5:00pm resulted in an abrupt fall in body temperature at this time of day as compared to saline injection. Figure 2 presents the temperature and activity profiles of a control day and the day of injection. Figure 3 presents the data from the day of the injection by breaking the 24 hour day into intervals consisting of: I) 12:00pm - 4:30pm; II) 6:00pm - 9:00pm; III) 9:30pm - 5:00am and IV) 5:30am - 11:30am. It is apparent from both Figures 2 and 3 that the administration of the antipyretic drugs resulted in a dramatic fall in body temperature. Significant differences were noted between the saline and sodium salicylate groups (Interval II: 6:00pm - 9:00pm), $p < .0001$, and between saline and aspirin groups (Interval II), $p = .0110$. Repeated measures analysis of variance for the interval 6:00pm - 9:00pm indicated a significant difference betweeen the groups with $p = .0001$. The salicylate and aspirin groups were significantly different from the control day for the 6:00pm - 9:00pm interval, with $p < .0001$ and $p = .0158$ respectively. The onset of the effect of sodium salicylate and acetylsalicylic acid was quite rapid following injection and persisted for 4-6 hours. The fall in body temperature at night following the injection of the salicylates was not associated with an alteration in the normal level of activity (Fig. 2). Further, the injection of the salicylates did not result in a shift in the phase of the temperature rhythm. Interestingly, there was a tendency for a slight hyperthermia on

the morning following the injection of the antipyretic drugs at 5:00pm compared to the day prior to the injection. The sodium salicylate group was significantly different from the saline group for the interval from 5:30am - 11:30am, p=.0260 and significantly different from the previous day for the same time interval, p=.0332.

In contrast to the results obtained when the antipyretic drugs were injected at 5:00pm, injection of the salicylates at 9:00am did not result in a depression in body temperature or in activity at that time of the day (Fig. 4,5). It is noteworthy that 9:00am injections of saline, sodium salicylate and acetylsalicylic acid all resulted in a transient elevation in both temperature and activity, which is likely to be the result of the stress of handling and injection. The same response was not as apparent for the respective 5:00pm injections, presumably because the animals are already in the rising phase of temperature and activity cycles at this time of day.

C. Indomethacin Experiments

The administration of the non-antipyretic doses of indomethacin (5 and 7.5mg/kg) had no significant effect on body temperature or on activity (Fig. 6,7). The injection of antipyretic doses of indomethacin (10, 15, and 20mg/kg) at 5:00pm resulted in a profound depression in body temperature with an onset of approximately 5-6 hours following the injection as compared to controls (Fig. 6,7). Repeated measures analysis of variance indicated a significant difference between the groups for the intervals 6:00pm - 12:00am and 12:30am - 5:00am (following injection of the indomethacin), with p =.0005 and p=.0001 respectively. Between 1:00am and 6:00am the temperatures of the animals injected with these higher doses of indomethacin actually fell below normal daytime temperatures. Associated with this reduction in body temperature was a reduction in activity (Fig. 6). These levels of activity were not below

the typical level of activity observed during the daytime; therefore, it is unlikely that this relative inactivity could explain the fall in body temperature that followed the administration of these doses of indomethacin. Further, the decline in activity associated with the injection of indomethacin followed the onset of the depression in body temperature, suggesting that the reduction in activity may have been the result of the fall in body temperature, rather than the cause of the change in temperature. If the animals were cold, it is likely that they remained relatively stationary and curled up to conserve heat rather than to expend the calories for activity. For two to three days following the administration of indomethacin (doses 10, 15 amd 20mg/kg), the normal temperature rhythm was distorted (data not shown). The rats failed to display the normal rise and fall in temperature but instead maintained relatively steady values (temperatures similar to normal afternoon values).

Interestingly, the administration of indomethacin at 9:00am at a dose of 10mg/kg had no effect on body temperature during the day, but soon after the onset of darkness, body temperature fell dramatically. Figure 8 presents the temperature and activity profiles of a control day and the day of injection. Figure 9 presents the data from the day of injection by dividing the 24 hour day into intervals consisting of: I) 12:00pm - 5:30pm; II) 6:00pm - 12:00am; III) 12:30am - 5:00am and IV) 5:30am - 11:30am. Injection of indomethacin at 9:00am resulted in a significant difference between the day of injection and the control day for Interval III (12:30am - 5:00am), $p=.0385$. In a manner similar to the 5:00pm injections of this dose, activity declined in parallel with the fall in body temperature (Fig. 8).

DISCUSSION

The administration of the prostaglandin synthesis inhibitors sodium salicylate, acetylsalicylic acid and indomethacin resulted in a depression in temperature at night when the body temperature of rats is normally elevated. Injection of these same drugs in the morning did not depress the daytime temperatures of these animals. These data add support to the concept of a circadian rhythm in thermoregulatory set-point. Further, these data support our hypothesis that prostaglandins play a role in the normal circadian rise in the body temperature of the rat.

The patterns of the temperature responses to the injection of indomethacin and the salicylates at 5:00pm are clearly not the same. The onset of the effect of acetylsalicylic acid and sodium salicylate was relatively rapid (within 1 hour) following the 5:00pm injection. Temperature returned to normal within about 5-6 hours following injection of these drugs. In contrast, the injection of indomethacin (10, 15, 20mg/kg doses) produced a depression in body temperature that started approximately 6 hours following the 5pm injection and persisted for 9 hours or longer. Indomethacin has been shown to be a more potent inhibitor of prostaglandin synthesis (cyclooxygenase enzyme) in isolated systems than the salicylates (15,16), which may partially explain the longer duration of the effect on temperature.

The reason for the delay in the onset of an effect on body temperature is less clear. We have demonstrated that the 10, 15 and 20mg/kg doses of indomethacin are antipyretic for endotoxin induced fevers (data not shown). An intraperitoneal injection of E. coli endotoxin (50ug/kg) will produce a fever of about 1.5 °C, which begins

approximately 2 hours following the injection of endotoxin. An intraperitoneal injection of indomethacin given 1 hour prior to the endotoxin will completely block the pyrogen induced fever. This would suggest that a 6 hour delay is not necessary for the drug to block the synthesis of prostaglandins in the central nervous system sites important for the development of a fever. However, these experiments were performed in the morning, and may not be relevant to a 5:00pm injection of indomethacin in terms of the time of onset for effective inhibition of prostaglandin synthesis in the central nervous system. Labrecque et al. have examined the plasma concentrations of indomethacin in rats following an oral dose (3mg/kg) when given at 8:00am, 2:00pm or 8:00pm (23). These investigators found a trend for a lower peak height and longer time to reach peak plasma levels when indomethacin was given at 8:00am as compared to 2:00pm or 8:00pm. Based upon these results, we would predict that the injection of indomethacin at 5:00pm would not require an extended time to reach peak plasma concentrations. Clearly this does not explain the results obtained in the study presented here. It is possible that the delay noted in our studies may be due to the time necessary for the drug to reach sufficient concentrations to inhibit prostaglandin synthesis in the thermoregulatory centers in the central nervous system.

In the present study, the administration of sodium salicylate and acetylsalicylic acid to rats at 9:00am did not produce a fall in body temperature during the day. It must be noted that Satinoff (28) and Solomonovich (30) have published data indicating that sodium salicylate (300mg/kg) given to rats during the day results in a fall in temperature, particularly when the animals are placed in the cold (4-5°C). These studies differ from the present study both in the method for temperature measurement (rectal thermistor probe vs. biotelemetry) and the "neutral"

ambient temperature (23°C vs. 26±1°C). It is not clear whether these differences in protocol can explain the difference in results.

If the circadian rise in body temperature is a prostaglandin-induced elevation in thermoregulatory set-point, then it is tempting to speculate that a mediator such as interleukin-1 may be driving the nighttime rise in thermoregulatory set-point. Interleukin-1 has been shown to stimulate an elevation in prostaglandin levels in many tissues including the central nervous system (cerebrospinal fluid) (7), cultured hypothalamic cells (24), synovial fluid (9,22), fibroblasts and endothelial cells (1), and skeletal muscle (4,19). Many interleukin-1-induced fevers are believed to be mediated by prostaglandins (6,7,29,32,36), although a few studies have demonstrated a dissociation between interleukin-1 fever and central prostaglandin levels (see, for example, 10,11). Interleukin-1 has been shown to be secreted from many cell types both outside the central nervous system (13) and within the brain (17,18). It is possible that interleukin-1 release from either the central nervous system or the periphery could be responsible for the daily changes in prostaglandin synthesis.

Based on the data presented in Figures 2-9, we have proposed a model for the normal circadian rhythm in body temperature in the rat (Figure 10). The light/dark cycle is known to be an entraining agent of the circadian rhythm in body temperature (25). Light and dark cues are likely to be integrated via the suprachiasmatic nuclei (25). Although the onset of darkness and light alone could not be responsible for driving the elevation and depression in temperature, we would speculate that the integration of these cues exerts a modulatory role over the endogenous system that controls the 24 hour rhythm in temperature. Prior to the onset of darkness, perhaps as a result of anticipatory behavior,

an elevation of prostaglandin levels in the central nervous system may occur either directly, or perhaps via a mediator such as interleukin-1 (see left side of figure). In a similar manner to a fever, the elevation in prostaglandins could result in an elevation in thermoregulatory set-point, and body temperature would rise as a result. Maintenance of the elevation in prostaglandin levels may continue throughout much of the dark phase of the light/dark cycle. Prior to the onset of light, the stimulus for the elevation in prostaglandin levels may diminish, resulting in a fall in thermoregulatory set-point and core temperature would drop as a consequence. A prostaglandin independent "cryogenic" agent that also displays a circadian rhythm, but slightly offset from the stimulus that results in an elevation in body temperature may oppose the nighttime rise in temperature, and hence contribute to the early morning decline in core temperature (see right side of figure). Many endogenous antipyretics and cryogenic factors have been reported in the past few years including vasopressin, alpha melanocyte stimulating hormone and endogenous cryogen (3,20,21,26). Such a factor could help to explain the reduction in body temperature below daytime levels following administration of indomethacin (see Figures 6 & 8). The indomethacin seems to exert the most profound effect on temperature between 12:00am - 6:00am when injected at 5:00pm. The blockade of the prostaglandin component of the elevation in core temperature at this time may unmask the presence of a cryogenic agent. It is possible that such a substance may normally oppose the nighttime rise in body temperature, and modulate the elevation in temperature in much the same way as insulin, glucagon and other hormones modulate plasma glucose concentrations.

ACKNOWLEDGEMENT

The authors wish to thank Arthur J. Vander for critically evaluating the manuscript.

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FIGURE LEGENDS

FIGURE 1: The normal circadian rhythm in body temperature and activity in rats. Mean ± SEM. N=64 rats. Lights on 6:00am - 6:00pm. Lights off 6:00pm - 6:00am. Average body temperature between 12:00pm and 4:30pm was 37.36 ± 0.3°C. Dark bar represents the lights off period.

FIGURE 2: Effect of injection of saline, sodium salicylate (300mg/kg) and acetylsalicylic acid (300mg/kg) at 5:00pm, Day 2 on temperature and activity in rats. Day 1 is a control day prior to the day of injection. Dark bar represents the lights off period. N= sample size.

FIGURE 3: Effect of injection of saline, sodium salicylate (300mg/kg) and acetylsalicylic acid (300mg/kg) at 5:00pm on temperature. Temperature data (mean ± SEM) are plotted as 4 intervals on the day of injection. I) 12:00pm-4:30pm; II) 6:00pm-9:00pm; III) 9:30pm-5:00am; IV) 5:30am-11:30am. N= sample size.

FIGURE 4: Effect of injection of saline, sodium salicylate (300mg/kg) and acetylsalicylic acid (300mg/kg) at 9:00am, Day 2 on temperature and activity in rats. Day 1 is a control day prior to the day of injection. Dark bar represents the lights off period. N= sample size.

FIGURE LEGENDS

FIGURE 5: Effect of injection of saline, sodium salicylate (300mg/kg) and acetylsalicylic acid (300mg/kg) at 9:00am on temperature. Temperature data (mean ± SEM) are plotted as 4 intervals on the day of injection. I) 12:00am-8:30am; II) 10:00am-1:00pm; III) 1:30pm-5:00pm; IV) 5:30pm-11:30pm. N= sample size.

FIGURE 6: Effect of injection of indomethacin at doses of 5, 7.5, 10, 15 and 20mg/kg at 5:00pm, Day 2 on temperature and activity in rats. Day 1 is a control day prior to the day of injection. Dark bar represents the lights off period. N= sample size.

FIGURE 7: Effect of injection of vehicle (control) and indomethacin at doses of 5, 7.5, 10, 15 and 20mg/kg at 5:00pm on temperature in rats. Temperature data (mean ± SEM) are plotted as 4 intervals on the day of injection. I) 12:00pm-4:30pm; II) 6:00pm-9:00pm; III) 9:30pm-5:00am; IV) 5:30am-11:30am. N= sample size.

FIGURE 8: Effect of injection of indomethacin at 10mg/kg at 9:00am, Day 1 on temperature and activity in rats. Dark bar represents the lights off period. N= sample size.

FIGURE LEGENDS

FIGURE 9: Effect of injection of indomethacin at 10mg/kg at 9:00am on temperature in rats. Temperature data (mean ± SEM) are plotted as 4 intervals on the day of injection. I) 12:00pm-5:30pm; II) 6:00pm-9:00pm; III) 9:30pm-5:00am; IV) 5:30am-11:30am. Dark bar represents the lights off period. N= sample size.

FIGURE 10: A model for the normal circadian rhythm in body temperature in the rat.

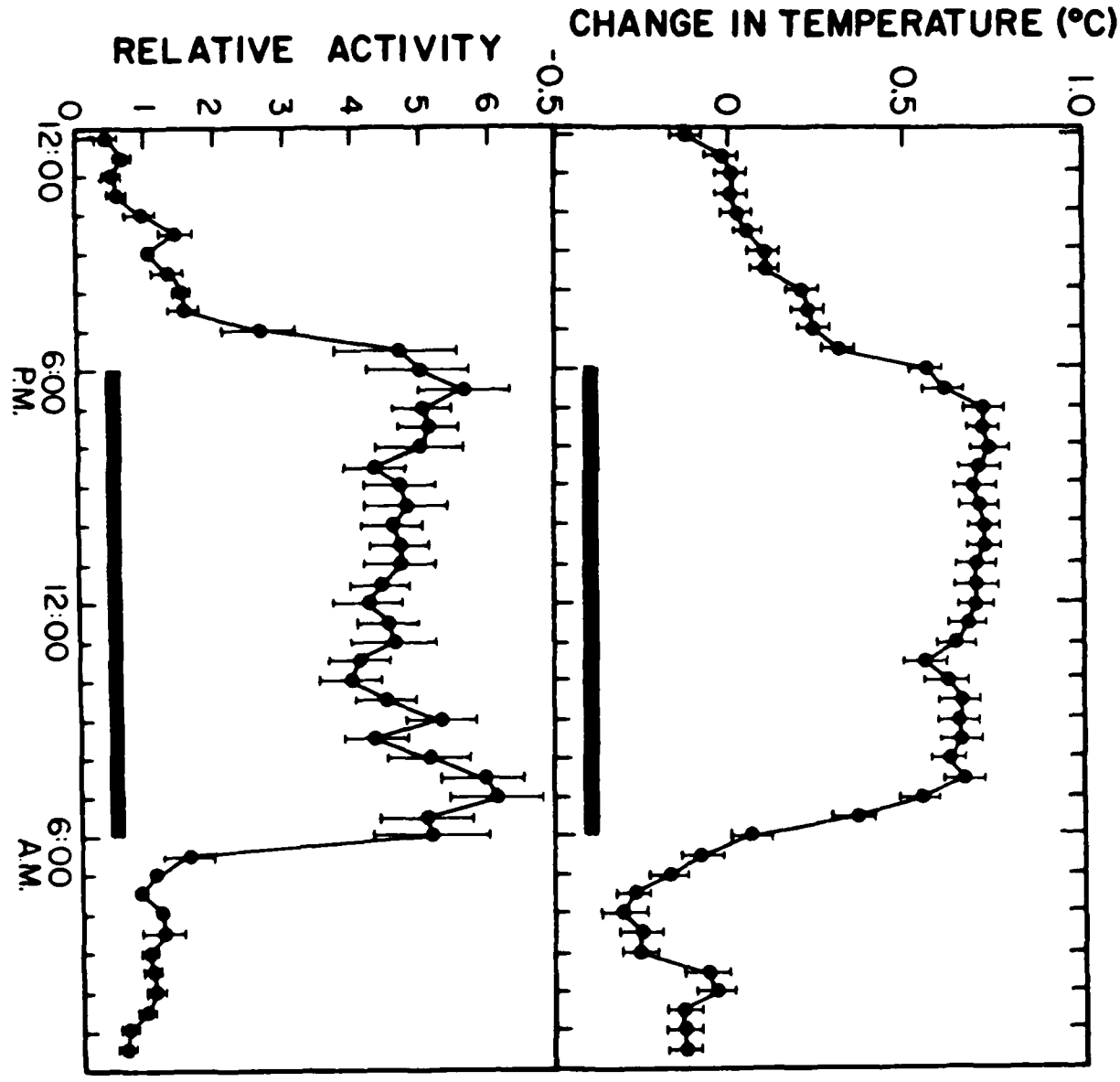
RELATIVE ACTIVITY
CHANGE IN TEMPERATURE (°C)
0
1
2
3
4
5
6
-0.5
0
0.5
1.0
12:00
6:00 P.M.
12:00
6:00 A.M.
TIME OF DAY

FIGURE 1

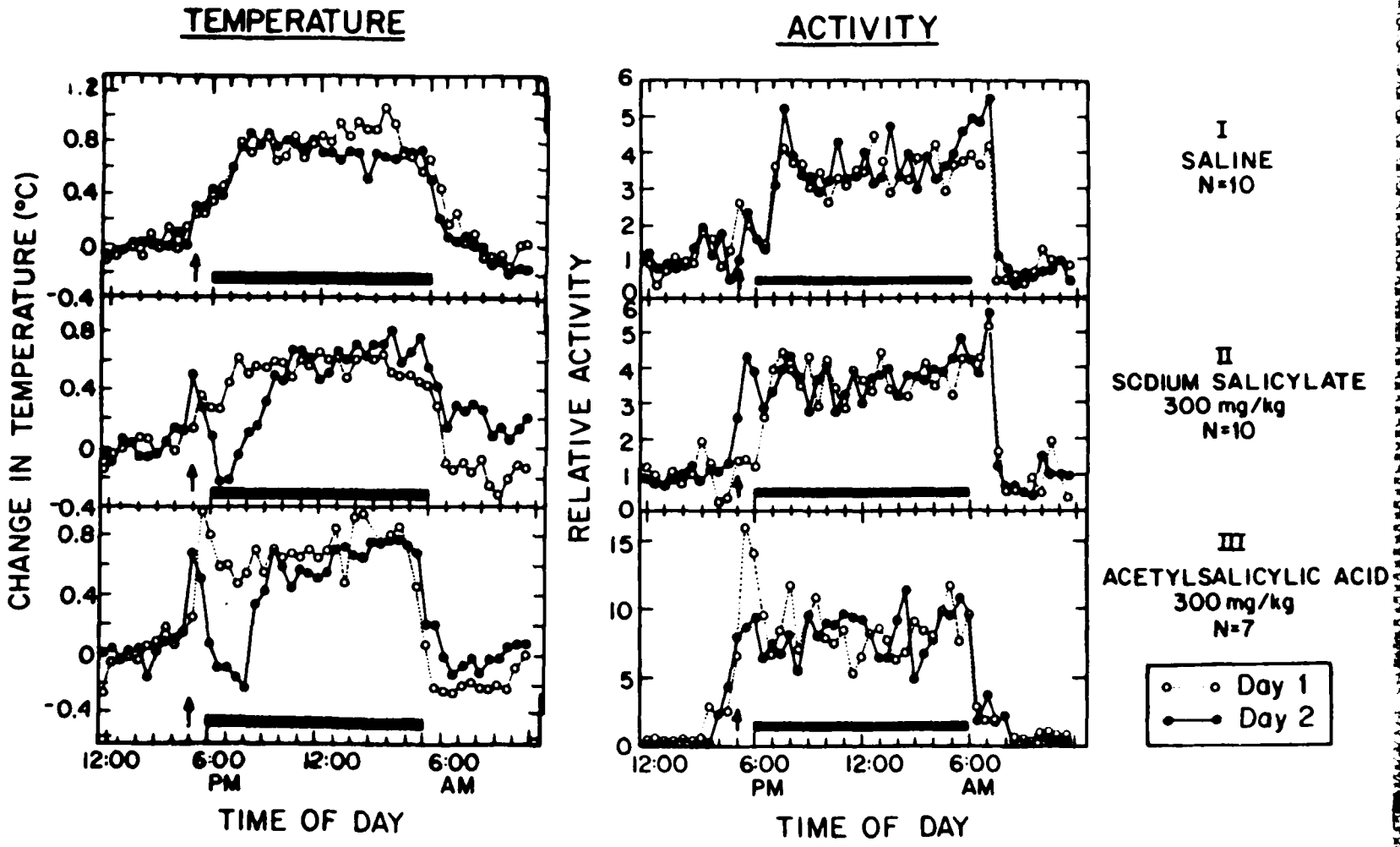
TEMPERATURE
ACTIVITY
CHANGE IN TEMPERATURE (°C)
RELATIVE ACTIVITY
1.2
0.8
0.4
0
-0.4
6
5
4
3
2
1
0
15
10
5
12:00
6:00 PM
12:00
6:00 AM
TIME OF DAY
I
SALINE
N=10
II
SODIUM SALICYLATE
300 mg/kg
N=10
III
ACETYLSALICYLIC ACID
300 mg/kg
N=7
Day 1
Day 2

FIGURE 2

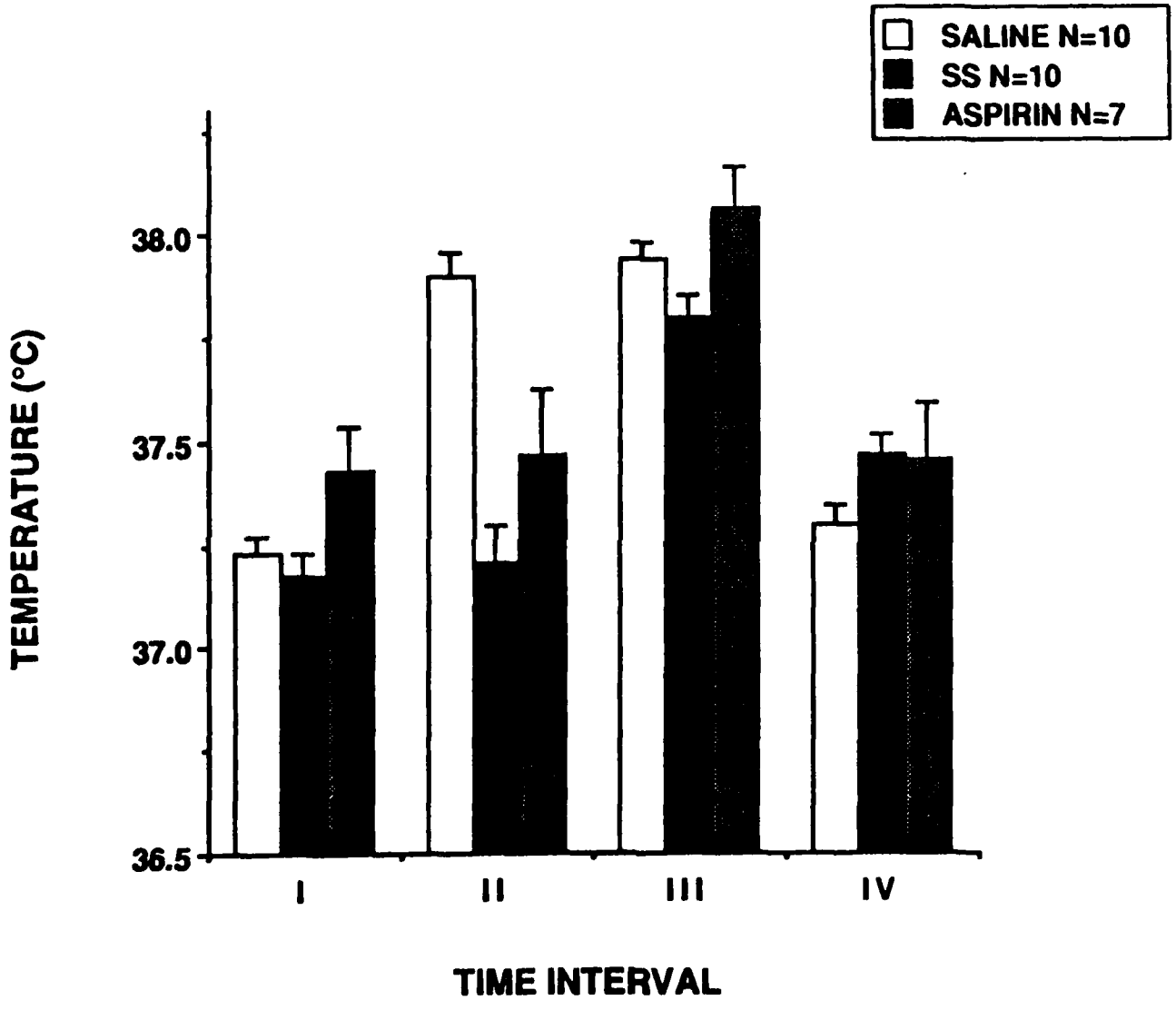
SALINE N=10
SS N=10
ASPIRIN N=7
38.0
37.5
37.0
36.5
TEMPERATURE (°C)
I
II
III
IV
TIME INTERVAL

FIGURE 3

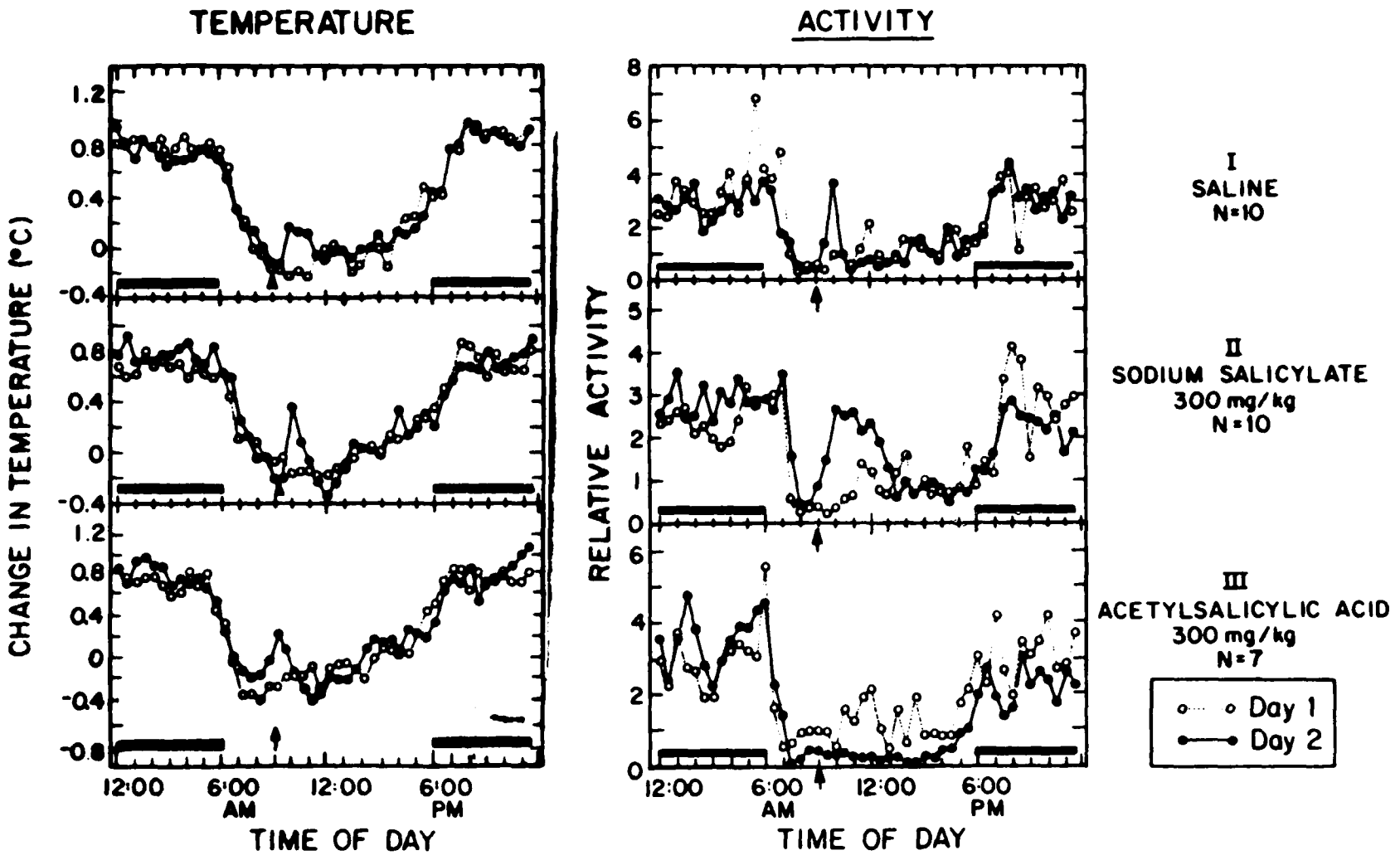
TEMPERATURE
ACTIVITY
CHANGE IN TEMPERATURE (°C)
RELATIVE ACTIVITY
1.2
0.8
0.4
0
-0.4
-0.8
8
6
4
2
5
3
1
12:00
6:00 AM
12:00
6:00 PM
TIME OF DAY
I
SALINE
N=10
II
SODIUM SALICYLATE
300 mg/kg
N=10
III
ACETYLSALICYLIC ACID
300 mg/kg
N=7
Day 1
Day 2

FIGURE 4

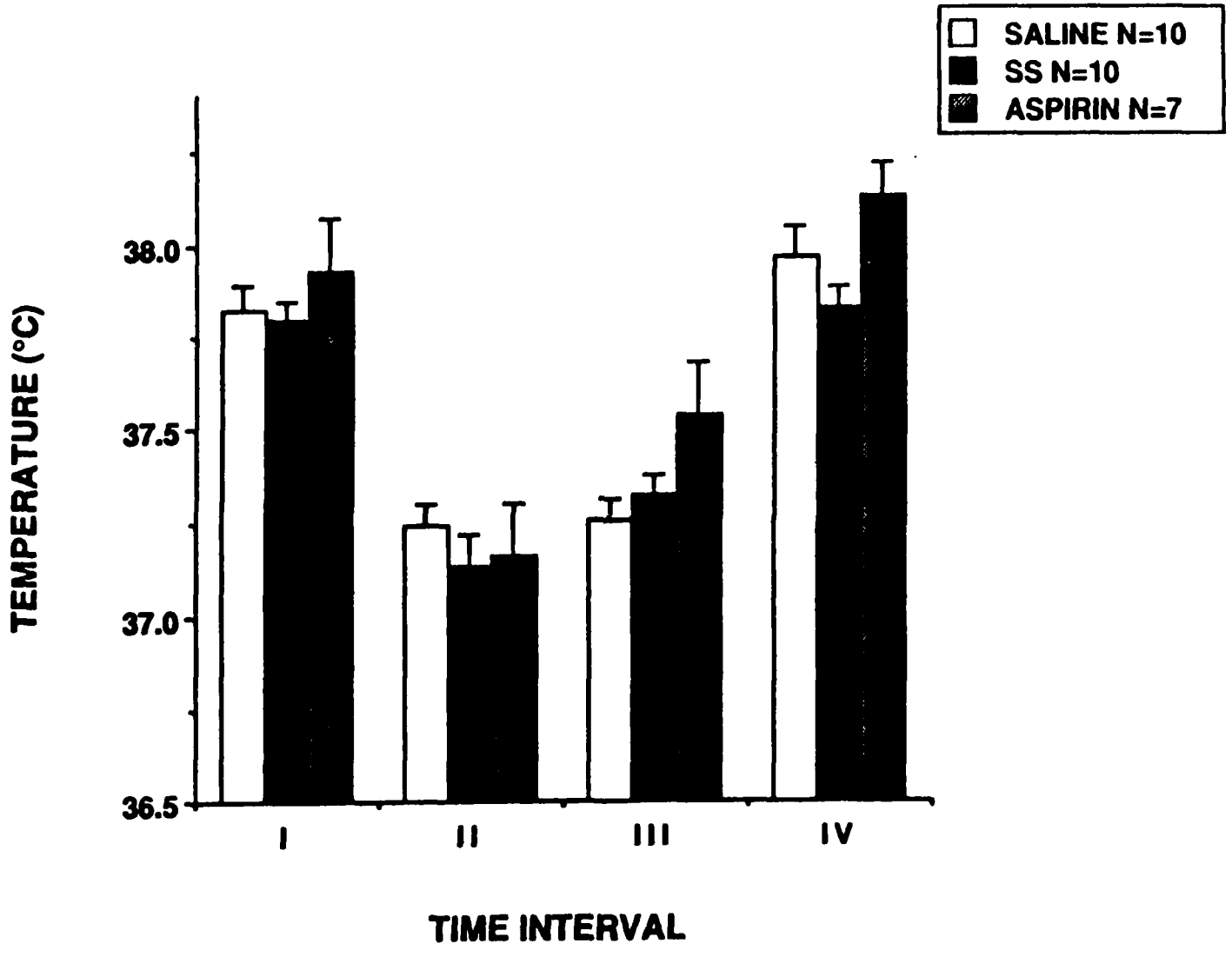
SALINE N=10
SS N=10
ASPIRIN N=7
TEMPERATURE (°C)
38.0
37.5
37.0
36.5
I
II
III
IV
TIME INTERVAL

FIGURE 5

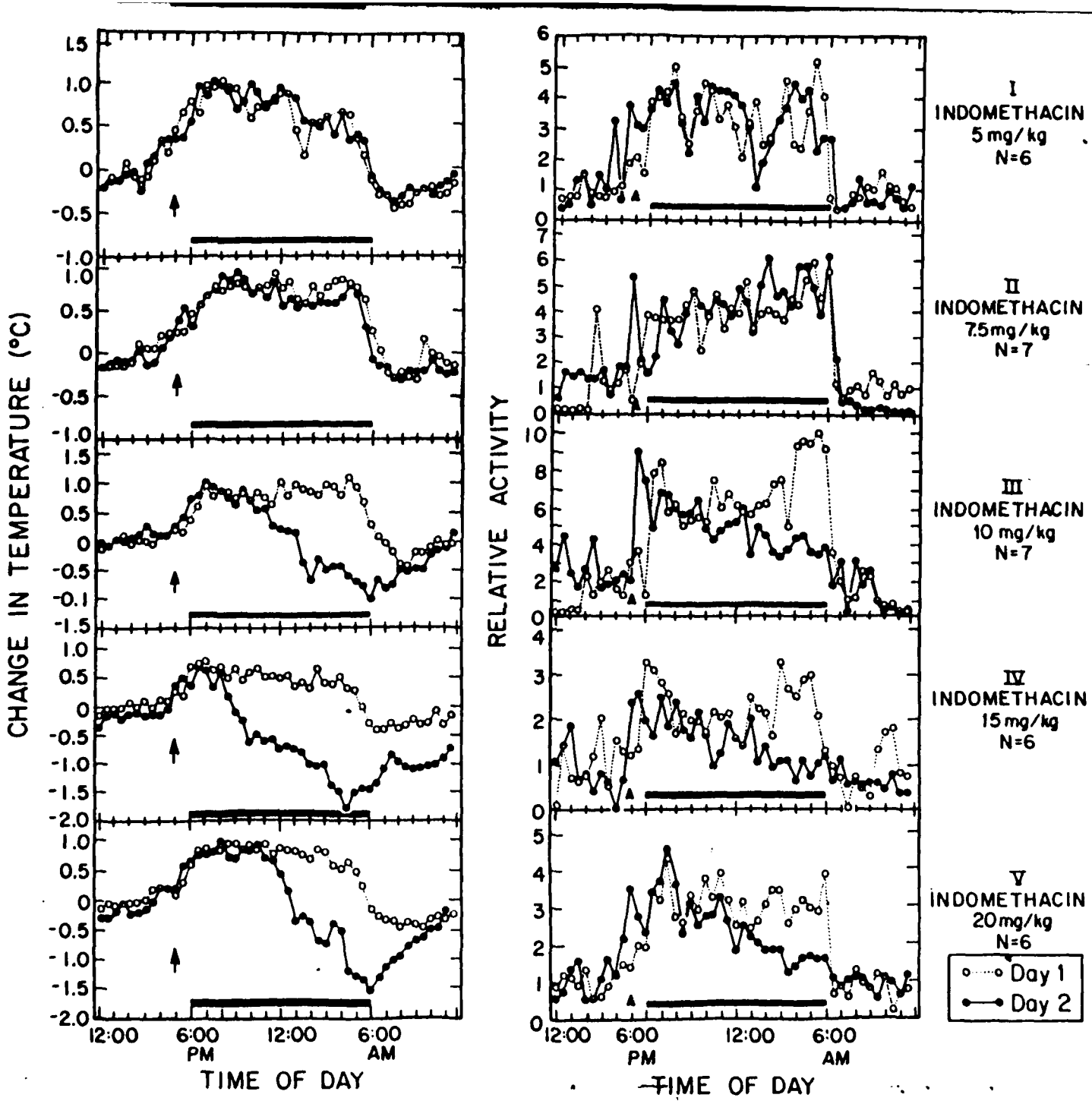
CHANGE IN TEMPERATURE (°C)
RELATIVE ACTIVITY
I
INDOMETHACIN
5 mg/kg
N=6
II
INDOMETHACIN
7.5mg/kg
N=7
III
INDOMETHACIN
10 mg/kg
N=7
IV
INDOMETHACIN
15 mg/kg
N=6
V
INDOMETHACIN
20mg/kg
N=6
Day 1
Day 2
12:00
6:00
PM
12:00
6:00
AM
TIME OF DAY

FIGURE 6

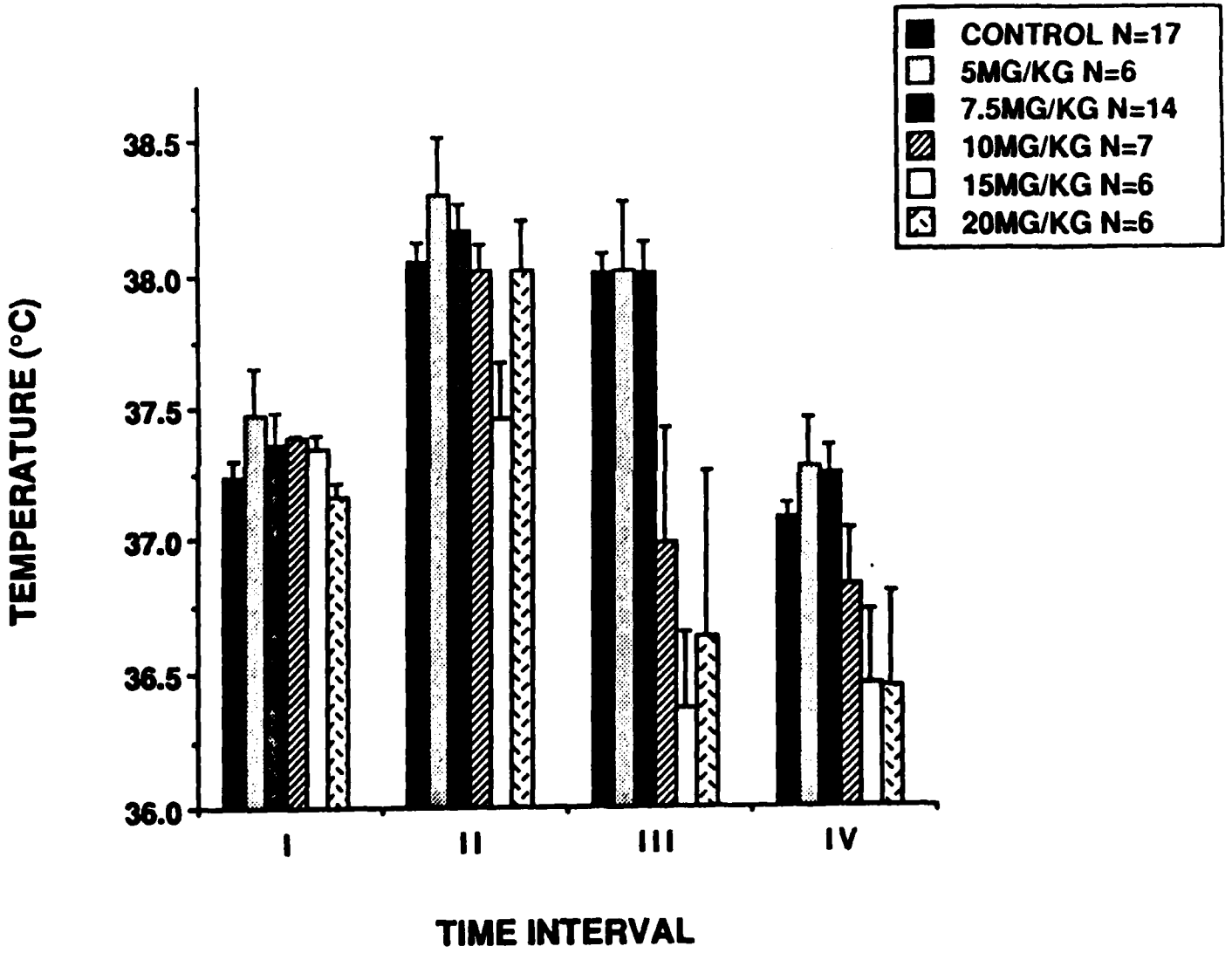
CONTROL N=17
5MG/KG N=6
7.5MG/KG N=14
10MG/KG N=7
15MG/KG N=6
20MG/KG N=6
TEMPERATURE (°C)
38.5
38.0
37.5
37.0
36.5
36.0
I
II
III
IV
TIME INTERVAL

FIGURE 7

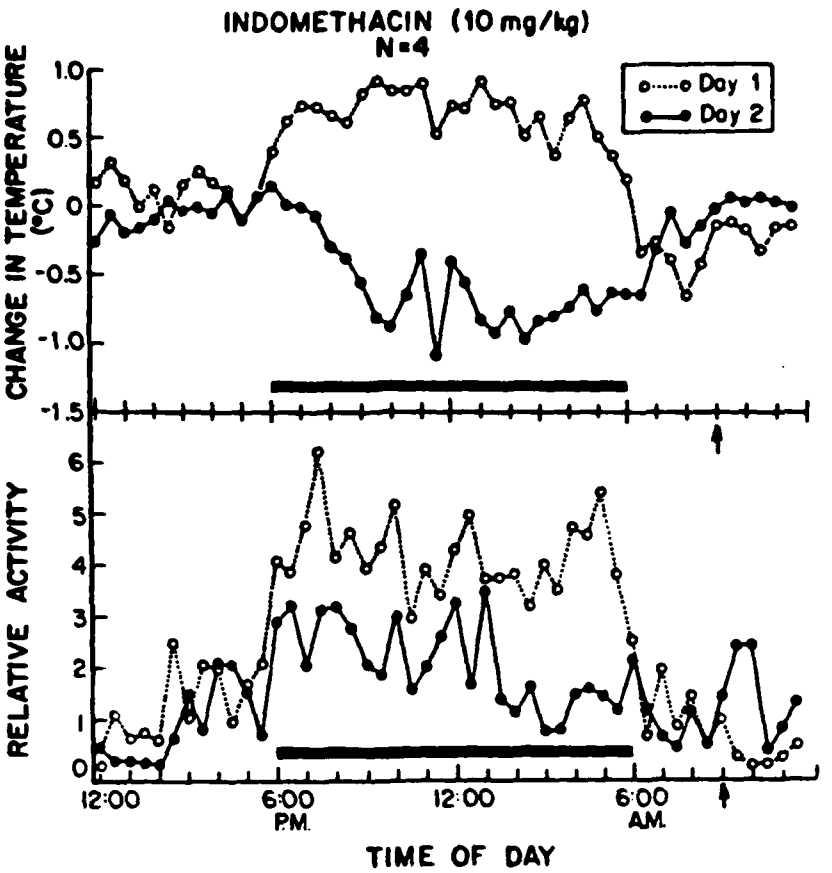
INDOMETHACIN (10 mg/kg)
N=4
Day 1
Day 2
CHANGE IN TEMPERATURE (°C)
1.0
0.5
0
-0.5
-1.0
-1.5
RELATIVE ACTIVITY
6
5
4
3
2
1
0
12:00
6:00 P.M.
12:00
6:00 A.M.
TIME OF DAY

FIGURE 8

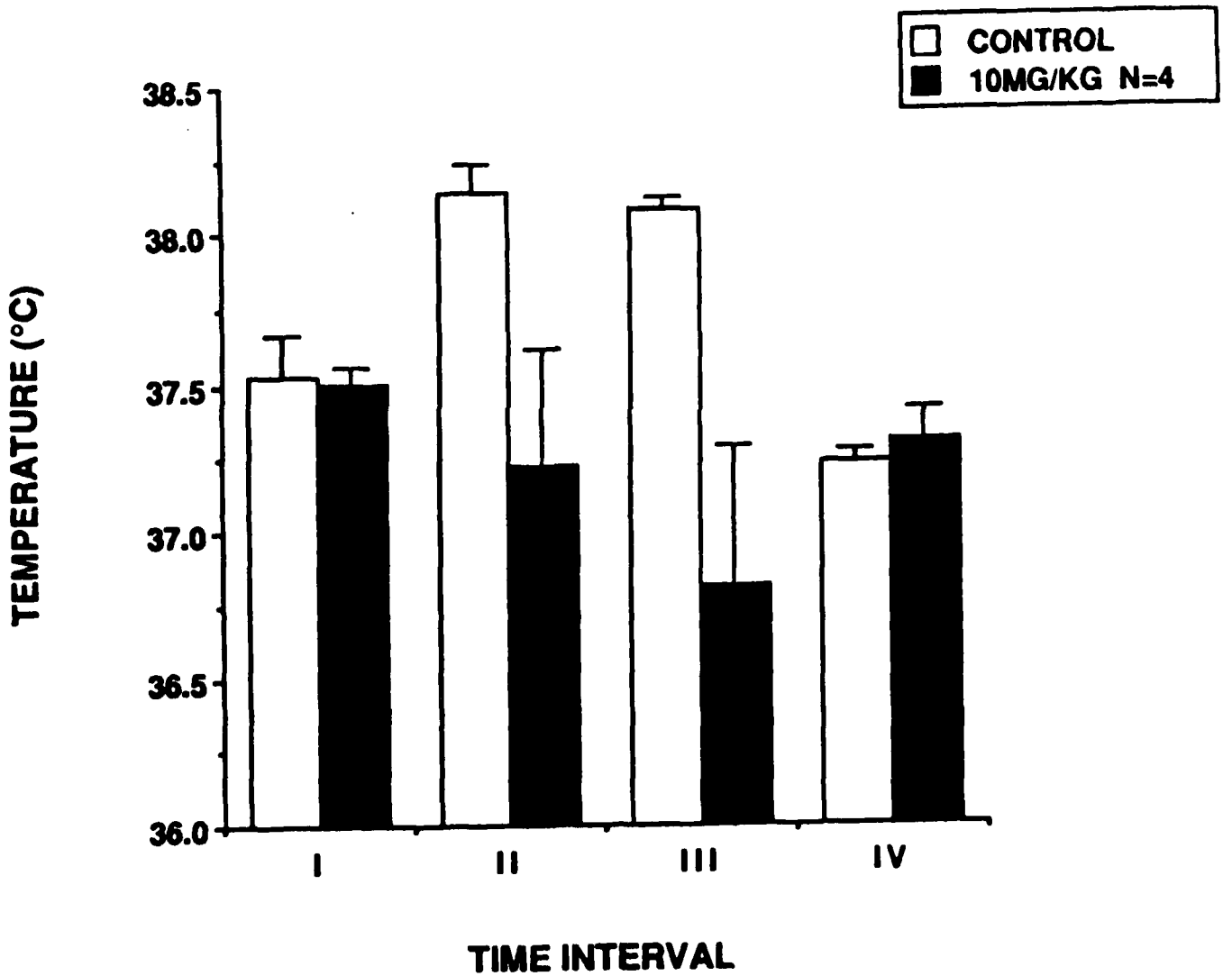
CONTROL
10MG/KG N=4
38.5
38.0
37.5
37.0
36.5
36.0
TEMPERATURE (°C)
I
II
III
IV
TIME INTERVAL

FIGURE 9

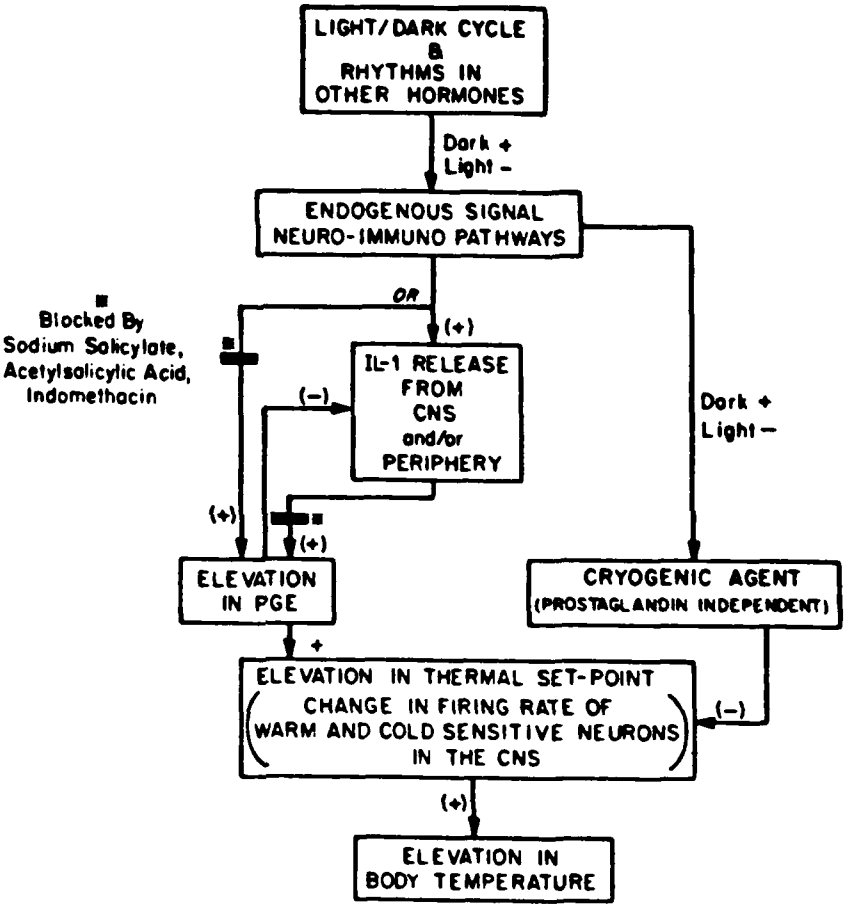
LIGHT/DARK CYCLE
&
RHYTHMS IN
OTHER HORMONES
Dark +
Light –
ENDOGENOUS SIGNAL
NEURO-IMMUNO PATHWAYS
OR
(+)
Blocked By
Sodium Salicylate,
Acetylsalicylic Acid,
Indomethacin
IL-1 RELEASE
FROM
CNS
and/or
PERIPHERY
(–)
Dark +
Light –
(+)
(+)
ELEVATION
IN PGE
CRYOGENIC AGENT
(PROSTAGLANDIN INDEPENDENT)
+
ELEVATION IN THERMAL SET-POINT
CHANGE IN FIRING RATE OF
WARM AND COLD SENSITIVE NEURONS
IN THE CNS
(–)
(+)
ELEVATION IN
BODY TEMPERATURE

FIGURE 10

END

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