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EFFECT OF AMBIENT TEMPERATURE ON BRAIN TEMPERATURE AND SLEEP-WAKEFULNESS IN MEDIAL PREOPTIC AREA LESIONED RATS

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Abstract : The changes in brain temperature and sleep-wakefulness were studied in rats during their exposure to different ambient temperatures of 18°C, 24°C and 30°C, before and after N-methyl D-aspartic acid lesion of the medial preoptic area. The medial preoptic area lesion produced a decrease in sleep, and increase in brain temperature except at 30°C. Increase and decrease in brain temperature with slow wave sleep and paradoxical sleep respectively, were observed both in normal and lesioned rats. Sleep-wakefulness and brain temperature cycle durations were increased and their frequencies decreased at higher ambient temperature in normal rats. After the medial preoptic area lesion, sleep-wakefulness cycle duration was decreased and frequency increased at 30°C. There was no significant change in brain temperature cycles at higher ambient temperature in lesioned rats. The medial preoptic area, in normal rats, possibly interlinks the neuronal circuits involved in regulating brain temperature and sleep-wakefulness cycles. The medial preoptic area is essential for increasing the sleep-wakefulness cycle duration with higher ambient temperature. The possible contribution of the increased brain temperature variation in producing sleep-wakefulness changes cannot be ruled out. The results of the study show that this area may serve as a fine tuning mechanism which helps to interlink the sleep-wakefulness with the thermoregulation.

Key words : sleep-wakefulness brain temperature ambient temperature medial preoptic area slow wave sleep paradoxical sleep

INTRODUCTION

Sleep-related changes in brain temperature (Tbr), and the changes in sleep on manipulations of environmental and preoptic area (POA) temperatures, gave rise to the hypothesis that sleep is modulated by thermosensitive elements of the brain (1, 2, 3, 4, 5). The medial preoptic area (mPOA) participates in the regulation of sleep and

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body temperature (6, 7, 8, 9, 10, 11). It was suggested that the thermoreceptors in the POA may provide the input to the sleep-regulating mechanisms situated in and around this area (12). As many thermosensitive neurons of the POA showed alterations in their firing rate with changes in the vigilance states, their involvement in the regulation of both slow wave sleep (SWS) and body temperature has been suggested (13). Ambient temperature (Ta) can influence S-W regulating structures (14). Moderate increase in Ta significantly enhanced sleep (3, 5). When the cats were exposed to 13°C, 23°C and 33°C, they slept the maximum at 23°C. But, after the lesion of the mPOA, sleep was maximum at 33°C (15). The study also showed that sleep was restored in the lesioned animals, when they were exposed to a higher atmospheric temperature. But according to an earlier report, the rats had maximum SWS and paradoxical sleep (PS) at 30°C and least at 20°C, when they were exposed to ambient temperatures of 20°C, 25°C and 30°C (16). Following a lesion of the POA, SWS and PS were highest at 25°C. The mPOA is essential for sleep maintenance and improving the quality of sleep with higher ambient temperature (17).

The body temperature and brain temperature (Tbr) in the rat increase by more than 1°C if the Ta is increased from 21°C to 29°C (18). This increase in Tbr and body temperature can evoke an increase in SWS (4, 19, 20, 21). It was even proposed that the function of SWS is to cool the brain (4). Changes in brain temperature induce a shift in the EEG (22). The level of brain cooling activity oscillates across the NREM-REM cycle (23). In the present study, the changes in Tbr and sleep were examined during exposure to different Ta in normal and the mPOA lesioned animals, to determine if sleep disturbance, evoked by the mPOA cell loss could be correlated to altered Tbr.

METHODS

In this study, S-W and Tbr were monitored, in six rats, before and after chronic lesion of the mPOA, when they were kept in different ambient temperatures. In this study, the changes in various parameters after neurotoxic lesion of the mPOA were compared with the recordings taken from the same set of animals, before the lesion. So, it was considered not very essential to have another control group of animals, where the mPOA were not lesioned. Male Wistar rats, weighing between 225 and 300 g each, maintained in an animal room with controlled temperature (24 ± 1°C) and 14 h light (illumination above 200 lux) and 10 h dark (illumination below 5 lux) cycle, were used for this study. Food and water were provided *ad libitum*. Surgery was conducted under pentobarbital sodium anaesthesia (40 mg/kg, ip). Electrodes for electroencephalogram (EEG), electromyogram (EMG) and electrooculogram (EOG) were chronically implanted, as described earlier (8). In addition, a thermistor was inserted between the skull and dura, through a hole over the right parietal cortex, for assessment of Tbr. The electrodes and thermistor were soldered to a connector that was fixed to the skull with dental cement. After a seven-day recovery period, for three days, the rats were allowed to move around freely in the recording cage for 7 h with the attached cables. Flexible cables with

connectors, plugged to the rats' heads, and taken out through a microswivel, were connected to the input of the polygraph. EEG, EMG, EOG and Tbr were recorded continuously for 5 h (11.30 h–16.30 h) at 18°C, 24°C and 30°C, on three alternate days. The animals were allowed to get habituated to the Ta in the recording chamber for 2 h, before each recording session. The 5 h sleep-wakefulness (S-W) recordings were split into epochs of 30 seconds duration and visually scored as described earlier (24). The wakeful period was classified into two stages, ie, active wakefulness (W1) and quiet wakefulness (W2). The sleep period was classified into light slow wave sleep (S1), deep slow wave sleep (S2) and paradoxical sleep (PS). The Tbr values were noted at 15 seconds intervals and plotted along with the concomitant S-W stage (Fig. 1).

After control recording of S-W at different Ta, the rats were anaesthetised with sodium pentobarbitone (40 mg/kg, body weight), and 5 µg N-methyl D-aspartic acid (NMDA, Sigma, St. Louis, USA), in 0.2 µl distilled water, neutralised with NaOH was injected bilaterally, with the help of a slow injector (Palmer, England), at co-ordinates A 7.8, H -1.5 and L 0.6, as per DeGroot atlas, to destroy the mPOA neurons (25). The injector cannula was kept in place for five minutes to facilitate the diffusion of the drug. All the parameters for the assessment of S-W and Tbr were again recorded continuously for 5 h (11.30 h–16.30 h) at 18°C, 24°C and 30°C, on three alternate days, starting from the tenth day after the NMDA injection. No two rats had the same sequence of exposure to different temperatures. At the end of the experiment, all the rats were perfused with 10%

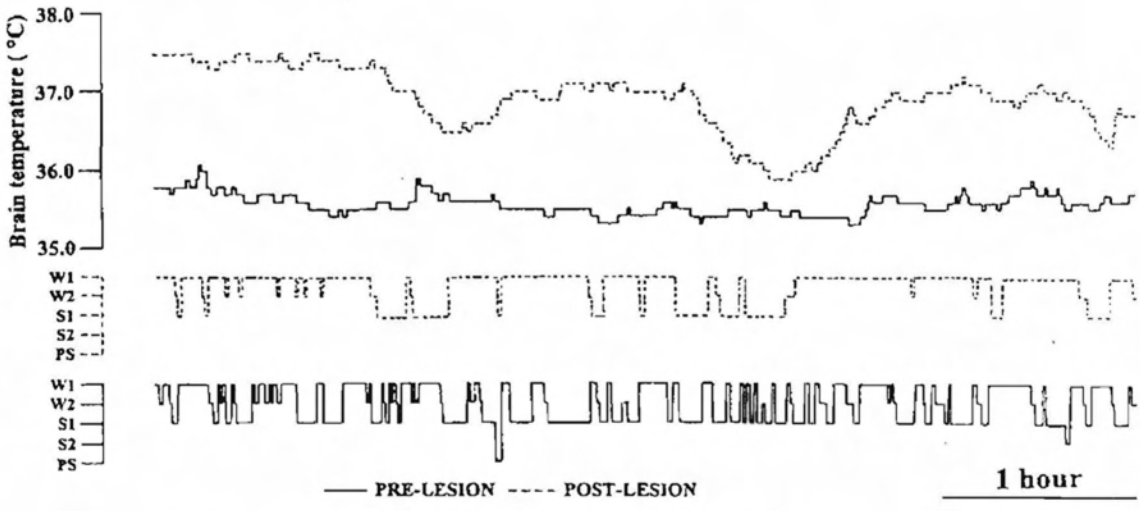

Fig. 1: The brain temperature and concomitant sleep-wakefulness stages for 5 h recordings at 18°C in one rat. Solid lines show the recording in the normal rat, and broken lines show the recording in the same animal after the lesion of the mPOA. W1-active wakefulness, W2-quiet wakefulness, S1-light slow wave sleep, S2-deep slow wave sleep, PS-paradoxical sleep.

formaline under sodium pentobarbitone anaesthesia (45 mg/kg, bw). The brains were then removed and processed for histological examination of the lesion site, in cresyl violet stained slides.

The mean Tbr at different Ta were found out by averaging pooled Tbr values of the entire 5 h recordings. The pre and post-lesion Tbr values at each Ta were compared to find out the effect of the mPOA lesion. Tbr values of each stage of S-W before and after the lesion were noted and compared. Tbr cycle frequency, duration and the amplitude of fluctuations were also similarly compared. The Tbr values at S-W stages were pooled and compared to find out the mean brain temperature of the animals at various vigilance states, before and after lesion of the mPOA. To understand the changes in Tbr with transition from one S-W state to another, four minute episodes, with two minutes spent in two different stages of S-W were selected. Tbr values at 30 seconds intervals were pooled and plotted (Fig. 2). Similarly a change in S-W during a fall or rise in Tbr from 36.5°C, 37.0°C and 38.0°C were also plotted (Fig. 3). While selecting these episodes, the only criterion followed was that the animal should be having one of the above mentioned Tbr for at least two minutes. The W1, W2, S1 and

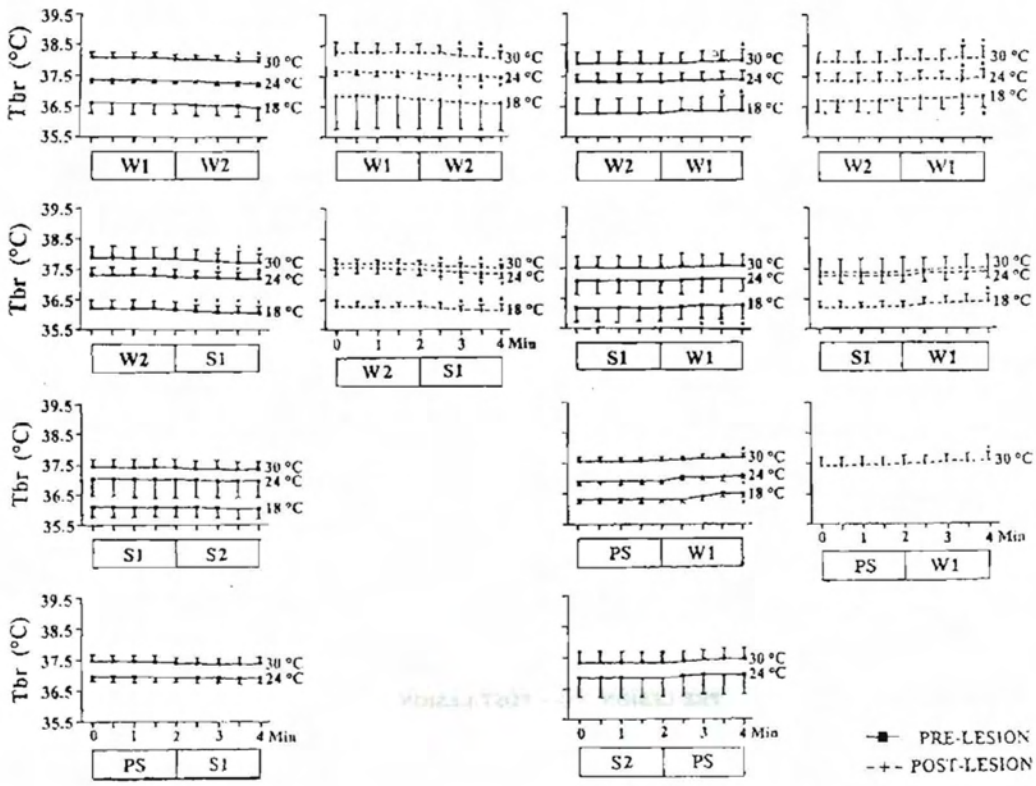

Fig. 2 : Changes in brain temperature (Tbr) with transition from one S-W state to another. Episodes of change in S-W with two minutes spent in two different stages were selected. Tbr values are plotted at 30 seconds intervals. *P<0.05, significance compared to first epoch. Abbreviations of S-W stages same as Fig. 1.

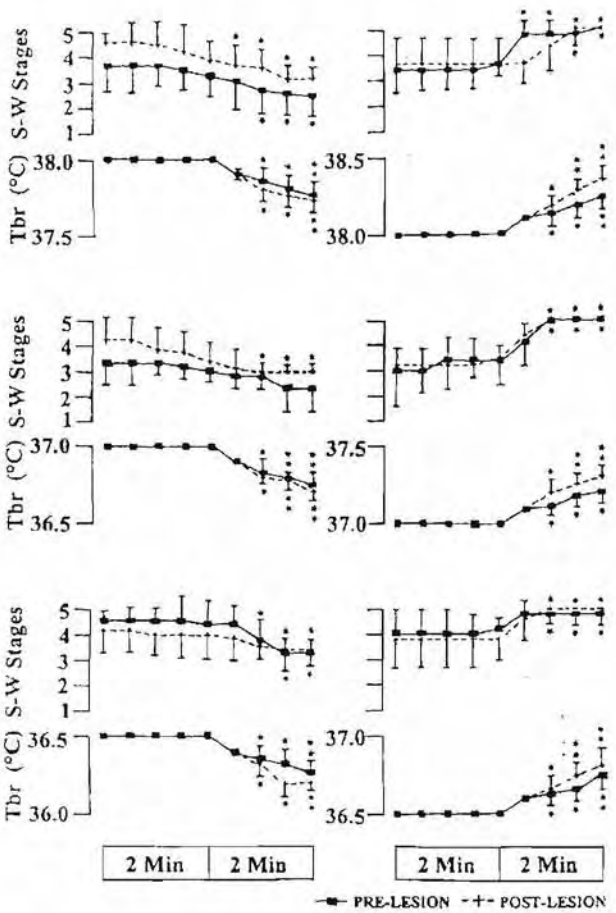

Fig. 3: Changes in S-W and Tbr with rise and fall in Tbr. Recordings were selected where Tbr remained at 36.5°C, 37.0°C and 38.0°C for two minutes before they changed. Those showing increase and decrease in Tbr are shown separately. Tbr and S-W are plotted at 30 seconds intervals. W1, W2, S1 and S2 were arbitrarily given the values 5, 4, 3 and 2 respectively. The averaged S-W and Tbr values were plotted against time. *P<0.05, **P<0.01, significance compared to first epoch.

S2 were arbitrarily given the values 5, 4, 3 and 2 respectively. The pooled S-W values were then plotted against time, along with the averaged temperature values.

Total sleep time (TST) were calculated before and after lesion of the mPOA at different Ta. The number and duration of S-W cycles before and after lesion were also compared. Two way analysis of variance (ANOVA) was used to compare all the values of these parameters. The pre and post-lesion values were compared using Student's paired *t* test for those parameters showing significant differences between columns in ANOVA. For studying the effect of temperature on S-W parameters, the values at 18°C were compared with those of 24°C and 30°C.

RESULTS

The data obtained before and after the mPOA lesion are described separately.

Pre-lesion : Tbr was higher at higher Ta (Fig. 4). There was a linear increase in TST with higher Ta, though it was not statistically significant (Fig. 4). Tbr cycle frequency decreased and its duration increased with increase in Ta (Fig. 5B). The frequency of S-W cycles decreased and its duration increased with increase in Ta (Fig. 5A). The change in Ta did not significantly affect the magnitude of Tbr fluctuations. The average variation in Tbr was 0.26 ± 0.06°C at 18°C, 0.28 ± 0.03°C at 24°C and 0.29 ± 0.06°C at 30°C. There were ultradian alterations in Tbr at all the Ta. The average Tbr values at W1, W2, S1 and S2, when plotted, showed a gradual decrease, as the animal passed from active wakefulness to deep slow wave sleep, at all Ta (Fig. 6A). A shift from S2 to PS produced slight increase in the average Tbr at 18°C and 24°C. The temperature changes at different vigilance states were visible

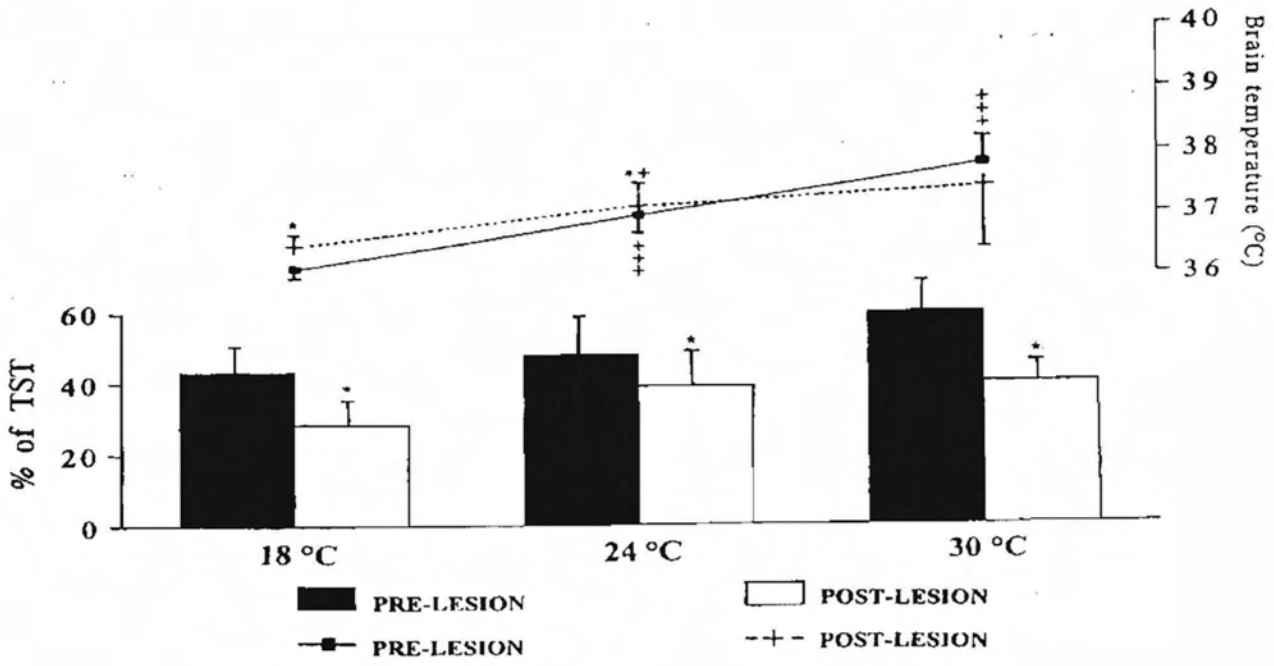

Fig. 4 : Total sleep time (TST) and Tbr of 5 h recordings before and after the mPOA lesion at 18°C, 24°C and 30°C. *P<0.05, significance compared to pre-lesion values, ·P<0.05, ···P<0.001, significance compared to 18°C.

even when the Tbr during S-W transitions were plotted (Fig. 2). When S-W stages were given arbitrary values and plotted against temperature fall and rise, it was seen that increased vigilance was associated with rise in Tbr and decreased vigilance with fall in Tbr (Fig. 3). Changes in S-W occurred before the Tbr alterations.

After mPOA lesion: The mPOA lesion produced hyperthermia when the rats were maintained at 18°C and 24°C, but there was no significant change in Tbr when they were kept at 30°C (Fig. 4). S-W cycle frequency was increased and duration reduced at 30°C in the lesioned rats (Fig. 5A). This is in contrast to the trend observed in normal rats. Unlike the normal rats, there was no significant change in Tbr cycles with changes in Ta after the mPOA lesion (Fig. 5B). The Tbr variations were higher in the lesioned rats, though the increases were not statistically significant. The average ultradian variations in Tbr were 0.32 ± 0.05°C at 18°C, 0.28 ± 0.08°C at 24°C and 0.33 ± 0.05 at 30°C. The maximum deviation in Tbr changed from 1.46 ± 0.43°C before lesion to 2.2 ± 0.76°C after lesion at 18°C (Fig. 1). At 24°C, it changed from 1.51 ± 0.27°C to 1.69 ± 0.29°C, and at 30°C, it changed from 1.4 ± 0.25°C to 2.18 ± 0.63°C. There was a small decrease in the average Tbr with changes in S-W from W1 to S2 (Fig. 6B). It was difficult to appreciate the change in Tbr with S-W as S2 and PS were drastically reduced (especially at 18°C) after

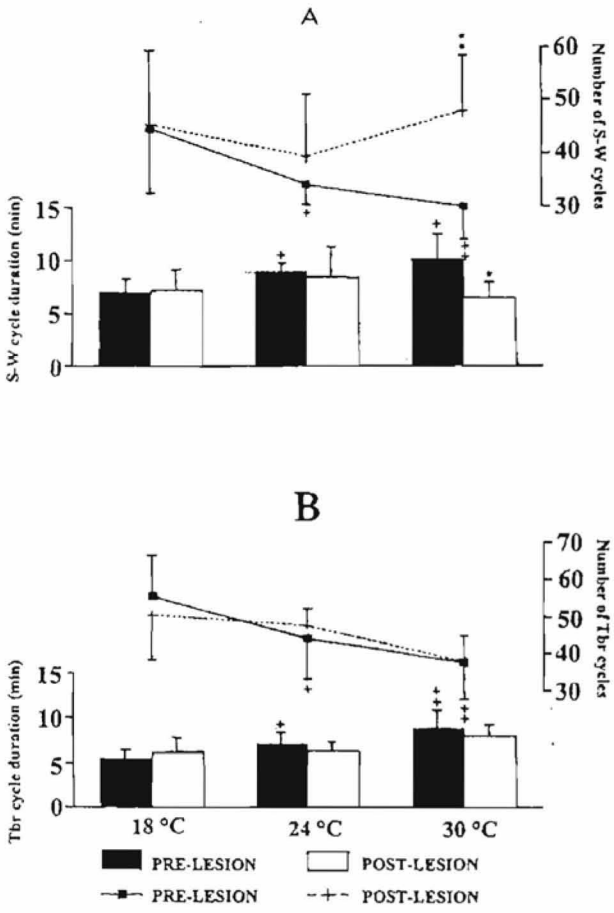

Fig. 5 : Upper figure (A) shows frequency (line) and duration (bar) of S-W cycles before and after the mPOA lesion at 18°C, 24°C and 30°C. Lower figure (B) shows the frequency (line) and duration (bar) of Tbr cycles before and after lesion of the mPOA at 18°C, 24°C and 30°C. *P<0.05, **P<0.01, significance compared to pre-lesion values, ⁺P<0.05, ⁺⁺P<0.01, significance compared to 18°C.

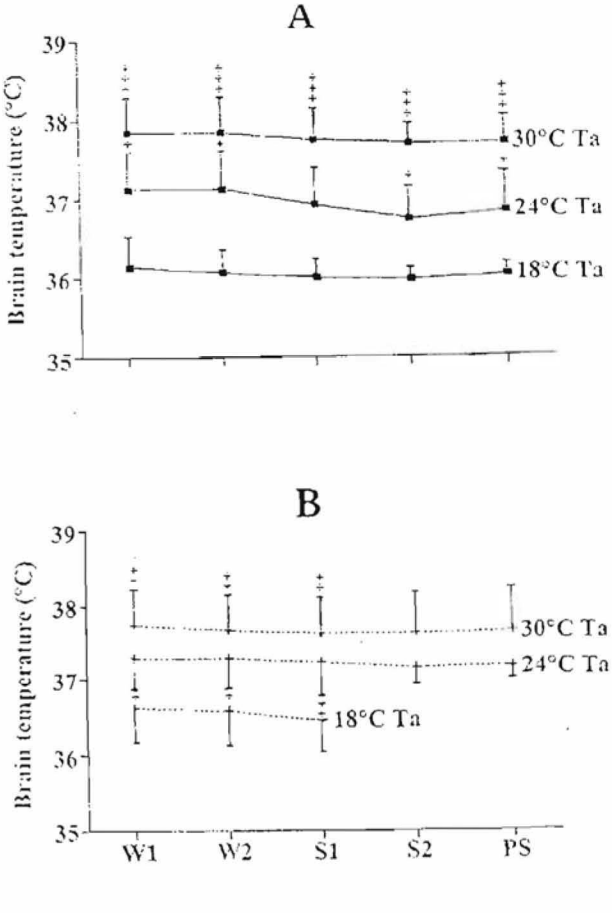

Fig. 6 : Brain temperatures (mean±SD) at different vigilance states before (A) and after (B) lesion of the mPOA at 18°C, 24°C and 30°C. ⁺P<0.05, ⁺⁺P<0.01 and ⁺⁺⁺P<0.001, significance compared to 18°C. Abbreviations of S-W stages same as Fig. 1.

the lesion (Figs. 2, 6B). Changes in the vigilance state with the change in Tbr were also present in the lesioned rats (Fig. 2).

Histology

There was extensive destruction of neurons in the mPOA in all the rats (Fig. 7). Though there was a variation in the size and extent of the lesion, all the rats had bilateral lesion at the mPOA. The neurons of the mPOA were replaced with glial cells. Though most of the destroyed regions had total loss of neurons, it was often possible to see a small surrounding area where a few neurons were visible in between the glial cells. It was possible to demarcate the boundary of the destroyed area. Though the lesions were primarily

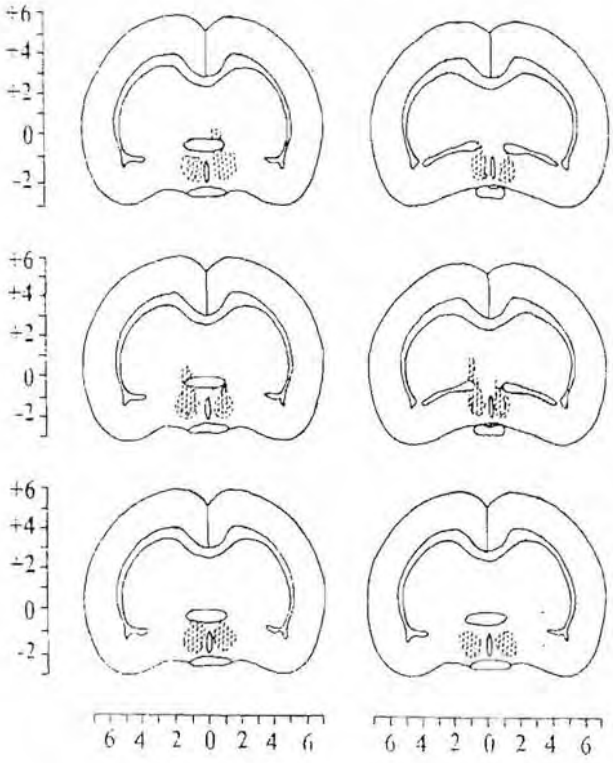

Fig. 7: The NMDA lesion sites in six rats shown diagramatically. Hatched area shows the brain regions with severe and moderate neuronal loss. Lesioned are was drawn with the help of camera lucida. Co-ordinates shown are as per DeGroot atlas.

confined to mPOA, the brain regions along the needle tract were also destroyed in some rats.

DISCUSSION

The study showed that there were changes in Tbr with changes in vigilance states, which were observed even after the mPOA lesion. The increase in average Tbr, produced by an increase in Ta, was more prominent in normal rats. The mPOA lesion produced a decrease in sleep, and increase in Tbr except at 30°C. S-W and Tbr cycle durations were increased and their frequencies decreased at higher Ta in normal rats. After the mPOA lesion, S-W cycle duration was decreased and frequency increased at 30°C. There was no significant change in Tbr cycles at higher Ta in lesioned rats.

Effect of mPOA lesion on Tbr

The increase in Tbr after the mPOA lesion is in agreement with the earlier reports (2, 15, 26). The increase in brain temperature could be partially attributed to an increase in the awake period after the mPOA lesion. Hyperthermia, resulting from the mPOA lesion was taken to indicate a failure in the heat loss mechanism of the POA (27). But recent studies, using neurotoxic lesion of the neurons of the mPOA, have shown that the lesioned rats had the ability to defend the body temperature in a heat stress (10). This may partially explain the lack of change in Tbr in NMDA lesioned rats when they were exposed to 30°C.

Tbr changes with S-W stages in normal and the mPOA lesioned rats

There was a decrease in Tbr as the animal shifted from active wakefulness to deep SWS. A shift from S2 to PS produced an increase in Tbr. Fall in Tbr during SWS and increase in the same during PS is in agreement with the earlier reports (18, 28). This increase in Tbr with PS was attributed to an increase in local metabolic rate, and to changes in cerebral blood flow (29). It has been suggested that the PS acts as a thermoregulatory mechanism during which the brain is selectively heated (30). Down

regulation of Tbr during non-REM sleep gave rise to the hypothesis that the non-REM sleep intensity is a function of the heat load accumulated during prior wakefulness (19). It was proposed that the function of SWS is to cool the brain (4). It was thus suggested that non-REM sleep (or SWS) is a part of the thermoregulatory process that controlled the body and brain temperature. Behavioral state-dependent selective brain cooling may underlie a thermal feedback mechanism differentiating the relative influences of hypothalamic and extra-hypothalamic thermoreceptors on the thermoregulatory system during quiet wakefulness and non-REM sleep (31). When S-W changes are plotted against Tbr change, it was seen that the vigilance change occurred earlier than the Tbr change. So it confirms the earlier contention that the ultradian Tbr change is the result of an alteration in vigilance state. Moreover, this interrelationship was observed even after the mPOA lesion. As the deep stages of sleep were reduced after the mPOA lesion, it was difficult to observe the Tbr changes with S-W alterations in the lesioned rats. But it was still possible to see some alterations in Tbr with S-W changes. So, even if it is accepted that the Tbr alteration during S-W change is an active process, it is likely that the mPOA may not be responsible for the changes in Tbr with alteration in S-W.

Effect of Ta on Tbr and S-W cycles in normal and the mPOA lesioned rats

Higher Tbr observed at higher Ta is in agreement with the earlier reports (18, 32). In rats, the cortical temperature varied even when the Ta was altered within the thermoneutral range (33). Inspite of this alteration, Tbr is regulated within a defended range (7). In normal rats, there was an increase in the duration and a decrease in the frequency of ultradian Tbr cycle with increase in Ta, but the magnitude of the fluctuation was not affected. This also is in agreement with the earlier report which showed that the amplitude and acrophase were not altered by modification of the ambient temperature (20°C to 25°C, 25°C to 30°C) but each elevation of the ambient temperature produced a rise in the mean internal temperature of the rat (34). Frequency of S-W cycles, on the other hand, decreased with increase in Ta, in normal rats. In other words, a moderately warm ambient temperature, by promoting sleep duration produced a decrease in the number of ultradian sleep-wake cycles. The changes in frequency and duration of S-W and Tbr cycles at different Ta, in normal rats, could indicate that the same servo-control system may be involved in the homeostatic regulation of sleep and temperature. Earlier studies have also suggested a possible interrelationship between the regulations of body temperature and S-W (4, 35, 36). In the mPOA lesioned rats, there was an increase in the frequency of S-W cycles on exposure to higher Ta of 30°C, and a decrease in the duration of these cycles. Though the S-W cycles were altered, the duration of Tbr cycles did not vary much after lesion of the mPOA. So, it may be possible that the mPOA in normal rats interlinks the neuronal circuits involved in regulating Tbr and S-W cycles.

The role of the mPOA in fine tuning the thermoregulation

The magnitude of Tbr variations were generally increased after the mPOA lesion,

though the changes were not statistically significant. It is already reported that, the amplitude of the circadian rhythm of the body temperature was much larger than normal in rats with mPOA lesions (2, 37). One suggested function of the mPOA is to provide fine tuning of the energy balance (9, 38). It could be also involved in the fine tuning of the set point for thermoregulation ie, to prevent large deviations from the normal thermal set point, by promptly activating appropriate thermoregulatory responses. Without the mPOA, these responses would not be as effective as in the normal, and the ultradian and circadian deviations would therefore be much larger. Change in Ta could be a greater challenge for rats with mPOA damage, than for the normal. This is reflected in the much higher. Tbr changes in response to changes in Ta. The delayed thermoregulatory responses of the mPOA damaged rats would have produced the exaggerated temperature fluctuations. The increased amplitude of the Tbr variations after the lesion indicates the possibility that the mPOA thermoregulatory system may oppose rather than defend the ultradian and circadian alterations of body temperature in normal rats. This could also suggest the possibility that the larger deviation in the body temperature may also contribute towards the increase in wakefulness.

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REFERENCES

1. Parmeggiani PL, Agnati LF, Zamboni G, Cianci T. Hypothalamic temperature during the sleep cycle at different ambient temperatures. *Electroenceph Clin Neurophysiol* 1975; 38: 589–596.
2. Satinoff E, Liran J, Clapman R. Aberrations of circadian body temperature rhythms in rats with medial preoptic lesions. *Am J Physiol* 1982; 242: R352–R357.
3. Obal F Jr, Tobler I, Borbley AA. Effect of ambient temperature on 24 h sleep-wake cycle in normal and capsaician treated rats. *Physiol Behav* 1983; 30: 425–430.
4. McGinty D, Szymusiak R. Keeping cool a hypothesis about the mechanisms and functions of slow-wave sleep. *Trends Neurosci* 1990; 13: 480–487.
5. Finn DA, Bejanian M., Jones BL, Babbini M, Syapin PJ, Alkana RL. The relationship between brain temperature during intoxication and ethanol sensitivity in LS and SS mice. *Alcohol Clin Exp Res* 1991; 15: 717–724.
6. Nauta WJH. Hypothalamic regulation of sleep in rats-an experimental study. *J Neurophysiol* 1946; 9: 285–316.
7. Satinoff E. Disturbances in circadian body temperature rhythms in rats with hypothalamic damage. *J Therm Biol* 1983; 8: 149–157.
8. John J, Kumar VM., Gopinath G, Ramesh V, Mallick HN. Changes in sleep-wakefulness after kainic acid lesion of the preoptic area in rats. *Jpn J Physiol* 1994; 44: 231–242.
9. John J, Kumar VM. Effect of NMDA lesion of the medial preoptic neurons on sleep and other functions. *Sleep* 1998; 21: 585–597.
10. Kumar VM, Khan NA. Role of the preoptic neurons in thermoregulation in rats. *Arch Clin Exp Med* 1998; 7: 24–27.
11. Thomas TC, Kumar VM. Role of medial preoptic neurons in the regulation of sleep and brain temperature under different ambient temperatures. *Sleep Research Online* 1999; 2(s): 630.
12. Roberts WW, Robinson TCL. Relaxation and sleep induced by the preoptic region and anterior hypothalamus in cats. *Exp Neurol* 1969; 25: 282–294.
13. Alam MN, McGinty D, Szymusiak R. Preoptic/anterior hypothalamic neurons: Thermosensitivity

in wakefulness and non rapid eye movement sleep. *Brain Res* 1996; 29: 76–82.

14. Morrisstte RN, Heller HC. Effects of temperature on sleep in the developing rat. *Am J Physiol* 1998; 274: 1087–1093.
15. Szymusiak R, Danowski J, McGinty D. Exposure to heat restores sleep in cats with preoptic/anterior hypothalamic cell loss. *Brain Res* 1991; 541: 134–138.
16. Szymusiak R, Satinoff E. Ambient temperature dependence of sleep disturbances produced by basal forebrain damage in rats. *Brain Res Bull* 1984; 12: 295–305.
17. Thomas TC, Kumar VM. Effects of ambient temperature on sleep-wakefulness in normal and preoptic area lesioned rats. *Sleep Research Online* 2000; 3: 141–145.
18. Alfoldi P, Rubicsek G, Cserni G, Obal FJr. Brain and core temperature and peripheral vasomotion during sleep and wakefulness at various ambient temperatures in the rat. *Pflugers Arch* 1990; 417: 336–341.
19. Horne JA, Shackell BS. Slow-wave sleep elevations after body heating. Proximity to sleep and effects of Aspirin. *Sleep* 1987; 10: 383–392.
20. Berger RJ, Philips NH. Comparative aspects of energy metabolism, body temperature and sleep. *Acta Physiol Scand* 1988; 574: 21–27.
21. Morairty S, Szymusiak R, McGinty D. Heat loads evoke delayed enhancement of deep slow wave sleep in rats. *J Sleep Res* 1992; 21: 181.
22. Deboer T. Brain temperature dependent changes in the electroencephalogram power spectrum of humans and animals. *J Sleep Res* 1988; 7: 254–262.
23. Schwartz PJ, Rosenthal NE, Kajimura N, Han L, Turner EH, Bender C, Wehr TA. Ultradian oscillations in cranial thermoregulation and electroencephalic slow-wave activity during sleep are abnormal in humans with annual winter depression. *Brain Res* 2000; 866: 152–167.
24. Ramesh V, Kumar VM. Changes in sleep-wakefulness after 6-hydroxydopamine lesion of the preoptic area. *Neuroscience* 2000; 98: 549–553.
25. DeGroot J. The rat forebrain in stereotaxic co-ordinates. *Trans R Neth Acad Sci* 1959; 52: 1–40.
26. Sallanon M, Denoyer M, Kitalama C, Alibert N, Gay N, Jouvet M. Long lasting insomnia induced by preoptic neuron lesions and its transient reversal by muscimol injection into the posterior hypothalamus in the cat. *Neuroscience* 1989; 32: 669–683.
27. Myers RD. Hypothalamic control of thermoregulation: Neurochemical Mechanisms. In: PJ Morgane and J Panksepp (Eds), Handbook of the hypothalamus 1980; Vol. 3A, Marcel Dekker, Inc., New York, pp.83–181.
28. Palaca JW, Walker JM, Berger RJ. Thermoregulation, metabolism and stages of sleep in cold-exposed men. *J Appl Physiol* 1986; 61: 940–947.
29. Denoyer M., Sallanon M, Buda C, Delhomme G, Dittmar A, Juvet M. The posterior hypothalamus is responsible for the increase of brain temperature during paradoxical sleep. *Exp Brain Res* 1991; 84: 326–334.
30. Wehr T. A brain-warming function for REM sleep. *Neurosci Biobehav Rev* 1992; 16: 379–397.
31. Azzaroni A, Parmeggiani PL. Changes in selective brain cooling across the behavioral states of the ultradian wake-sleep cycle. *Brain Res* 1999; 844: 206–209.
32. Gao BO, Franken P, Tobler I, Borbley AA. Effect of elevated ambient temperature on sleep, EEG spectra and brain temperature in the rat. *Am J Physiol* 1995; 268: R1365–R1373.
33. Poole S, Stephanson JD. Body temperature regulation and thermoneutrality in rats. *Quart J Exp Physiol* 1977; 62: 143–149.
34. Roussel B, Chouvet G, Debilly G. Circadian rhythms of rat internal temperatures and thermal ambience. *Pflugers-Arch* 1976; 365: 183–189.
35. Alam MN, McGinty D, Szymusiak R. Neuronal discharge of preoptic/anterior hypothalamic thermosensitive neurons: Relation to NREM sleep. *Am J Physiol* 1995; 269: 1240–1249.
36. McGinty D, Szymusiak R, Thomson D. Preoptic/anterior hypothalamic warming increases EEG delta frequency activity with non rapid eye movement sleep. *Brain Res* 1994; 667: 273–277.
37. Osborne AR, Refinetti R. Effects of hypothalamic lesions on the body temperature rhythm of the golden hamster. *Neuroreport* 1995; 13: 187–192.
38. Kumar VM. Neuronal regulation of glucose homeostasis. *Indian J Physiol Pharmacol* 1999; 43: 415–424.