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GABA-A receptors in mPOAH simultaneously regulate sleep and body temperature in freely moving rats

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Abstract

Sleep–wakefulness and body temperature are two circadian rhythmic biological phenomena. The role of GABAergic inputs in the medial preoptico-anterior hypothalamus (mPOAH) on simultaneous regulation of those phenomena was investigated in freely moving normally behaving rats. The GABA-A receptors were blocked by microinjecting picrotoxin, and the effects on electrophysiological parameters signifying sleep–wakefulness, rectal temperature and brain temperature were recorded simultaneously. The results suggest that, normally, GABA in the medial preoptic area acts through GABA-A receptor that induces sleep and prevents an excessive rise in body temperature. However, the results do not allow us to comment on the cause and effect relationship, if any, between changes in sleep–wakefulness and body temperature. The changes in brain and rectal temperatures showed a positive correlation, however, the former varied within a narrower range than that of the latter.

Keywords: GABA-A receptor; Medial preoptico-anterior hypothalamic area; Picrotoxin; Sleep–wakefulness and temperature

1. Introduction

The medial preoptico-anterior hypothalamus (mPOAH) regulates at least two circadian rhythmic phenomena viz., sleep–wakefulness and body temperature (Szymusiak, 1995). There are evidences from isolated independent studies that aminergic (Day et al., 1979; Mallick and Alam, 1992; Poole and Stephenson, 1979), cholinergic (Mallick and Joseph, 1997; Poole and Stephenson, 1979) and GABAergic (Ali et al., 1999; Gray et al., 1987; Mendelson et al., 1989; Osborne et al., 1994) inputs in the mPOAH affect both sleep–wakefulness, as well as body temperature. However, since mPOAH modulates both the functions simultaneously, to investigate the temporal and causal relationship between those changes, if any, it was necessary to study the effects of different neurotransmitters simultaneously on those changes. Based on microinjection of agonist of one of the receptors in the presence of antagonist of another, it has been proposed that while adrenergic inputs in the mPOAH might affect either sleep, wakefulness or body temperature independently (Mallick and Alam, 1992), the cholinergic inputs modulated those functions simultaneously (Mallick and Joseph, 1997). Subsequently, it has also been reported that the aminergic and the cholinergic inputs in the mPOAH interact for optimum regulation of sleep–wakefulness and thermoregulation (Mallick and Joseph, 1998).

The role of GABAergic inputs in the mPOAH simultaneously on sleep–wakefulness and body temperature was not known. Since both these phenomena follow circadian rhythm and they may influence each other, the effects on both these functions needed to be studied simultaneously. It was all the more necessary because isolated studies on the role of GABA inputs in the mPOAH on body temperature have reported contradictory results. Some studies reported hypothermia (Clark and Lipton, 1985; Gray et al., 1987; Serrano et al., 1985), while others reported hyperthermia (Drummer and Woolley, 1991; Osborne et al., 1994). Hence, in this study, picrotoxin, a GABA-A antagonist, was microinjected locally into the mPOAH and the effects were simultaneously studied on sleep–wakefulness and body temperature in freely moving normally behaving rats. Additionally, the body temperature was recorded from both the rectum, as well as the brain, so that any dissociated effect on them could also be known.

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2. Method

Male Wistar rats (250–300 g), maintained under 12:12 L/D cycle with food and water ad libitum, were used for the experiments. Under surgical anaesthesia (35 mg/kg ip Nembutal), the rats were prepared for chronic recording of bipolar electroencephalogram (EEG), electrooculogram (EOG) and electromyogram (EMG) as reported earlier (Alam and Mallick, 1990; Mallick and Alam, 1991, 1992). In short, two screw electrodes were bilaterally implanted on the skull for recording EEG and a third one was implanted on the midline to provide animal ground. A pair of flexible insulated wires (except at the tips) were connected in the dorsal cervical neck muscles to record EMG and another pair of wire was used to record EOG from the external canthus. The free ends of all the electrodes were connected to a nine-pin female plug, which, in turn, was fixed to the skull of the animal with dental acrylic. Bilateral chemitrode, made up of 24-gauge stainless-steel tubing (guide cannulae) along with respective blockers, were implanted through drill holes made in the skull at stereotaxic coordinates A −0.3 to −0.8 mm, L 0.6 to 1.2 mm (Paxinos and Watson, 1982) to microinject chemicals into the mPOAH. The chemitrode was fixed on the skull with dental acrylic once its tip reached H 6.0 mm. The injector made from 30-gauge stainless-steel tubing had a stopper arrangement so that it would protrude 2 mm beyond the guide cannula to reach mPOAH. A copper–constantan thermocouple was implanted at an angle so as to record brain temperature near the mPOAH (Fig. 1). The rats were allowed 4–5 days to recover from surgical trauma before recording was started. During this period, the rats were acclimatised to the recording cables connected to their head plugs, recording chamber and the rectal probe.

After recovery, bipolar EEG, EMG and EOG were recorded in three separate channels of a Grass polygraph. The rectal and brain temperatures were recorded every 10 min. The experiments were conducted between 10 AM–7 PM. The same animal served as its own control where recording was conducted without injection in normal condition (baseline), after bilateral saline injection (control) and after bilateral picrotoxin injection (experimental) into the mPOAH. Baseline recording was done on Day 1 followed by control that is recording after saline injection on Day 2. After a gap of 1 day, recording was done on Day 4 after picrotoxin injection into the mPOAH. In control and experimental groups, after normal recording of 1 h, 250 nl of either saline or 0.1% (250 ng in 250 nl) picrotoxin was locally microinjected bilaterally into the mPOAH at the rate of 100 nl/min. The injector was retained in the same position for at least 1 min after injection and then replaced by the blocker. The injection procedure took 7–8 min and no recording could be done during that period. After injection, the same parameters were recorded continuously for 8 h. At the end of the experiment, 250 nl of 2% pontamine sky blue was injected at the same site where saline and picrotoxin were injected. Thereafter, under deep anesthesia, the rat brains were

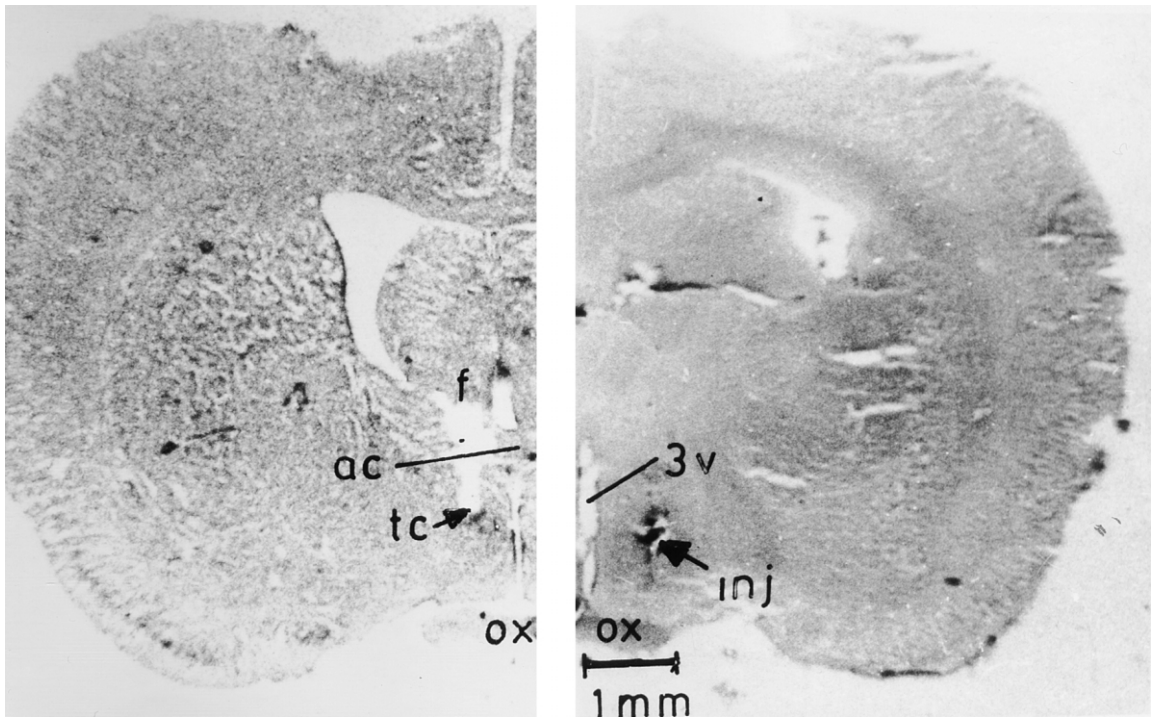

Fig. 1. This figure shows two halves of photomicrographs of the same rat brain through the mPOAH separated by 500 μm. The tip of the thermocouple (tc) is shown in the left half (A–P 0.3 mm) while the injection spot (inj.) is shown in the right half (A–P 0.8 mm) of the sections. Abbreviations of the anatomical terms: ac: anterior commissure; f: fornix; 3v: third ventricle; ox: optic chiasma.

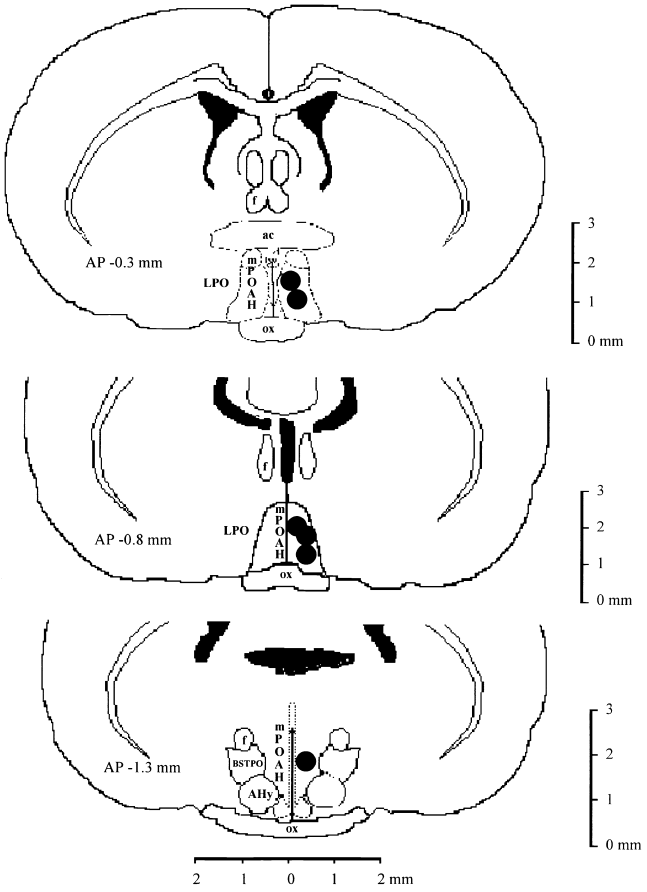

Fig. 2. Reconstruction diagram through medial preoptico-anterior hypothalamic area as per the atlas of Paxinos and Watson (1982) is shown in this figure. The filled circles represent the sites of injection of picrotoxin in the mPOAH. Although the injections were made bilaterally, however, for convenience, the sites of injections are shown on the right half while the abbreviations are marked on the left. Abbreviations: mPOAH: medial preoptico-anterior hypothalamic area; LPO: lateral preoptic area; ac: anterior commissure; f: fornix; ox: optic chiasma; BSTPO: Bed nucleus of stria terminalis preoptic; AH: anterior hypothalamus.

perfused intracardially with saline followed by 10% formalin. The site and spread of injection were confirmed from histological sections by the presence of blue spot (Fig. 1) and the location of each of injection sites has been shown in a reconstruction diagram (Fig. 2). Results from six rats where the blue colour was in mPOAH are presented here. The data from sites where the injections were away from the mPOAH have not been included. This was done to maintain uniformity and also because mPOAH is more effective in maintaining sleep–waking and body temperature as compared to that of lateral POAH (Alam and Mallick, 1990, 1991).

The electrophysiological records were divided into bins of 10 s, and then standard criteria (Mallick and Alam, 1992; Timo-Iaria et al., 1970) were followed to classify them into active wakefulness (AW), quiet wakefulness (QW), slow wave sleep (SWS), deep sleep (DS) and rapid eye movement (REM) sleep. The lengths of time spent by the rats in these stages before and after picrotoxin microinjection were statistically compared to respective values after saline injection in different groups of rats by applying ANOVA available from a statistical package. Similarly, the mean brain and rectal temperatures during pre- and post-picrotoxin injections were compared with that of after saline microinjection and baseline values by using Mann–Whitney test for different groups of rats and Wilcoxon matched-pair signed-rank test for the same group of rats (Alam and Mallick, 1991; Mallick and Alam, 1992).

3. Results

3.1. Effect on sleep and wakefulness

An hourwise analysis showed that saline microinjection into the mPOAH did not significantly affect S and W. However, picrotoxin microinjection (0.1%) significantly increased wakefulness (Fig. 3), i.e. sleep (deep sleep, as well as REM sleep) was significantly reduced. An hourwise analysis showed that total wakefulness remained significantly increased up to the 5th hour, while the increase in

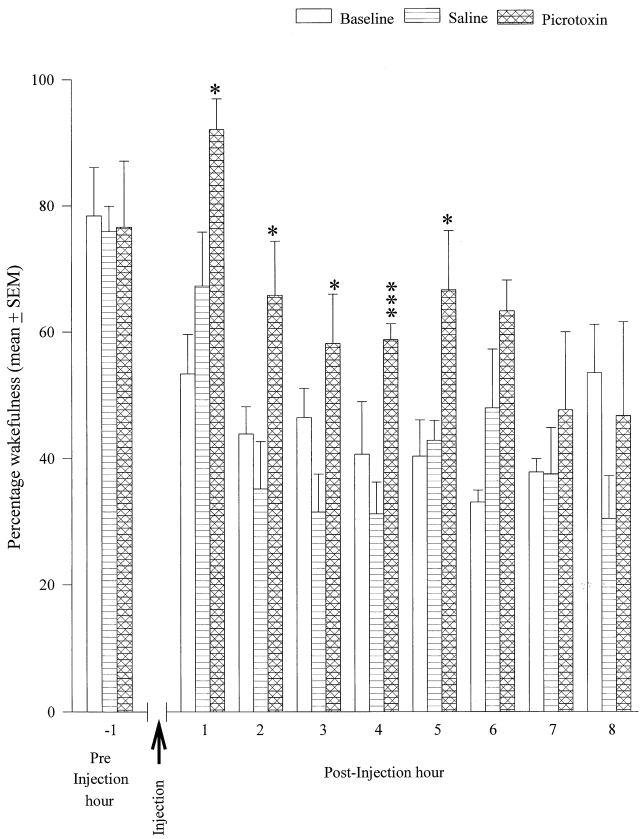

Fig. 3. The percentages (mean ± S.E.M.) of time spent in wakefulness every hour during baseline, after saline and after picrotoxin microinjection into the mPOAH are represented here. Significance levels as compared to saline, * $P<.05$, ** $P<.01$, *** $P<.001$.

Table 1
Mean percentages of time (±S.E.M.) spent in active and quiet wakefulness in baseline, saline-injected and picrotoxin-injected rats

			Postinjection							
		Preinjection (−1 h)	1 h	2 h	3 h	4 h	5 h	6 h	7 h	8 h
Quiet awake	Baseline	48.8±9.5	40.4±5.4	39.8±4.7	43.1±5.1	34.7±8.3	33.7±4.8	26.5±2.5	29.9±2.4	31.5±7.3
	Saline	38.3±2.4	34.3±4.6	29.4±5.3	28.4±5.7	19.8±6.1	35.3±3.4	26.5±5.1	33.1±7.5	23.7±5.0
	Picrotoxin	31.3±12.3	27±5.1	33.3±7.8	42.0±9.2	40.9±7.1	47.9±8.0	48.5±5.1	38.0±9.4	36.3±9.7
Active awake	Baseline	29.5±5.8	12.9±4.4	4.08±1.8	3.3±1.4	6.0±2.6	6.2±4.1	6.4±2.4	7.1±2.9	22.0±6.0
	Saline	37.6±3.6	33.0±6.0	7.6±3.4	3.1±1.3	10.3±4.3	7.6±3.4	21.3±7.4	4.4±1.2	6.8±1.9
	Picrotoxin	33.6±13.0	65.0±9.8**	33.0±15*	16.1±4.1*	18.4±6.3	18.8±10	14.8±5.5	9.9±5.1	10.4±4.3

* Significance as compared to saline. $P<.05$.
** Significance as compared to saline. $P<.01$.

active wakefulness was significant only up to the 3rd hour (Table 1).

3.2. Effect on rectal temperature

The mean (±S.E.M.) baseline rectal temperature was 37.4±0.04°C, and, after saline injection, it was 37.5±0.07°C. Picrotoxin infusion into the mPOAH significantly increased ($P<.001$) the mean rectal temperature to 39.3±0.05°C with a maximum of 40.02±0.2°C, which was recorded for more than 3 h after the injection (Fig. 4). The significant increase in the rectal temperature lasted for more than 6 h postinjection.

3.3. Effect on brain temperature

The mean (±S.E.M.) brain temperature after saline injection into the mPOAH was 38.5±0.03°C, which was not significantly different than that of its mean baseline value of 38.6±0.04°C (Fig. 4). However, after picrotoxin infusion the mean brain temperature significantly ($P<.001$) increased to 39.4±0.08°C (Fig. 4) with a maximum of 39.8±0.07°C, which was recorded 2 h after picrotoxin infusion. Like the rectal temperature, the significant increase in the brain temperature lasted until 6 h postinjection.

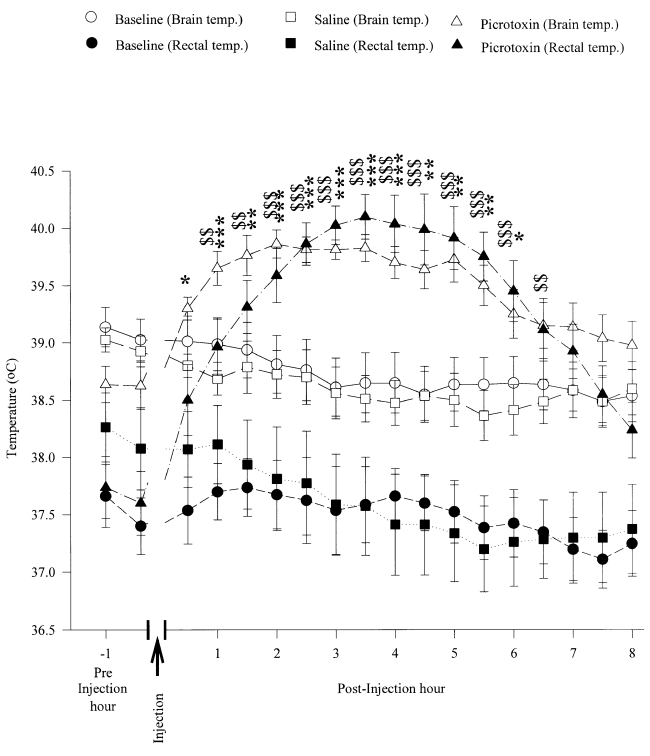

Fig. 4. The mean (±S.E.M.) brain and rectal temperatures every 30 min during baseline, after saline and after picrotoxin microinjections into the mPOAH are shown in this figure. Significance level after picrotoxin microinjection has been compared to that of saline. *: Significance level of brain temperature; $: significance level of rectal temperature. *, $ — $P<.05$; **, $$ — $P<.01$ and ***, $$$ — $P<.001$.

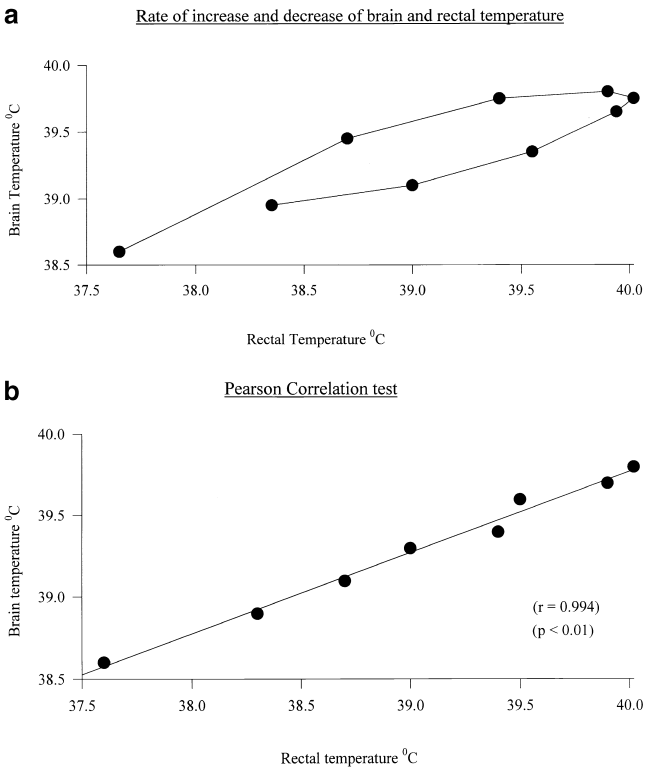

Fig. 5. (a) The brain temperature has been plotted against the rectal temperature after picrotoxin microinjection into the mPOAH. (b) Graphical representation of Pearson correlation test between brain and rectal temperatures after picrotoxin microinjection into the mPOAH is shown here. It shows that there was a significant positive correlation between those temperatures.

3.4. Correlation of brain and rectal temperatures

Comparison of the brain and rectal temperature in baseline and saline groups of rats showed that the brain temperature was always higher than that of the rectal temperature (Fig. 4). However, in the picrotoxin-infused groups, both the brain and the rectal temperatures were elevated and reached a comparable level. The rate of increase in the rectal temperature was higher than that of the rate of increase in the brain temperature (Fig. 5a). At the end of second hour postinjection, the rectal temperature was higher than that of the brain temperature, and it was maintained for the next 3 h (Fig. 4). Pearson correlation test showed that a linear correlation existed between the brain and the rectal temperature. It was observed that picrotoxin-induced increase in brain temperature correlated significantly positively (r=.994, P<.01) with picrotoxin-induced increase in the rectal temperature (Fig. 5b).

4. Discussion

It was observed in this study that picrotoxin microinjection into the mPOAH increased wakefulness, as well as body temperature. Since both the functions are known to be modulated by the mPOAH, it is reasonable that they were significantly affected. However, the effects were not due to physical interference or permanent damage to the mPOAH because the effects were reversible which lasted for about 5–6 h postinjection and then returned to baseline. On the other hand, the effects were specific to picrotoxin, because saline injection into the same site did not significantly affect either of those parameters. It may be clarified that saline affected S–W and T_{rec} nonspecifically for approximately half an hour as has been reported in a series of studies from this laboratory (Alam and Mallick, 1990, 1991; Mallick and Alam, 1992; Mallick and Joseph, 1997, 1998). However, in this study, when compared at 1 h, the effects were possibly neutralised and the difference did not reach the level of statistical significance. Nevertheless, in some studies (Mendelson and Martin, 1992), the nonspecific effect after microinjection in the preoptic area lasted for a longer duration. Since these were nonspecific effects (as the other authors also suggested), it is difficult to attribute any specific reason for it. Picrotoxin, a GABA-A blocker, significantly affected both sleep–wakefulness and body temperature. Hence, it is likely that GABA in the mPOAH is normally acting through the GABA-A receptors for spontaneous regulation of those functions. It may be argued that since picrotoxin is a chloride channel blocker, it could also block any other chloride channel, e.g. those sensitive to glycine (Karlsson et al., 1997). A more specific GABA receptor channel agonist or antagonist may be used for confirmation. However, it has been reported that GABA but not glycine in the preoptic area affected thermoregulation (Yakimova and Ovtcharov, 1989). Therefore, it is likely that, in this study, picrotoxin blocked GABA-mediated chloride channel. Although microinjection with remote control pump has been established, manual injection was preferred in this study so that specific and nonspecific results from previous independent studies where different agonists and antagonists of several neurotransmitters including that of GABA were manually injected could be compared.

The effects on either sleep–wakefulness or body temperature may be supported by earlier independent isolated reports where it has been shown that GABAergic mechanism in the mPOAH may affect sleep–wakefulness (Ali et al., 1999; Mendelson et al., 1989) and body temperature (Osborne et al., 1994). Intraperitoneal administration of muscimol, a GABA-A receptor agonist, in the rats induced a decrease in wakefulness and an increase in sleep (Lancel, 1999). A comparable finding was also observed in humans where a single oral dose of Gaboxadol (THIP), a partial GABA-A receptor agonist, was found to significantly increase sleep (Faulhaber et al., 1997). Based on the results of this study, it may be said that the effect of GABA in those studies might have been mediated through mPOAH. Microinjection of picrotoxin into the mPOAH is effectively similar to that of a reduction in the level of GABA. This view may be supported by the fact that the GABA level was found to decrease in the microdialysed samples collected from the septal region of basal forebrain during wakefulness in freely moving normally behaving cats (Mallick et al., 1997). Thus, it may be said that GABA in mPOAH is normally active to induce sleep and to reduce excessive activity.

Picrotoxin not only increased wakefulness but also induced hyperthermia. Central and systemic application of GABA and GABA agonists caused a fall in core temperature, while antagonists induced hyperthermia (Clark and Lipton, 1985; Serrano et al., 1985). Therefore, it may be said that the effects of systemic application of GABA agonist and antagonist might have been mediated through the mPOAH. It has been reported that muscimol, a GABA-A agonist, decreased the tonic activity of a majority of warm sensitive neurons in the mPOAH in contrast to bicuculline, a GABA-A antagonist (Yakimova et al., 1996). In another recent study, it has been shown that synaptic transmission through Ca-independent release of neurotransmitter on the warm sensitive neurons was completely blocked by GABA-A receptor antagonist, which, in turn, might modulate directly or indirectly tonic firing of the warm sensitive neurons (Hori et al., 1999). Based on these reports, the results of this study may be interpreted as that picrotoxin might have blocked the activity of the warm sensitive neurons in the mPOAH resulting in hyperthermia. However, it needs to be confirmed if the thermosensitive neurons in the mPOAH possess GABA-A receptors. Results of our ongoing microiontophoretic experiments support such a possibility (Jha et al., 2001).

Both the brain and the rectal temperatures were increased after picrotoxin injection into the mPOAH. The correlation analysis showed that the rate of increase of brain and rectal temperatures went hand in hand for 2 h. Thereafter, the rate

of increase of rectal temperature was higher than that of the brain temperature. The Pearson correlation test indicated that both brain and rectal temperatures had a tendency to increase simultaneously, however, the brain temperature varied within a relatively narrower range as compared to that of the rectal temperature. This suggests that the brain has a better heat dissipating mechanism, and rightly so considering its sensitive nature. It may also be argued that physiologically the brain may not be capable of withstanding a wider variation in temperature, however, it has the ability to redistribute the heat to peripheral parts of the body. A rapid decrease in brain tissue pH at higher temperature (Katsumura et al., 1995) may also be an underlying possible mechanism for a better heat dissipating ability of the brain.

After picrotoxin microinjection into the mPOAH, the wakefulness and the hyperthermia went hand in hand, which lasted for 5 and 6 h, respectively. The duration of effect was comparable to our previous results of picrotoxin microinjection in different regions of the brain under similar conditions (Ali et al., 1999; Kaur et al., 1997). The wakefulness lasted longer than that of active movement suggesting that neither wakefulness nor hyperthermia was due to increased movement or related muscular activity. The changes in wakefulness and increased body temperature were temporally correlated. The mPOAH might have either influenced both the functions simultaneously or the primary effect was on one of the functions, which, in turn, affected the other function. Both these phenomena may be supported by previous reports. It has been reported that although norepinephrine in the mPOAH might independently modulate sleep–wakefulness and body temperature (Mallick and Alam, 1992), acetylcholine did not (Mallick and Joseph, 1997). In addition, the body temperature rises during wakefulness and decreases during sleep (McGinty and Szymusiak, 1990), while increased body temperature (or warming) induced sleep (Nakao et al., 1995; Roberts and Robinson, 1969) and a decreased body temperature (or cooling) induced wakefulness (Szymusiak and Satinoff, 1984). Therefore, although the results of this study showed that picrotoxin simultaneously modulated sleep–wakefulness and body temperature, it could not be established if there was any cause and effect relationship between these changes.

The injection of picrotoxin induced wakefulness and hyperthermia for a comparable length of time. This suggests either or both the following two possibilities. First, that GABA-A receptors are present on both sleep–wake-related neurons, as well as on temperature-sensitive neurons, and, second, that GABA-A receptors are present on neurons related to either sleep–wakefulness or thermoregulation so as to affect either of the functions, however, since, sleep–wakefulness and thermoregulation are known to influence each other, both the functions were affected. There are evidences to show that in the mPOAH, some of the sleep-related neurons are GABAergic (Gallopin et al., 2000; Szymusiak, 1995), and in vivo (Jha et al., 2001), as well as in vitro (Yakimova et al., 1996), studies have shown that temperature sensitive neurons are GABAceptive. The mPOAH may receive GABAergic inputs from distant sites (Szymusiak, 1995) or from local interneurons (Tappaz and Brownstein, 1977). Since picrotoxin is an antagonist of GABA-A receptor and GABA is an inhibitory neurotransmitter, it may be interpreted that, normally, GABA is active in the mPOAH to keep those functions inhibited or at a low level so that when the GABA-A receptors were blocked opposite responses were expressed. It may also be said that, normally, GABA in the mPOAH prevents the subjects to go to excessive wakefulness (or excitable state) and associated hyperthermic condition or vice versa.

Acknowledgments

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