PROSTAGLANDINS LEUKOTRIENES AND ESSENTIAL FATTY ACIDS

Prostaglandins Leukotrienes and Essential Fatty Acids (1994) 51, 87-93

Effects of Prostaglandin D_2, Lipoxins and Leukotrienes on Sleep and Brain Temperature of Rats

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ABSTRACT. **Prostaglandin (PG) D_2 and four lipoxygenase-derived eicosanoids [lipoxins (LX) A_4 and B_4, and leukotrienes (LT) C_4 and D_4] were examined for their effects on sleep and brain temperature in freely-behaving rats. In the first series of experiments, PGD_2 was infused into the third ventricle at four different locations between 23:00 and 05:00. In a location apposed to the medial preoptic area (MPO), PGD_2 at doses 1, 10 and 100 pmol/min, increased the slow wave sleep (SWS) by 23% ($p \leq 0.01$), 35% ($p \leq 0.05$) and 44% ($p \leq 0.01$), respectively, during the infusion period. In the second series of experiments, LXs and LTs were infused at the location apposed to MPO. Significant increases in SWS were detected with LXA_4 at 100 pmol/min (14%, $p \leq 0.05$), LXB_4 at 100 pmol/min (20%, $p \leq 0.05$), and LTD_4 at 10 pmol/min (17%, $p \leq 0.05$). An increase in paradioxical sleep (PS) was produced by PGD_2 at 1 and 10 pmol/min infusion ($p \leq 0.05$), but not by any of the lipoxygenase-derived eicosanoids examined. PGD_2 also elevated the mean brain temperature during infusion by 0.2°C and 0.9°C at infusion doses 10 and 100 pmol/min, respectively. But PGD_2 infusion at 1 pmol/min did not elevate the brain temperature. LXs (excluding LXB_4 at 100 pmol/min) and LTs did not alter the brain temperature significantly at the tested doses. We conclude that PGD_2 is the most effective sleep promoter among the eicosanoids examined so far.**

INTRODUCTION

The brain of many mammals, including humans, actively synthesizes prostaglandin (PG) D_2 (1–3). Past studies (4–6) have shown that continuous infusion of PGD_2 into the third cerebral ventricle of rats during nocturnal hours increased the slow wave sleep (SWS) and paradoxical sleep (PS). Similarly, continuous infusion of PGD_2 into the lateral cerebral ventricle of monkeys during the diurnal period induced a sleep pattern similar to physiological night sleep (7). Among the other cyclooxygenase-derived prostanoids examined for sleep promotion in monkeys, only PGD_3 appeared to be somnogenic, though to a milder degree in comparison to PGD_2; but, PGD_1, $PGF_{2\alpha}$ and PGE_2 were ineffective in promoting sleep (8).

Lipoxins (LXs) and leukotrienes (LTs) are eicosanoids formed via the lipoxygenase pathway (9, 10). During the last decade, the presence of LTs (11–16) and LXs (17) in the brain of mammals has been reported. Though the physiological roles of LTs and LXs in the brain in vivo have not been clarified (18), at picomolar concentrations LTC_4 relased luteining hormone from dispersed rat anterior pituitary cells (19). LTC_4 also elicits a prolonged excitation of cerebellar Purkinje neurons of rats (20). Pathological conditions such as cerebral ischemia cause elevation in the amounts of LTs in gerbils (21) and humans (11). Furthermore, Genis et al (22) recently reported that human immunodeficiency virus-infected monocytes cocultured with human glia released increased amounts of LXA_4 and other lipoxygenase-derived eicosanoids such as LTB_4 and LTD_4.

The objective of this study was 3-fold; (A) to identify the location in the third cerebral ventricle where PGD_2 promotes sleep most efficiently, (B) to determine whether eicosanoids such as LXs and LTs also possess sleep promoting activity at the same location, and (C) to evaluate the effect of infusions of these eicosanoids on the brain temperature. Though one recent report (23) had questioned the sleep promoting effect of PGD_2 in rabbits, we demonstrate that PGD_2 increased sleep markedly and dose-dependently during the nocturnal hours when continuously infused at a location apposed to the

Date received 8 December 1993
Date accepted 7 February 1994

medial preoptic area (MPO) in freely-behaving rats. While LXA_4, LXB_4 and LTD_4 also increased the SWS when infused at the same location, the dose-response profiles and the magnitude of the increase in SWS reveal that PGD_2 is still the most effective sleep-promoting eicosanoid in rats. Preliminary results of this study have already been published in an abstract (24).

MATERIALS AND METHODS

Animals

Male rats of the Sprague-Dawley strain, weighing between 300–350 g were used in these experiments. The animals were housed prior to experimentation in individual cages set in a sound-proof chamber at an ambient temperature of 25°C and 60% relative humidity. The chamber was maintained on a 12 h light (08:00–20:00)/ dark (20:00–08:00) cycle. Food and water were supplied ad libitum. Rats anesthetized with intraperitoneal injections of pentobarbital sodium (50 mg/kg body wt) underwent surgery for insertion of a stainless steel cannula for infusion of eicosanoids, and electrodes for electroencephalogram and electromyogram as described previously (25, 26). A thermistor probe (o.d., 0.75 mm, Technol Seven, Yokohama) to monitor brain temperature was also inserted into the right cerebral hemisphere through a hole bored in the skull and positioned to allow the sensor portion to penetrate approximately 2 mm into the cortex.

Four locations chosen for placing the cannula inside the third cerebral ventricle are shown in Figure 1. These selected locations, spread over the areas of von Economo's conception (27, 28) of the locus of the 'Schlafsteuerungszentrum' (sleep steering center), were as follows:

location 1: apposed to the MPO (AP –0.8, ML 1.4, DV 8.2, angle 10°)

location 2: apposed to the region above MPO (AP –0.8, ML 1.6, DV 6.2, angle 15°)

location 3: apposed to the posterior part of anterior hypothalamic area (AHP) (AP –2.1, ML 1.5, DV 8.6, angle 10°)

location 4: apposed to the region near the aqueduct of Sylvius (AP –4.8, ML 2.0, DV 6.0, angle 20°).

All coordinates, adopted from the atlas of Paxinos and Watson (29), represent mm adjustments with bregma as the reference point (AP and ML) and below the dural surface (DV). The angle refers to the degree between the entry plane of the cannula into the brain and the mid-sagittal plane of the skull. Each rat was only used in one experimental session in which the effect of a single dose of one eicosanoid was assessed. For confirmatory purposes, each infusion dose of every eicosanoid was tested in several experimental sessions.

Experimental procedure

Following the surgery, rats were allowed a minimum 10 day recovery period and then placed in one of the experimental chambers of the specially designed in vivo bioassay system, described previously (26). A minimum of 72 h acclimation period was allowed inside the experimental chambers, during which sterile saline was continuously infused into the third ventricle of the rat. Since each rat served as its own control, following the 72 h acclimation period, baseline recordings were taken, while saline was being continuously infused. On the

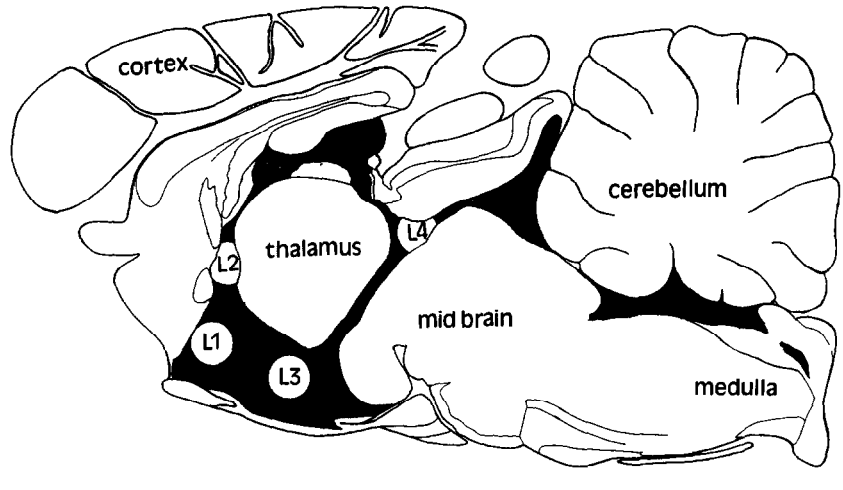

Fig. 1 Schematic sagittal section of rat brain showing the infusion locations. Location of the infusion cannula in the third ventricle, based on the stereotaxic coordinates adopted from the atlas of Paxinos and Watson (29) with bregma as the reference point, are shown as follows:
L1 (Location 1); apposed to the medial preoptic area (MPO)
L2 (Location 2); apposed to the region above MPO
L3 (Location 3); apposed to the posterior part of anterior hypothalamic area (AHP)
L4 (Location 4); apposed to the region near the aqueduct of Sylvius
D3V: Dorsal third ventricle; Aq: Aqueduct of Sylvius; 4V: Fourth ventricle.

subsequent day, PGD_2 or one of the lipoxygenase-derived eicosanoids was infused at a rate of 1, 10 or 100 pmol/0.2 µl/min for 6 h (23:00–05:00). The sleep-wake activity and brain temperature were monitored in the rat for at least a 72 h period (baseline 24 h, experiment 24 h and recovery 24 h). After an experiment, rats were killed with an overdose of pentobarbital sodium. To facilitate the verification of the site of infusion, pontamine sky blue dye solution (0.5% w/v) was injected in microquantity via the cannula. The excised brains were fixed in 10% formalin solution and the track of the cannula was checked with the aid of the atlas (29).

Chemicals

PGD_2, supplied in a crystalline form, was a gift from Ono Pharmaceutical Co. (Osaka, Japan). The stock solution of PGD_2 was made in 99.5% ethanol. LXA_4 and LXB_4, supplied in ethanol, were purchased from Cayman Chemical Co. (Ann Arbor, Michigan, USA). LTC_4 and LTD_4, supplied in methanol: water (70:30), were obtained from Cascade Biochem Ltd (Reading, Berkshire, England). Just before use, stock solutions of prostanoids were dried with a stream of N_2 gas and working solutions were prepared in pyrogen-free sterile saline.

Analysis of data

The sleep-wake activity was measured by visual scoring of the periods of wakefulness, SWS and PS in the generated polygraph recordings by two researchers independently. The minimal scoring interval was set at 15 s of recording time. Deviations in brain temperature from the baseline during the infusion period of eicosanoids are given as the temperature change (ΔT). Data are expressed as the mean ± SEM and were statistically analyzed by the paired t-test.

RESULTS

The rats continuously infused with PGD_2 at 1, 10 and 100 pmol/min for 6 h between 23:00 and 05:00 at a location apposed to the MPO (location 1) showed a marked and dose-dependent increase in the amount of SWS during the infusion period (Table 1). At this location, PGD_2 at doses 1, 10 and 100 pmol/min, increased SWS by 23% ($p \leq 0.01$), 35% ($p \leq 0.05$) and 44% ($p \leq 0.01$), respectively. The PS increase due to PGD_2 infusion was also significant at 1 and 10 pmol/min. In the circadian sleep profile of the rats infused with PGD_2 at 100 pmol/min in location 1 (Fig. 2, panel A), hourly amounts of SWS were above the baseline level throughout the PGD_2-infusion period and this increment was maintained until 1 h after the cessation of the infusion. A significant increase occurred 2 h after the commencement of infusion. When PGD_2 was infused at the rate of 100 pmol/min in location 2 (approximately 2 mm upstream towards the dorsal third ventricle and lateral ventricle from location 1), and location 3, the somnogenic response became weakened (Fig. 2, panels B and C). No sleep promoting effect was noticed when PGD_2 was infused at location 4 (Fig. 2, panel D). Furthermore, administration of PGD_2 at 1 pmol/min (n = 18) and 10 pmol/min (n = 12) in locations 2 and 3 did not elicit any significant increase in either SWS or PS (data not shown).

Table 1 shows the effect on sleep due to infusion of LXA_4, LXB_4, LTC_4 and LTD_4 at location 1. At 100 pmol/min infusion, both LXA_4 and LXB_4 increased SWS by 14% ($p \leq 0.05$) and 20% ($p \leq 0.05$) respectively. However, infusion of LXs at rates 1 pmol/min and 10 pmol/min did not result in any significant increase in either SWS or PS. Of the LTs examined, LTD_4 infusion at 10 pmol/min at location 1 also increased SWS by 17% ($p \leq 0.05$), though this increase in SWS was not confirmed at 100 pmol/min infusion rate. But, LTC_4 failed to produce significant changes in

Table 1 Effects of infused eicosanoid on sleep promotion in rats

Infused eicosanoid	Infusion rate (pmol/min)	n	Amount of SWS (min) (B)	(E)	mean % increase in SWS	Amount of PS (min) (B)	(E)	mean % increase in PS
PGD_2	1	5	98 ± 5	121 ± 8**	23	15 ± 3	24 ± 4*	63
	10	6	89 ± 8	120 ± 8*	35	19 ± 4	31 ± 5*	63
	100	7	92 ± 10	132 ± 8**	44	12 ± 2	17 ± 2	42
LXA_4	1	8	82 ± 7	91 ± 10	11	14 ± 3	16 ± 2	14
	10	7	90 ± 10	91 ± 8	1	10 ± 2	13 ± 2	30
	100	8	95 ± 7	108 ± 9*	14	12 ± 2	14 ± 3	17
LXB_4	1	3	83 ± 4	95 ± 4	14	17 ± 4	19 ± 4	12
	10	4	97 ± 9	101 ± 16	4	20 ± 3	20 ± 3	0
	100	7	94 ± 6	113 ± 7*	20	16 ± 5	20 ± 3	25
LTC_4	10	5	97 ± 13	107 ± 5	10	25 ± 2	25 ± 4	0
	100	3	79 ± 15	84 ± 3	6	7 ± 4	8 ± 3	14
LTD_4	10	6	84 ± 8	98 ± 7*	17	18 ± 5	22 ± 4	22
	100	6	100 ± 6	96 ± 7	0	19 ± 5	14 ± 4	0

SWS and PS values are expressed as cumulative mean ± SEM (min) during the 6 h infusion period (23:00–05:00) at location apposed to the medial preoptic area (location 1).

(B), baseline value; (E), experimental value. *, $p \leq 0.05$; **, $p \leq 0.01$ (significant differences from corresponding baseline values, by paired t-test).

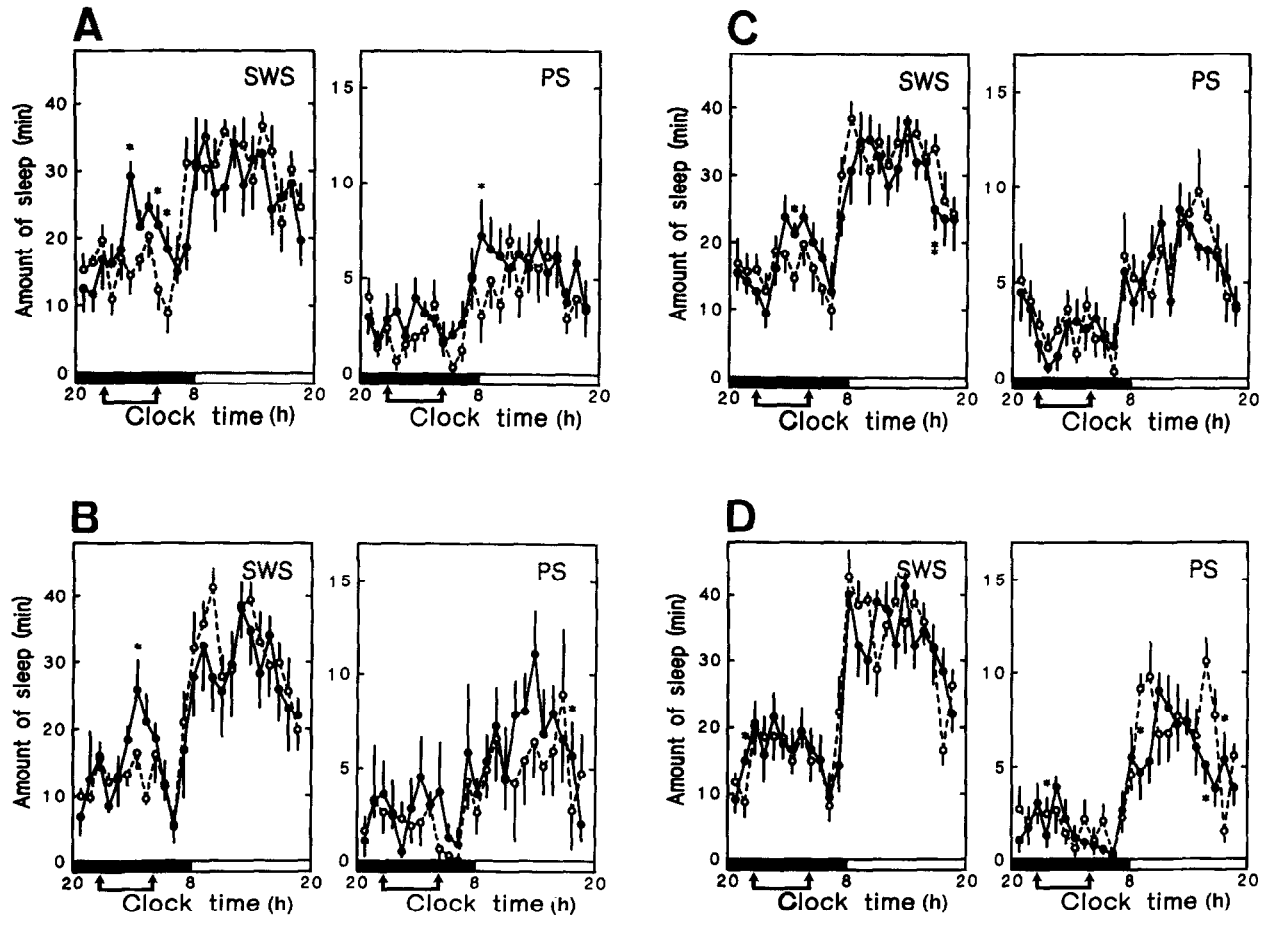

Fig. 2 Hourly amounts of SWS and PS, due to PGD_2 infusion (100 pmol/0.2 µl/min) at four locations in the third ventricle. Details for location 1–4 are described in Materials and Methods, and shown in Figure 1. (A) Location 1 (n = 7); (B) Location 2 (n = 4); (C) Location 3 (n = 7); and (D) Location 4 (n = 6). ○, Baseline day, sterile saline was continuously infused. ●, Experimental day, PGD_2 was infused for 6 h (23:00–05:00), shown by the arrows under the abscissa. Before and after the infusion of PGD_2, saline was continously infused. Vertical bars represent SEM *, $p \leq 0.05$, **, $p \leq 0.01$ (by paired t-test).

the amounts of SWS and PS at either 1- pmol/min or 100 pmol/min infusion doses.

Comparison of the somnogenic responses produced by PGD_2, LXA_4 and LXB_4 in terms of sleep parameters, viz, the number and duration of SWS episodes was also made in rats which showed a significant increase in SWS. When PGD_2 was infused at location 1 at 100 pmol/min, SWS promotion during the infusion period was observed with an increased number of SWS episodes (88 ± 5 for PGD_2 vs 73 ± 7 for saline, mean ± SEM; n = 5; $p \leq 0.05$) and a prolonged duration of SWS episodes (92 ± 7 s for PGD_2 vs 76 ± 5 s for saline; mean ± SEM; n = 5; $p \leq 0.05$). However the increase in SWS produced by LXA_4 infusion at 100 pmol/min in location 1 was accompanied only by prolonged duration of SWS episodes (70 ± 9 s for LXA_4 and 62 ± 8 s for saline) without any change (from the baseline) in the number of episodes. The changes in the number and duration of SWS episodes were not clear-cut for the SWS increase caused by LXB_4 infusion at 100 pmol/min to location 1.

The changes in brain temperature due to infusion of eicosanoids are presented in Table 2. In location 1, PGD_2 elevated the mean brain temperature during infusion by 0.2°C ($p \leq 0.05$) and 0.9°C ($p \leq 0.01$) at infusion doses of 10 and 100 pmol/min, respectively. The dose-response profile observed for the brain temperature response was also similar to that of increase in SWS. However, PGD_2 infusion at 1 pmol/min in location 1 did not alter the brain temperature, though it significantly increased the amount of SWS. While PGD_2 infusion in location 2 at 100 pmol/min elevated the brain temperature by 0.8°C ($p \leq 0.05$), infusions of PGD_2 in locations 3 and 4 at the same dose did not show marked responses. Among the lipoxygenase derived eicosanoids studied, though LXB_4 at 100 pmol/min in location 1 elevated the brain temperature by 0.4°C ($p \leq 0.01$), LXA_4 infusion at 100 pmol/min in location 1 did not alter the brain temperature significantly. Also, infusions of LTC_4 or LTD_4 at 100 pmol/min in location 1 did not bring any noticeable variation in the brain temperature of the rats.

DISCUSSION

Among the four locations of the third cerebral ventricle examined in this study, the location apposed to MPO appeared to be the most effective in promoting sleep,

Table 2 Effects of infused eicosanoid on brain temperature

Compound	Infusion location in third ventricle	Infusion dose (pmol/min)	n	Mean T_{br} (°C) Baseline	Expt	ΔT (°C)
PGD_2	L1	1	7	38.4 ± 0.1	38.3 ± 0.1	[–0.1]
		10	5	38.2 ± 0.1	38.4 ± 0.1*	0.2
		100	6	37.9 ± 0.7	38.8 ± 0.2**	0.9
PGD_2	L2	1	5	38.1 ± 0.2	38.2 ± 0.2	0.1
		10	8	38.1 ± 0.1	38.5 ± 0.2	0.4
		100	4	38.3 ± 0.1	39.1 ± 0.3*	0.8
PGD_2	L3	1	8	38.4 ± 0.1	38.4 ± 0.1	0
		10	4	38.1 ± 0.1	38.1 ± 0.1	0
		100	5	38.1 ± 0.1	38.6 ± 0.3	0.5
PGD_2	L4	100	5	38.3 ± 0.2	38.5 ± 0.2	0.2
LXA_4	L1	1	7	38.3 ± 0.1	38.3 ± 0.2	0
		10	2	38.1	38.1	0
		100	7	38.0 ± 0.4	38.1 ± 0.4	0.1
LXB_4	L1	1	3	37.4 ± 0.5	37.4 ± 0.4	0
		10	4	37.5 ± 0.4	37.6 ± 0.3	0.1
		100	7	38.1 ± 0.1	38.5 ± 0.1**	0.4
LTC_4	L1	100	2	38.1	38.3	0.2
LTD_4	L1	100	4	38.1 ± 0.1	38.3 ± 0.1	0.2

Brain temperature (T_{br}) values are expressed as mean ± SEM during the 6 h infusion period (23:00–05:00) of the eicosanoid. Infusion locations are identified in Figure 1. *, $p \leq 0.05$; **, $p \leq 0.01$ (significant differences from corresponding baseline values, by paired t-test).

when PGD_2 was infused. Infusion of PGD_2 in the other locations, especially locations 3 and 4, situated in the direction downstream of the flow of cerebrospinal fluid, resulted in a noticeable decrease in the somnogenic response. These data indicate that PGD_2 exhibits its sleep promoting property by acting in the rostral region surrounding the ventricular system of the brain, rather than in the caudal regions.

Previously, Ueno et al (4) had reported a 26–33% increase in SWS and 56–78% increase in PS, When PGD_2 was continuously infused for 10 h (19:00–05:00) at the rates of 0.6–6 pmol/min into the third ventricle of rats. In the present study, PGD_2 infusion at rates of 1 and 10 pmol/min resulted in a 23–35% increase in SWS from the baseline values. The increase in PS amounted to 63% at both infusion rates of PGD_2 (Table 1). While Ueno et al (4) infused PGD_2 between 19:00 and 05:00 and measured the amounts of sleep during the period between 20:00 and 08:00, in the present study, PGD_2 was infused between 23:00 and 05:00 and amounts of SWS and PS were measured during the same period. Despite the variation in the experimental protocols, similar somnogenic responses obtained in the present study confirming the results reported by Ueno et al (4).

The sleep promoting effects of LXs and LTs were examined by infusing mainly at location 1 for two reasons. First, the maximum increase in SWS and PS due to PGD_2 infusion occurred at this location. Secondly, it is located near the preoptic area, a purported sleep center. In comparison to PGD_2, the overall sleep promoting responses shown by LXs and LTs were characterized by the absence of a definite dose-response relationship and smaller magnitudes of the generated somnogenic responses. However, when infused at 100 pmol/min, LXB_4 significantly increased the amount of SWS at location 1. These results indicate that LXB4 also possesses a SWS-promoting property. LXA_4, like LXB_4, also showed a detectable SWS-promoting property, though it did not significantly alter the brain temperature in comparison to LXB_4.

Little is known about the physiological role of LXs in the brain, if they do possess one. Previously, Busija et al (30) had reported that both LXA_4 and LXB_4 dilate cerebral arterioles of newborn pigs. This observation suggests a possibility of linking the SWS-promoting effect of LXs to dilation of cerebral arterioles. But, both (sleep promoting) PGD_2 and (sleep-suppressing) PGE_2 also dilate pial arterioles in cats (31). Therefore, it is uncertain whether the SWS-increasing effect of LXs is mediated via their actions on the arterioles. Infusion of LTD_4 at 10 pmol/min also increased the SWS though this effect could not be confirmed at 100 pmol/min infusion rate. Thus the effect of LTD_4 on sleep needs further verification, since the exhibited increase in SWS appears relatively weak and variable. The responses obtained with LTC_4 could serve as a negative control in these experiments for the sleep promoting properties of eicosanoids.

The variations in brain temperature were also recorded in combination with the sleep-wake activity in this study. An elevation of brain temperature, not exceeding 1°C, was observed during PGD_2 infusion. A consensus is lacking on the available information related to the variation in body temperature in response to PGD_2 administration into the brain. In 1982, Ueno et al (32) reported that 881 ng (2.5 nmol) of PGD_2, when microinjected into the preoptic area of rats caused a fall in colonic temperature (–0.9°C) after a lapse of 1 h from the sleep promotion caused by PGD_2. However, Siren (33) showed that injection of PGD_2 at 100 ng, 1 mg and 10 mg doses into the right lateral ventricle of rat brain increased the rectal temperature by 0.7 to

1.7°C. Subsequently, Förstermann et al (34, 35) demonstrated that while injection of a bolus dose of 20.0 mg PGD_2 into the ventricle of rats increased the rectal temperature by nearly 1°C, a bolus dose of 2.0 mg PGD_2 decreased the rectal temperature by 0.5°C. According to Matsumura et al (25), microinjection of a bolus dose of 881 ng (2.5 nmol) PGD_2 into the preoptic area resulted in a 0.5°C increase in the rectal temperature. From these results, one can only infer that the effect of PGD_2 administration into the brain on body/brain temperature may vary depending on the administered dose, route and time, as well as the arousal state of the rat. A mild elevation in rectal temperature due to PGD_2 infusion into the third ventricle of cats (36) and lateral ventricle of monkeys (6) have also been reported previously. The data obtained in the present study also agrees with the results of O'Rourke and Rudy (37) reporting an absence of febrile effect due to intracerebroventricular injection of LTC_4 and LTD_4.

The present results, considered together with the findings of previous studies from our group, demonstrate that PGD_2 is the most effective endogenous somnogenic substance in rats among the eicosanoids examined so far. This sleep promoting effect was most efficiently exhibited when PGD_2 was infused into the third ventricle at the location apposed to the preoptic area when compared with the infusion to the locations caudal towards the downstream of the cerebrospinal fluid flow.

Acknowledgements

We thank Tomoko Nakajima and Natsue Seki for their skillful technical assistance and Dr Toshimasa Osaka for critical reading of the manuscript. This study was supported in part by a Grant-in-Aid for Scientific Research and a Grant-in-Aid for Developmental Scientific Research from the Ministry of Education, Science and Culture of Japan, and by a Takeda Science Foundation fellowship to the senior author (SSK).

References

1. Ito S, Narumiya S, Hayaishi O. Prostaglandin D_2: a biochemical perspective. Prostaglandins Leukot Essent Fatty Acid 1989; 37: 219–234.
2. Hyslop S, De Nucci G. Prostaglandin biosynthesis in the microcirculation: Regulation by endothelial and non-endothelial factors. Prostaglandins Leukot Essent Fatty Acid 1993; 49: 723–760.
3. Spatz M, Stanimirovic D, Uematsu S, Roberts II L J, Bembry J, McCarron R M. Prostaglandin D_2 and endothelin-1 induce the production of prostaglandin $F_{2\alpha}$, 9α, 11β-prostaglandin F_2, prostaglandin E_2, and thromboxane in capillary endothelium of human brain. Prostaglandins Leukot Essent Fatty Acid 1993; 49: 789–793.
4. Ueno R, Honda K, Inoue S, Hayaishi O. Prostaglandin D_2, a cerebral sleep inducing substance in rats. Proc Natl Acad Sci USA 1983; 80: 1735–1737.
5. Inoue S, Honda K, Komoda Y, Uchizono K, Ueno R, Hayaishi O. Differential sleep promoting effects of five sleep substances nocturnally infused in unrestrained rats. Proc Natl Acad Sci USA 1984; 81: 6240–6244.
6. Hayaishi O. Molecular mechanisms of sleep-wake regulation: roles of prostaglandin D_2 and E_2. FASEB J 1991; 5: 2575–2581.
7. Onoe H, Ueno R, Fujita I, Nishino H, Oomura Y, Hayaishi O. Prostaglandin D_2, a cerebral sleep-inducing substance in monkeys. Proc Natl Acad Sci USA 1988; 85: 4082–4086.
8. Onoe H, Kim K, Hayaishi O. Prostaglandin D_2 as an endogenous sleep-inducing factor in the mammalian brain. In: Inoue S, Krueger J M, eds. Endogenous sleep factors. Netherlands: Academic Publishing bv, 1990: 69–76.
9. Samuelsson B, Dahlen S E, Lindgren J A, Rouzer C A, Serhan C N. Leukotrienes and lipoxins: structures, biosynthesis and biological effects. Science 1987; 237: 1171–1176.
10. Serhan C N. Lipoxins: Eicosanoids carrying intra- and intercellular messages. J Bioenerg Biomembr 1991; 23: 105–122.
11. Lindgren J A, Hokfelt T, Dahlen S E, Patrono C, Samuelsson B. Leukotrienes in the rat central nervous system. Proc Natl Acad Sci USA 1986; 81: 6212–6216.
12. Miyamoto T, Lindgren J A, Samuelsson B. Isolation and identification of lipoxygenase products from the rat central nervous system. Biochim Biophys Acta 1987; 922: 372–378.
13. Miyamoto T, Lindgren J A, Hokfelt T, Samuelsson B. Regional distribution of leukotriene and monohydroxyeicosatetraenoic acid production in the rat brain. FEBS Lett 1987; 216: 123–127.
14. Coceani F, Bishai I, Lees J, Hynes N. Leukotrienes in cerebrospinal fluid of the conscious cat: effect of platelet activating factor and pyrogens. Adv Prostaglandins Thromboxane Leukot Res 1990; 21: 480a–484d.
15. Yates S L, Levine L, Rosenberg P. Leukotriene and prostaglandin production in rat brain synaptosomes treated with phospholipase A_2 neurotoxins and enzymes. Prostaglandins 1990; 39: 425–438.
16. Aktan S, Aykut C, Ercan S. Leukotriene C_4 and prostaglandin E_2 activities in the serum and cerebrospinal fluid during acute cerebral ischemia. Prostaglandins Leukot Essent Fatty Acid 1991; 43: 247–249.
17. Kim S J, Tominaga T. Formation of lipoxins by the brain: ischemia enhances production of lipoxins. Ann N Y Acad Sci 1989; 559: 461–464.
18. Simmet T, Peskar B A. Lipoxygenase products of polyunsaturated fatty acid metabolism in the central nervous system: biosynthesis and putative functions. Pharmacol Res 1990; 22: 667–682.
19. Hulting A L, Lindgren J A, Hokfelt T et al. Leukotriene C_4 as a mediator of luteinizing hormone release from rat anterior pituitary cells. Proc Natl Acad Sci USA 1985; 82: 3834–3838.
20. Palmer M R, Mathews R, Murphy R C, Hoffer B J. Leukotriene C elicits a prolonged excitation of cerebellar Purkinje neurons. Neurosci Lett 1980; 18: 173–180.
21. Moscowitz M A, Kiwak K J, Hekimian K. Synthesis of compounds with properties of leukotrienes C_4 and D_4 in gerbil brains after ischemia and reperfusion. Science 1984; 224: 886–889.
22. Genis P, Jett M, Bernton E W et al. Cytokines and arachidonic metabolites produced during human immunodeficiency virus (HIV)-injected macrophage-astroglia interactions: implications for the neuropathogenesis of HIV disease. J Exp Med 1992; 176: 1703–1718.
23. Krueger J M, Kapas L, Opp M R, Obal Jr F. Prostaglandin E_2 and D_2 have little effect on rabbit sleep. Physiol Behav 1992; 51: 481–485.
24. Sri Kantha S, Matsumura H, Takahata R, Kubo E, Serhan C N, Hayaishi O. Comparison of sleep induction by prostaglandin D_2, lipoxins and leukotrienes in rats [Abstract]. Sleep Res 1993; 22: 486.
25. Matsumura H, Goh Y, Ueno R, Sakai T, Hayaishi O. Awaking effect of PGE_2 microinjected into the preoptic area of rats. Brain Res 1988; 444: 265–272.
26. Matsumura H, Takahata R, Hayaishi O. Inhibition of sleep in rats by inorganic selenium compounds, inhibitors of prostaglandin D synthase. Proc Natl Acad Sci USA 1991; 88: 9046–9050.

27. Economo von C. Sleep as a problem of localization. J Nerv Mental Dis 1930; 71: 249–259.
28. Nauta W J H. Hypothalamic regulation of sleep in rats; an experimental study. J Neurophysiol 1946; 9: 285–316.
29. Paxinos G, Watson C. The rat brain in stereotaxic coordinates. San Diego: Academic Press, 1986.
30. Busija D W, Armstead W, Leffler C W, Mirro R. Lipoxins A_4 and B_4 dilate cerebral arterioles of new born pigs. Am J Physiol 1989; 256: H468–H471.
31. Ellis E F, Wei E P, Kontos H A. Vasodilation of cat cerebral arterioles by prostaglandin D_2, E_2, G_2 and I_2. Am J Physiol 1979; 237: H381–H385.
32. Ueno R, Ishikawa Y, Nakayama T, Hayaishi O. Prostaglandin D_2 induces sleep when microinjected into the preoptic area of conscious rats. Biochem Biophys Res Comm 1982; 109: 576–582.
33. Siren A L. Central cardiovascular and the thermal effects of prostaglandin D_2 in rats. Prostaglandins Leukot Med 1982; 8: 349–359.
34. Förstermann U, Heldt R, Hertting G. Effects of intracerebroventricular administration of prostaglandin D_2 on behavior, blood pressure and body temperature as compared to prostaglandins E_2 and $F_{2\alpha}$. Psychopharmacology 1983; 80: 365–370.
35. Förstermann U, Heldt R, Hertting G. Studies on the mechanism of central cardiovascular and temperature responses to prostaglandin D_2. Prostaglandins Leukot Med 1985; 18: 301–308.
36. Ewen L, Milton A S, Smith S. Effects of prostaglandin $F_{2\alpha}$ and prostaglandin D_2 on the body temperature of conscious cats. J Physiol 1976; 258: 121P–122P.
37. O'Rourke S T, Rudy T A. Intracerebroventricular and preoptic injections of leukotrienes C_4, D_4 and E_4 in the rat: lack of febrile effect. Brain Res 1984; 295: 283–288.