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INTERLEUKIN-1β INDUCES SLEEP INDEPENDENT OF PROSTAGLANDIN D_2 IN RATS AND MICE

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Abstract—Interleukin-1β (IL-1β) and prostaglandin (PG) D_2 are endogenous sleep-promoting substances. Since it was reported that a highly selective cyclooxygenase-2 (COX-2) inhibitor, NS398, completely inhibited IL-1β-induced sleep in rats, IL-1β-induced sleep had been believed to be mediated by prostanoids, most probably PGD_2. However, in the present study, pretreatment of rats with NS398 (3 mg/kg) did not suppress the 64.2% increased non-rapid eye movement (non-REM, NREM) sleep during infusion of IL-1β (10 ng) for 6 h in the nocturnal (active) period between 23:00 and 5:00 into the subarachnoid space of the PGD_2-sensitive sleep-promoting zone of the basal forebrain. Meanwhile, IL-1β at doses of 1.7 and 5 μg/kg also significantly increased NREM sleep for 6 h after intraperitoneal injection at 20:00 (light-off time) by 76.8% and 121.1%, respectively, in wild-type (WT) mice, by 67.7% and 147.3%, respectively, in WT mice pretreated with NS398 (5 mg/kg) and by 108.9% and 121.6%, respectively, in PGD_2 receptor (DP_1R) knockout mice. These results indicate that IL-1β-induced NREM sleep is independent of the PGD_2/DP_1R system and other COX-2-derived prostaglandins in rats and mice.

Key words: cytokine, prostaglandin D_2, sleep, body temperature, slow-wave activity, COX-2 inhibition.

INTRODUCTION

Cytokines, most prominently Interleukin-1β (IL-1β), have been implicated in the regulation of non-rapid eye movement (non-REM, NREM) sleep (Krueger et al., 2001; Opp, 2005). Systemic or intracerebroventricular administration of IL-1β increases NREM sleep in several species, whereas antagonizing the IL-1β system with IL-1β receptor antagonists (Opp and Krueger, 1991) or antibodies (Opp and Krueger, 1994) reduces NREM sleep under physiological conditions and inhibits NREM sleep rebound after sleep deprivation. IL-1β type I receptors knockout (KO) mice show decreased NREM sleep (Fang et al., 1998). IL-1β mRNA exhibits higher expression in the rat brain during the light (sleep) period than the dark (active) period (Taishi et al., 1997) and is increased by sleep deprivation (Mackiewicz et al., 1996). Cerebrospinal fluid (CSF) levels of IL-1β protein vary with the sleep–wake cycle in cats (Alue et al., 1988). Furthermore, IL-1β is detected more frequently in human plasma samples during sleep than during wakefulness (Gudewill et al., 1992).

Many of the biologic responses initiated by IL-1β are mediated by other downstream systems, including prostaglandins (PG). IL-1β increases the expression of cyclooxygenase-2 (COX-2) in the brain (Lacroix and Rivest, 1998). COX-2 is an inducible enzyme involved in inflammation and catalyzes the formation of PGH_2, a common precursor of various prostanoids, from arachidonic acid, which is the rate-limiting step of the prostanoid cascade. PGH_2 is immediately converted by terminal PG synthases to PGD_2, PGE_2, $PGF_{2\alpha}$, PGI_2, and thromboxane A_2. The most abundant prostanoid in the brains of rats and other mammals is PGD_2 (Narumiya et al., 1982). PGD_2 is produced by lipocalin-type PGD synthase (L-PGDS), which is localized mainly in the leptomeninges, choroid plexus, and oligodendrocytes in the brain (Narumiya et al., 1982; Urade et al., 1993). PGD_2 circulates in the CSF as a sleep-promoting substance and binds to PGD_2 type DP_1 receptors (DP_1R) on leptomeningeal cells of the basal forebrain (Mizoguchi

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Abbreviations: COX-2, cyclooxygenase-2; CSF, cerebrospinal fluid; DMSO, dimethyl sulfoxide; DP_1R, DP_1 receptors; EEG, electroencephalogram; EMG, electromyogram; IL-1β, Interleukin 1 beta; KO, knockout; LC–MS/MS, liquid chromatography–tandem mass spectrometry; L-PGDS, lipocalin-type PGD synthase; LPS, lipopolysaccharide; NREM, non-rapid eye movement; PG, prostaglandins; PGEM, PGE_2 metabolite 9,15-dioxo-11α-hydroxy-2,3,4,5-tetranorprostan-1,20-dioic acid; PGDM, PGD_2 metabolite 11,15-dioxo-9α-hydroxy-2,3,4,5-tetranorprostan-1,20-dioic acid; SWA, slow-wave activity; TMN, tuberomammamillary nucleus; VLPO, ventrolateral preoptic area; WT, wild-type.

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et al., 2001) to promote physiological sleep (Mizoguchi et al., 2001; Qu et al., 2006; Huang et al., 2007). We previously demonstrated that the L-PGDS/PGD_2/DP_1R system is crucial for the regulation of physiological sleep (Qu et al., 2006).

NS398 is a selective COX-2 inhibitor. NS398 inhibits COX-2 activity ($IC_{50} = 3.8 \times 10^{-6}$ M), but does not affect COX-1 activity at concentrations up to 10^{-4} M (Futaki et al., 1994). In 1998, Terao et al. (Terao et al., 1998) reported that pretreatment of rats with NS398 completely blocked the sleep-promoting effect of IL-1β infused into the subarachnoid space of the PGD_2-sensitive sleep-promoting zone of the basal forebrain. Based on their results, it had been proposed that PGD_2 may be involved in interleukin-induced sleep [see reviews, (Krueger et al., 2001, 2003)]. However, we could not reproduce their results by using the same COX-2 inhibitor, i.e., NS398. Infusion of IL-1β into the subarachnoid space of the basal forebrain of rats significantly increased NREM sleep; however, IL-1β-induced sleep was not affected by the pretreatment with NS398. Finally, we found that IL-1β-induced sleep was observed in DP_1R KO mice to the same extent as in wild-type (WT) mice. All results together indicate that IL-1β induced sleep through pathway(s) different from the PGD_2/DP_1R system and other COX-2-derived prostaglandins.

EXPERIMENTAL PROCEDURES

Animals and chemicals

Male DP_1R KO and WT mice of the inbred C57BL/6 strain (Matsuoka et al., 2000), weighing 23–27 g (11–13 weeks old), were obtained from Oriental Bioservice, Ltd. (Kyoto, Japan). Male Sprague–Dawley rats weighing 250–320 g (8–10 weeks) were purchased from Japan SLC, Inc. (Shizuoka, Japan). Both mice and rats were housed under controlled temperature (24 ± 0.5 °C), humidity (60 ± 2%), and a 12-h:12-h light–dark cycle with lights on at 8:00). Food and water were provided *ad libitum*. All procedures were approved by the Animal Care Committee of the University of Tsukuba. Recombinant mouse IL-1β (BD Biosciences, San Jose, CA, USA) was stocked at –20 °C, diluted with PBS or artificial CSF for intraperitoneal (i.p.) injections or intracerebroventricular infusions, respectively, and stored in aliquots at −20 °C until use. IL-1β did not contain carrier proteins. The dose of IL-1β and route of administration were based on a previous study (Terao et al., 1998). NS398 (Cayman Chemicals, Ann Arbor, MI, USA) was dissolved in dimethyl sulfoxide (DMSO) and further diluted in saline before use.

Measurement of core-body temperature and locomotor activity

Deep body temperature of the mice was measured with an accuracy of ±0.1 °C by using a biotelemetry device (Mini Mitter Company, Sunriver, OR, USA). Under pentobarbital anesthesia (50 mg/kg, i.p.), mice were implanted with a calibrated telemeter (dimensions: 8.1 × 22.7 mm; wt 1.55 g), as previously described (Lazarus et al., 2007). After implantation, the mice were allowed to recover for at least 2 weeks before experiments. Output was monitored by a mounted antenna (receiver board) placed under each animal cage and fed into a peripheral processor connected to a computer. In this system, changes in activity are detected by changes in position of the implanted telemeter over the receiver board. This results in a change in the signal strength that is detected by the receiver and recorded as a pulse of activity. The signal was recorded by using VitalView software (Mini-Mitter Company). Locomotor activity and body temperature were recorded continuously at 10-min intervals in freely moving mice after their recovery from surgery.

Electroencephalogram and electromyogram recordings

After telemeter implantation, mice were implanted with electrodes for recording of electroencephalogram (EEG) and electromyogram (EMG), as previously described (Lazarus et al., 2011; Xu et al., 2014; Wang et al., 2015; Chen et al., 2016; Oishi et al., 2016). Briefly, for monitoring EEG signals, 2 stainless steel EEG recording screws were positioned 1 mm anterior to bregma or lambda, both 1.5 mm lateral to the midline, according to the atlas of Franklin and Paxinos (Paxinos and Franklin, 2001). EMG activity was monitored by placing stainless steel, Teflon-coated wires bilaterally into both trapezius muscles. The electrodes were fixed to the skull with dental cement.

Rats were anesthetized with pentobarbital (50 mg/kg, i.p.), and implanted with electrodes for EEG and EMG recordings together with a cannula that was inserted into the subarachnoid space under the rostral basal forebrain (AP = 1.1 mm, DV = 7.8–8 mm) (Terao et al., 1998). After an 8–10-day recovery period, rats or mice were placed in soundproof recording chambers and the EEG/EMG electrode assembly on the head was connected to a recording cable.

Artificial CSF was infused into the rat brain at a flow rate of 0.2 μl/min. EEG and EMG signals (EEG: 128-Hz sampling, 0.5–30-Hz filtered; EMG: 20–200-Hz filtered) were continuously recorded for 48 h by SleepSign as previously described. The first-day recording began at 20:00 and served as the control for the same animal. On the next day, IL-1β (10 ng/6 h) was infused into the rat brain between 23:00 and 5:00. NS398 was dissolved in DMSO and further diluted in saline before use. NS398 (3 mg/kg in 0.5 ml) or vehicle containing the same amount of DMSO (10%, *v*/*v*) was injected i.p. at 3 h before infusion of IL-1β in rats. We confirmed the position of the cannula by immunohistochemistry at the end of the microinfusion experiment.

For the mice experiments, each mouse was injected i.p. with saline (10 ml/kg body weight) at 20:00 on the first day, and with IL-1β on the next day. Vehicle containing 10% DMSO or NS398 (5 mg/kg) containing 10% DMSO was injected i.p. 1 h before administration of IL-1β in mice.