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PHYSIOLOGICAL REVIEW

Prostaglandin D_2 and sleep/wake regulation

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SUMMARY

Prostaglandin (PG) D_2 is the most potent endogenous sleep-promoting substance. PGD_2 is produced by lipocalin-type PGD synthase localized in the leptomeninges, choroid plexus, and oligodendrocytes in the brain, and is secreted into the cerebrospinal fluid as a sleep hormone. PGD_2 stimulates DP_1 receptors localized in the leptomeninges under the basal forebrain and the hypothalamus. As a consequence, adenosine is released as a paracrine sleep-promoting molecule to activate adenosine A_{2A} receptor-expressing sleep-promoting neurons and to inhibit adenosine A_1 receptor-possessing arousal neurons. PGD_2 activates a center of non-rapid eye movement (NREM) sleep regulation in the ventrolateral preoptic area, probably mediated by adenosine signaling, which activation inhibits the histaminergic arousal center in the tuberomammillary nucleus via descending GABAergic and galaninergic projections. The administration of a lipocalin-type PGD synthase inhibitor ($SeCl_4$), DP_1 antagonist (ONO-4127Na) or adenosine A_{2A} receptor antagonist (caffeine) suppresses both NREM and rapid eye movement (REM) sleep, indicating that the PGD_2-adenosine system is crucial for the maintenance of physiological sleep.

Introduction

The existence of endogenous chemicals that produce sleep was originally proposed by Ishimori[1] and Pieron.[2] Separately, these researchers proposed that, as a result of prolonged periods of wakefulness due to sleep deprivation, there is an accumulation of a hypothetical endogenous substance that induces sleep. At present, there are many endogenous molecules that have been isolated and identified as sleep-promoting substances, such as cytokines,[3] adenosine,[4–7] lipids like PGD_2[4,8] or anandamide,[9] and peptides including urotensin II.[10] Among these substances, the sleep-induction mechanisms of cytokines, adenosine, and PGD_2 have been relatively well characterized in terms of the production and action sites, and the signal transduction system including the receptors, by the use of various pharmacological tools, such as the inhibitors, receptor agonists or antagonists, and gene-knockout (KO) mice for their producing enzymes, transporters or receptors.

For almost 30 years after the first report of PGD_2-induced sleep in 1982,[11] we have been extensively studying the molecular mechanism of the PGD_2-induced sleep, by using biochemical, pharmacological, and molecular biological techniques summarized in several review articles.[4,8] As a consequence, PGD_2 is now recognized as the most potent endogenous sleep-promoting substance; and its action mechanism is the best characterized at the molecular level of the sleep-related molecules thus far reported. In this review, we summarize the short history and the recent progress in research on the molecular mechanism of PGD_2-induced sleep. We also review the basic and clinical studies on the roles of PGD_2 in the regulation of physiological sleep.

Sleep induction by PGD_2

PGs are a group of 20-carbon polyunsaturated fatty acids containing a unique 5-carbon ring structure. As shown in Fig. 1, PGs of the 2 series, such as PGD_2, PGE_2, $PGF_{2\alpha}$, PGI_2 (prostacyclin), and thromboxane A_2, are all produced from arachidonic acid (C20:4 fatty acid) via their common intermediate, PGH_2. The latter compound is produced by the action of cyclooxygenase/PGH synthase, a target of non-steroidal anti-inflammatory drugs such as aspirin and indomethacin. Each prostanoid is then produced from PGH_2 by its specific terminal PG synthase, e.g., PGD synthase (PGDS) in the case of PGD_2. PGD_2 had long been considered as a minor and biologically inactive PG. In the 1980's, however, PGD_2 was found to be the most abundant PG in the brains of rats[12] and other mammals including humans,[13] thus suggesting it to have an important function in the central nervous system (CNS).

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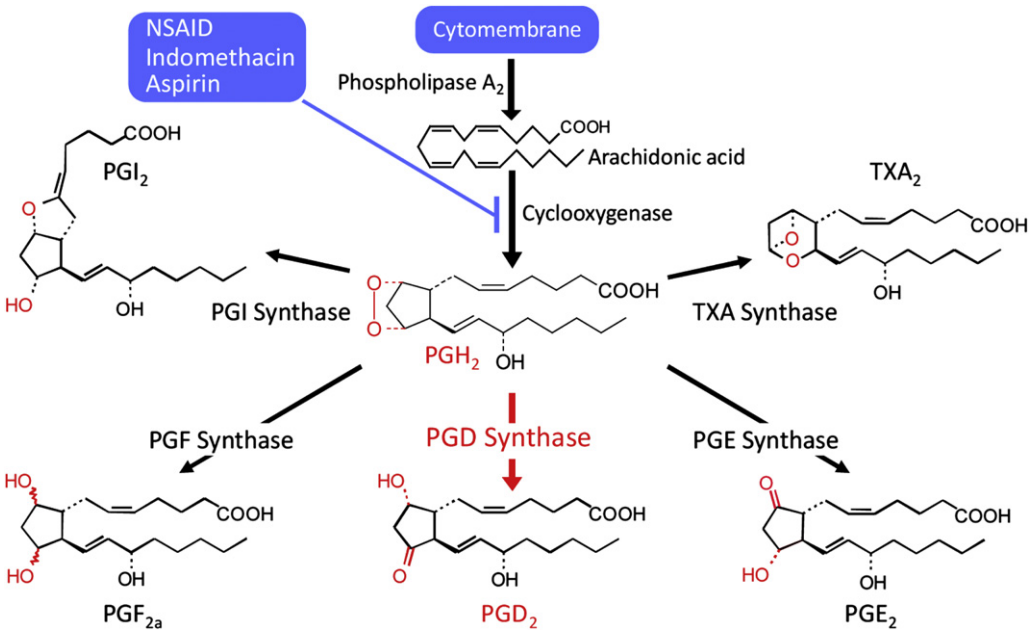

Fig. 1. Biosynthesis of prostaglandins (PGs). NSAID: non-steroidal anti-inflammatory drugs; TXA_2: thromboxane A_2.

The sleep-promoting effect of PGD_2 was discovered after the microinjection of nano-molar quantities of PGD_2 into the rat brain, which substance causes profound enhancement of both non-rapid eye movement (NREM) and rapid eye movement (REM) sleep.[11] By using a sleep bioassay system based on the recording of both electroencephalography (EEG) and electromyography (EMG) during the continuous intracerebroventricular (i.c.v.) infusion of drugs into freely moving rats, the somnogenic activity of PGD_2 was subsequently demonstrated to be both dose and time dependent.[14] Although the i.c.v. infusion of PGD_2 like interleukin (IL)-1β increases NREM sleep at femtomolar concentrations, PGD_2 maximally induces an amount of NREM sleep that is almost equal to the peak of natural sleep in rodents during daytime (about 35 min/h), thus making it a 2-fold more potent sleep inducer than IL-1β. Based on electrophysiological and behavioral criteria, PGD_2-induced sleep is indistinguishable from physiological sleep. During PGD_2 infusion, for instance, rats are easily aroused by a clap sound; and their sleep is episodic, indicating that PGD_2 does not interfere with the basal wakefulness crucial to the survival of the animal. The somnogenic effect of PGD_2 was later confirmed in a non-human primate, when the PG was infused via the i.c.v. route into a rhesus monkey (*Macaca mulatta*).[15] The EEG power spectrum of NREM sleep during the PGD_2 infusion into monkeys was the same as that of their natural sleep at night, but clearly different from benzodiazepine-induced sleep, which is characterized by a decrease in the theta range and the appearance of a rapid wave with a peak at around 20 Hz.

The PGD_2 concentration in rat cerebrospinal fluid (CSF) fluctuates with circadian rhythmicity in parallel with the sleep-wake cycle[16] and increases, with an increase in sleep propensity during sleep deprivation.[17] In addition, PGD_2 was reported to be involved in the pathogenesis of mastocytosis, a disorder characterized by episodic and endogenous production of PGD_2 that is accompanied by deep-sleep episodes.[18] Also, the PGD_2 concentration, but not the PGE_2 or IL-1β concentrations, is elevated time-dependently in the CSF of patients with African sleeping sickness, which is caused by an infection with *Trypanosoma*.[19] These findings suggest that PGD_2 induces sleep in humans as well as in rodents and monkeys.

Matsumura and colleagues[20] microinjected PGD_2 into hundreds of different sites in the rat brain and found that PGD_2-induced NREM sleep is the most prominent when PGD_2 is infused into the subarachnoid space of the ventral basal forebrain.[21] Then they found that the PGD_2-sensitive sleep-promoting zone is also sensitive to the sleep promotion by IL-1β and that the IL-1β-induced NREM sleep is completely inhibited by the pretreatment of rats with inhibitors of cyclooxygenase, the key enzyme of PG production. As various cytokines, such as IL-1β and tumor necrosis factor (TNF)α, induce cyclooxygenase in a variety of cells and increase the production of PGs, they proposed that IL-1β-induced NREM sleep depends on the production of PGs, the most likely one being PGD_2.

PGDS and PGD_2 receptor in the CNS

There are 2 distinct types of PGDS (PGH_2 D-isomerase, EC.5.3.99.2). One is lipocalin-type PGDS (L-PGDS)[22]; and the other, the hematopoietic one (H-PGDS).[23,24] We purified L-PGDS and H-PGDS, isolated their cDNAs and chromosomal genes of the human and mouse enzymes, determined their X-ray crystallographic structures, and demonstrated that these 2 enzymes are quite different from each other in terms of their amino acid sequence, tertiary structure, evolutional origin, and cellular distribution.[25,26] Two distinct subtypes of receptors for PGD_2 have been identified: one is the DP_1 (DP) receptor coupled to Gs-protein, originally identified as a homolog of other PG receptors[27]; and the other is the DP_2 (CRTH2) receptor, identified as a chemo-attractant receptor for PGD_2.[28] We developed inhibitors selective for either L-PGDS (AT-56)[29] or H-PGDS (HQL-79).[30] Selective agonists and antagonists for DP_1 or DP_2 are also available. These pharmacological tools have been used in our laboratories and in those of others for various studies including sleep research. In the CNS, L-PGDS and the DP_1 receptor are involved in the regulation of physiological sleep, as described in detail later, as well as in pain sensation,[31] neural protection in a genetic demyelination model of *twitcher* mice,[32] and food intake.[33] In addition, H-PGDS and the DP_1/DP_2 receptors are involved in the progression of neural inflammation in *twitcher* mice[34] and in neural protection in a neonatal hypoxic brain damage model.[35] In these disease models, we found that H-PGDS is induced in activated microglial cells, and DP_1/DP_2 receptors are induced in astrocytes and microglial cells, to increase the production of IL-1β