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Histamine-Interleukin-Prostaglandin Pathway: a Hypothesis For a Biochemical Cycle Regulating Sleep and Wakefulness

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Abstract — The probable existence of a biochemical cycle, involving histamine, interleukins and prostaglandins for regulating sleep and wakefulness in higher vertebrates is proposed in this paper. For convenience, it is given an acronym, H-I-P cycle. The proposed biochemical cycle consists of 13 essential steps, with four regulatory points. How this cycle differs from the previously described biochemical models for sleep and wakefulness, such as Jouvet's monaminergic cycle (5) and the multiple sleep factor model of Krueger (9,10) is also mentioned. The regional distribution of mast cells in the mammalian brain, the fluctuation of their numbers under different light regimen and a progressive decrease of their numbers with aging suggest that they may be the candidate 'black box' for the anatomical seat of sleep.

Introduction

Sleep deprivation and its side effects is a serious problem not only to patients who suffer from sleep disorders, but also to members of society at large, especially to those employed in the emergency services like doctors, para-medical personnel, law enforcement officials and armed forces. The deleterious effect of rotating shift work on sleep and health has also been highlighted (1–3). In this context, it is disappointing to note that though sleep is a vital need for maintaining the health of humans, very little is known scientifically about the neurobiochemical mechanisms which modulate this important physiological function.

In this paper, I venture to propose the existence of a biochemical cycle, involving histamine, interleukins and prostaglandins, for regulating sleep and wakefulness in higher vertebrates, including humans. Based on the three types of compounds which play the pivotal role in this proposed cycle, namely histamine, interleukins and prostaglandins, for purposes of brevity, I have coined the acronym H-I-P cycle. Inspiration for originating this biochemical model for sleep was derived from the review article authored by Baldwin and Krebs (4), on the evolution of metabolic cycles.

Previously described biochemical models for sleep

Before describing the proposed H-I-P cycle, brief mention is made to the two previously described biochemical models for sleep.

1. Jouvet's monaminergic cycle for sleep (1969)

Jouvet's monaminergic cycle (5), highlights the role of neurotransmitters in the sleep-wake balance. Sero-

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wave sleep phase. Acetyl choline, norepinephrine and dopamine, as well as the metabolite of serotonin (5-hydroxy indole acetic acid) were identified as the essential components for the transformation of slow wave sleep to the paradoxical sleep (rapid eye movement sleep). Since its formulation in 1969, experimental evidence has accumulated for and against the monaminergic cycle (6). In the wake of some valid criticism, Jouvet and his colleagues have modified their views from the 1969 version (7,8). Significantly, in the 1969 model, no mention was made of the important roles played by histamine, interleukins and prostaglandin in sleep-wake regulation. This is understandable, since many individual members of the interleukin and prostaglandin family were identified only in the 1970s and 1980s.

2. *Multiple sleep factor model of Krueger (1990)*

In this biochemical model of sleep activational system, Krueger (9,10) has linked the inter-relationship of 25 of the already identified 30 or more putative sleep factors. The emphasis has been placed on three types of chemical compounds. These are:

1. Cytokines (interleukin 1β, interferon α_2 and tumor necrosis factor α).
2. Polypeptides (muramyl peptides, delta sleep-inducing peptide, corticotropin-like intermediate lobe peptide).
3. Hormones (insulin, cholecystokinin, glucocorticoids, α melanocyte-stimulating hormone, growth hormone, somatostatin, cholecystokinin, prolactin, vasoactive intestinal peptide, corticotropin-releasing factor).

Though prostaglandin D_2 (PGD_2) and prostaglandin E_2(PGE_2) are also included in this biochemical model, their role has been less emphasized. Histamine has not been included, though its sleep-modulating effects have been documented (11).

H-I-P cycle

Hypothesis 1

Histamine, inerleukin-1 and/or 2, prostaglandin D_2 and E_2 are the pivotal chemicals which play a decisive role in regulating the physiological sleep-wake activity in mammals.

During the past decade, the role of prostaglandins D_2 and E_2 in modulating the physiological sleep-wake regulation in rats and monkeys has been extensively researched in the laboratory of Hayaishi and reviewed (12,13). The central hypothesis of Hayaishi is that, in mammals, while prostaglandin D_2 acts as a sleep promoter (14,15), prostaglandin E_2 is involved in maintaining the waking phase (16,17). The sleep-modulating effects of histamine (11,18) and interleukin-1 (19–21) have also been highlighted by the results from other research groups.

Hypothesis 2

The regional distribution of mast cells in the mammalian brain, the fluctuation of their numbers under different light regimen and a progressive decrease of their numbers with aging suggest that they may be the candidate 'black box' for the anatomical seat of sleep

One can begin with two of the purported sleep centers in the brain – thalamus and hypothalamus (22,23). The presence of mast cells in thalamus and hypothalamus has been reported (24,25) and histamine is predominantly stored in these mast cells (26,27). A histamine-release factor, probably IL-1 (28,29), would release histamine from the mast cells, which in turn will activate phospholipase A_2 to produce arachidonic acid from the phosphatidyl choline in cell membranes (30). PGD_2 and PGE_2 are then formed from the arachidonic acid via the action of prostaglandin H synthase, prostaglandin D synthase and prostaglandin E synthase (31–33).

Dropp (24,25) has reported the regional distribution of mast cells in the brains of 29 mammalian species, including humans. What is interesting is that, in some regions of the brain, mast cells were found to be most numerous in young individuals (0–19 years of age) and the mast cell numbers progressively decreased with aging. Furthermore, Mares et al (34) have shown that the number of mast cells in the rat brain changes under different light regimens. Since light also influences the sleep behavior (35), and the duration as well as the organization of sleep in humans have also been identified as influenced by the circadian rhythms (36), it seems plausible that the anatomical seat of sleep may be becoming apparent.

Steps of the proposed H-I-P cycle

One can identify at least 13 individual steps in the H-I-P cycle. The Figure provides a graphic illustration of this cycle. Each of the steps has been reported to occur in mammalian systems (in vivo and/or in vitro conditions), and most have been described in the regions of brain.

a. Release of free histamine from mast cells, influenced by interleukins, located in hypothalamus (27–29, 37–39).
b. Activation of phospholipase by free histamine, resulting in the formation of arachidonic acid from phosphatidyl choline (30).

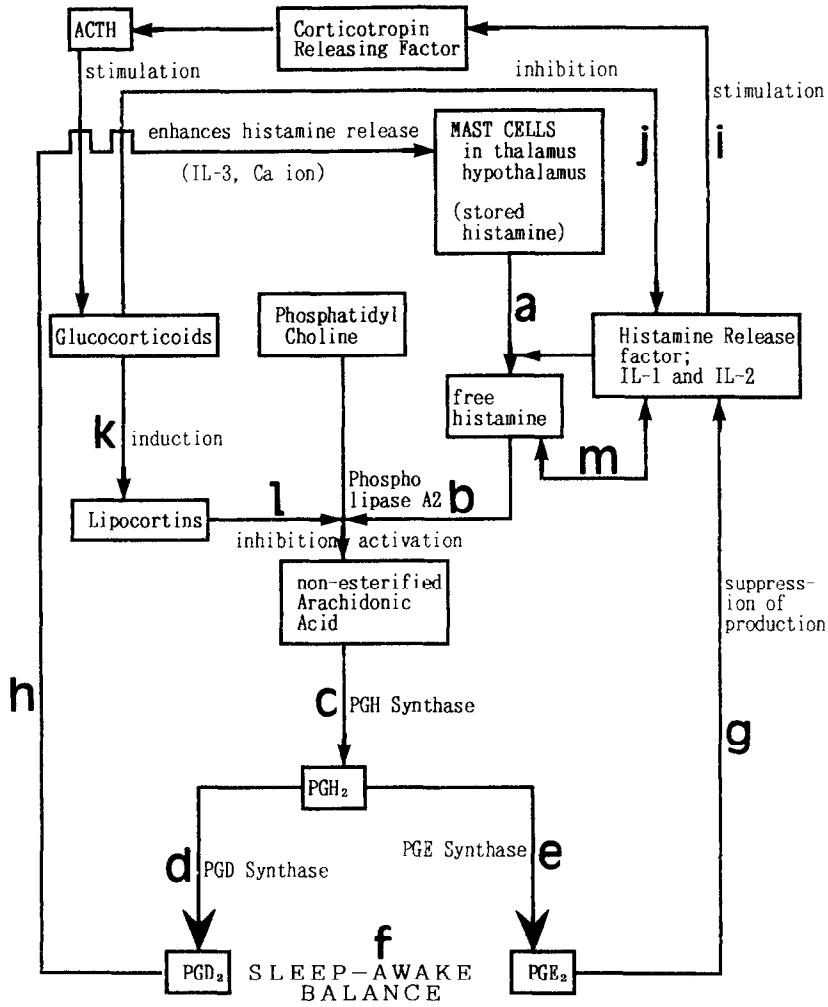

Fig. Proposed histamine-interleukin-prostaglandin pathway for sleep-wake regulation.

c. Formation of PGH_2 from arachidonic acid, by PGH synthase (31).
d. Formation of PGD_2 from PGH_2, by PGD synthase (32).
e. Formation of PGE_2 from PGH_2, by PGE synthase (33).
f. Sleep-wake balance maintained by the proportionate concentrations of PGD_2 and PGE_2 (12,13).
g. Suppression of production of interleukins by PGE_2(40,41).
h. Histamine release enhanced by PGD_2, in the presence of IL-3 and calcium ions (42).
i. Stimuulation of ACTH by interleukins to produce glucocorticoids (43–45).
j. Inhibition of production of interleukins by glucocorticoids (46).
k. Induction of lipocortins by glucocorticoids (47).
l. Inhibition of phospholipase by lipocortins (48).
m. Bi-directional interactions between histamine and interleukins (49,50).

The merits of H-I-P cycle

Baldwin and Krebs (4) defined metabolic cycles as 'processes in which an overall chemical change is brought about by a cyclic reaction sequence'. They also emphasized that a cyclic process is 'the only rational and economic mechanism for the organization of certain metabolic process' which have to repeatedly occur in the body at regular intervals. 'Multiple use of given resources', is another feature of a metabolic cycle (4). In this sense, the alternating

occurrence of sleep and wakefulness can only be rationally explained in terms of the presence of a metabolic cycle.

Baldwin and Krebs (4) also stressed the presence of regulatory control points in a metabolic cycle. One can identify at least four regulatory control points in the proposed H-I-P cycle.

1. Bi-directional interactions of interleukins and glucocorticoids (pro-inflammatory and anti-inflammatory responses).
2. Bi-directional interactions of interleukins and histamine.
3. Phospholipase A_2 activation (by histamine) and inhibition (by lipocortin).
4. Production of PGD_2 and PGE_2 from PGH_2; in which, PGD synthase in brain is glutathione non-dependent and PGE synthase is glutathione dependent.

Criticism of the H-I-P cycle

A few questions which can be raised about the validity of the H-I-P cycle also need mention. These include:

1. What crucial factors influence the critical balance between the PGD_2 and PGE_2 production from PGH_2 and how is this balance maintained?
2. How can the distinction between the slow wave sleep and paradoxical sleep (rapid eye movement sleep) phases be explained in biochemical terms? Does PGD_2 influence both phases of sleep equivalently?
3. How can the roles of neurotransmitters such as serotonin, acetyl choline and norepinephrine be tied with the sleep-wake balance maintained by PGD_2 and PGE_2

I believe that these questions regarding the validity of the H-I-P cycle will help to fill in some of the gaps currently existing in understanding the biochemical mechanisms of sleep.

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