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Hypothalamic Releasing Hormones Mediating the Effects of Interleukin-1 on Sleep

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Abstract There is a substantial literature describing the interactions between the endocrine and immune systems. Although such interactions are less well known within the brain, one major brain function altered during inflammation and infection and by several endocrine hormones is sleep. Pathological disturbances, be they inflammation, infectious disease, and/or sleep deprivation, result in altered hypothalamus-pituitary function and cytokine metabolism. In respect to hormone secretion from the pituitary, cytokines are now recognized to play an important role in modulating the neuroendocrine system. Changes in sleep provide a useful illustration of the interactions between cytokines and the hypothalamus-pituitary axis. Evidence linking interleukin-1 (IL-1) to growth hormone releasing hormone and to corticotropin releasing hormone in regard to their effects on sleep is reviewed. © 1993 Wiley-Liss, Inc.

Key words: cytokines, growth hormone releasing hormone, corticotropin releasing hormone, endocrine regulation, neuroendocrine

The host's initial response to infections is a nonspecific defense reaction called the acute phase response. The acute phase response promotes specific responses to the infectious agents mediated by cellular and humoral immune mechanisms. The acute phase response does this by several ways: the immune system is stimulated; an environment is provided which enhances the effectiveness of the specific immune response and at the same time is not optimal for the replication and spreading of the infectious agents; and the behavior and responsiveness to stimuli of the individual are modified in such a way that the exposure to further environmental challenges is reduced. These changes require substantial alterations in almost all functions of the body. The clinical manifestations of these alterations are the leading symptoms of sickness which are easily recognized by everybody: fever, somnolence, social withdrawal, reduced apetite, muscle pain, etc. Laboratory readings are also abnormal; changes are recorded in plasma proteins, in the number and percentage distribution of leukocytes, and in concentrations of various hormones: red blood cell sedimentation increases, and the basal metabolic rate is elevated [1]. An acute phase response, exaggerated in magnitude or prolonged, is detrimental to the individual. However, negative feedback mechanisms are also activated which attenuate various aspects of the functional changes and abolish the response when the infection is eliminated.

Much information has accumulated within the past few years indicating that most, if not all, aspects of the acute phase response are driven by a complex array of cytokines in association with classical stress hormones [2]. Most cytokines were first identified as immunocyte products involved in the amplification, coordination, and regulation of the immune response. Subsequently, many cytokines were shown to be products of many different cell types including neurons and glia [3–6]. Further, interleukin-1 (IL-1) is found in many fluid compartments such as milk, plasma, and cerebrospinal fluid [4,7]. Cytokine regulation is not fully understood and is greatly complicated by the fact that many cytokines induce each other's production and can induce their own production, and some inhibit the production of others. Currently, it seems

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that cytokines are induced by a complex array of microbial products, inflammatory cells, and factors released from injured tissues as well as by other cytokines. IL-1 seems to be of particular importance to the acute phase response in that the administration of exogenous IL-1 induces most facets of the acute phase response [2,3]. Further, an endogenous interleukin-1 receptor antagonist (IL-1RA) exists. Other cytokines lack an endogenous receptor antagonist.

The IL-1 family of molecules consist of five separate gene products. IL-1α, IL-1β, and the IL-1RA are structurally related to each other, sharing a limited degree of amino acid homology [3,4]. The two IL-1 receptor types I and II recognize IL-1α, β, and the IL-1RA. IL-1α and β are synthesized as precursor forms of about 31 kD; the 31 kD forms can be directly secreted or enzymatically processed into forms of about 17 kD. Only a few functional differences between IL-1α and IL-1β have been described. In brain only IL-1β seems to be constitutively expressed [4]. The IL-1RA seems to act as a brake on the actions of IL-1 [3,8]. IL-1β in high concentrations is toxic; the IL-1RA is in clinical trials for use in pathological conditions characterized by high IL-1 levels (e.g., septicemia). There also exists a soluble IL-1 receptor [9] which is the cleaved extracellular domain of the IL-1 receptor; it binds IL-1α, IL-1β, and the IL-1RA. Many second messenger systems activated by the IL-1 receptors have been described; the list includes cAMP, NO, prostaglandins, etc. [reviewed in 4].

There are many intriguing observations concerning IL-1 that currently are not fully understood. For example, normal individuals possess auto-anti-IL-1 antibodies [10]. It is not known if the soluble IL-1 receptors have a functional role. It is speculated that both the soluble receptor and auto-anti-IL-1 serve to protect IL-1 from proteases, thereby prolonging its effective half-life, but this is not experimentally verified. There is rather a heated argument currently underway as to whether IL-1 crosses the blood-brain barrier in physiological relevant amounts. This issue is complex [reviewed in 2,4]; important to this essay are the clear observations that systemic IL-1 induces central nervous system actions (e.g., sleep). Conversely, central IL-1 induces systemic effects (e.g., enhanced IL-6 production). Regardless of these many unknowns, it is currently clear that IL-1 is the major regulator of the acute phase response. In addition, IL-1 activates negative feedback mechanisms which inhibit further IL-1 production and IL-1 effects.

It is a common experience that somnolence is a symptom of infection. Bacterial and viral products have a sleep promoting activity [2]. At least two states of sleep are distinguished; the largest portion of sleep is occupied by non-rapid eye movement sleep (NREMS), which is characterized by electroencephalographic (EEG) slow wave activity, whereas REMS reoccurs regularly for relatively short periods of time and has a wake-like EEG activity. Bacterial and viral products stimulate NREMS. Recent studies show that responses of animals inoculated with bacteria, fungi, or viruses are characterized by enhanced NREMS in an initial phase followed by reduced NREMS (in terms of duration and intensity) during convalescence [reviewed in 1,2,11,12]. The initial enhancement of sleep has a predictive value concerning the outcome of the disease: larger increases in NREMS are followed by a higher probability of survival [1].

The increases and inhibition of sleep during the early phase of infection and convalescence, respectively, are regarded as manifestations of the activation and subsequent inhibition of the acute phase response. The alterations in sleep are likely to be mediated by cytokines. Many cytokines have sleep promoting activity; the effects of IL-1 are the best studied in this regard [2,11,12,13]. Exogenous administration of IL-1 elicits dose-related increases in NREMS in rabbits. In rats, small doses of IL-1 have similar effects on sleep as those observed in rabbits; the enhancement is followed by a suppression [14]. However, when dose is increased the sleep suppressive action also increases, sleep becomes fragmented, and eventually sleep duration decreases [15]. It is proposed that the sleep promoting and inhibiting effects of IL-1 are linked to the stimulations of two hypothalamic neurocrines, growth hormone releasing hormone (GHRH) and corticotropin releasing hormone (CRH) (Fig. 1). The importance of the stimulation of GHRH and CRH, however, goes beyond mediating the IL-1 effects on sleep. The activation of the GHRH-growth hormone (GH) hypothalamo-pituitary axis is part of the immunostimulatory mechanisms of IL-1. In contrast, the CRH-adrenocorticotropin hormone (ACTH) system is the major feedback mechanism activated by IL-1 which inhibits many IL-1 actions.

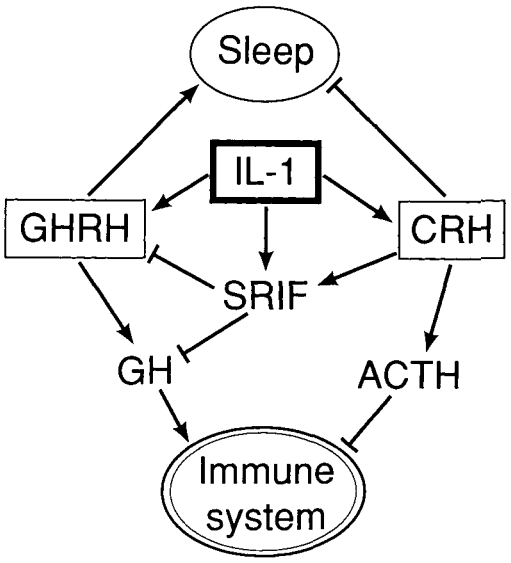

Fig. 1. Diagram illustrating relationships between interleukin-1 (IL-1) and various hormones in regards to sleep and immune system regulation. Abbreviations: CRH, corticotropin releasing hormone; GHRH, growth hormone releasing hormone; SRIF, somatostatin; GH, growth hormone; ACTH, adrenocorticotropic hormone. Arrows indicate stimulation, and the T-like connectors indicate inhibition. This scheme shows only a few of the substances regulating sleep or the immune response; both the brain and immune system are characterized by humoral regulatory redundancies. Nevertheless, the IL-1/GHRH/CRH interrelationships with regard to sleep are the best characterized to date.

PROMOTION OF SLEEP BY IL-1 VIA GHRH

Several lines of evidence indicate that GHRH is a physiological sleep promoting substance. It was reported more than 20 years ago that a major GH release occurs in association with NREMS. It was also clear, however, that these events are not directly related since they could dissociate. The sleep related GH release was attributed to a regulatory mechanism that stimulates both sleep and GHRH release simultaneously. Indeed, it turned out that GHRH not only stimulates pituitary GH secretion but also promotes sleep. Both the duration and the intensity of NREMS are increased in response to a intracerebroventricular (icv) injection of GHRH in rats and rabbits. Intravenous administration of GHRH enhances NREMS in human subjects and rats if GHRH is injected sometime after sleep onset. In contrast, spontaneous sleep is inhibited after icv injection of a GHRH-competitive antagonist or antibodies to GHRH in the rat. The antibodies to GHRH also prevented the enhancement of sleep normally observed after sleep deprivation. It has been suggested that the promotion of sleep and stimulation of GH secretion are mediated by two different outputs of the GHRH containing neurons, one releasing GHRH into the portal vessels at the median eminence and the other projecting to somnogenic structures in the preoptic region [for references see 12,16].

A stimulation of GH secretion was reported by Rettori et al. [17] after icv administration of IL-1; the GH releasing effect of IL-1 disappeared when the dose was increased. The effects of icv IL-1 on sleep and GH secretion in a dose-response study were determined in the rat [18]. The dose of IL-1, 2.5 ng, which was somnogenic [14,15] significantly stimulated GH secretion. In contrast, higher doses of IL-1 suppressed sleep and also inhibited GH secretion. Rettori et al. [17] suggested that the stimulation of GH secretion by IL-1 has a hypothalamic action site. Honegger et al. [19] demonstrated that IL-1 in fact stimulated GHRH release from hypothalamus preparations in vitro. The effect was blocked by cyclooxygenase inhibitors, suggesting the involvement of prostaglandins in the IL-1 effects on GHRH. Harbuz et al. [20] notes that IL-1 also increases GHRH mRNA expression in human lymphocytes. We studied the role of GHRH in the IL-1–induced GH secretion in vivo [18]. Rats were pretreated with antibodies to GHRH and then injected with IL-1. The antibodies inhibited the GH response to IL-1, indicating that the stimulation of GH release by IL-1 requires GHRH. Finally, the effects of IL-1 injections on sleep were studied in rats pretreated with antibodies to GHRH. In addition to reducing normal sleep, the antibodies to GHRH significantly attenuated the sleep promoting effect of IL-1 [21].

In conclusion, IL-1 stimulates GHRH which is implicated in the mediation of both the increased GH secretion and the enhanced sleep elicited by IL-1. In spite of the data suggesting a beneficial effect of sleep during infection, the mechanism of this action is not clear. There is an obvious reduction in energy expenditure during sleep which may allow the conserved energy to be used in host defense. Also, during infection an animal's responsiveness is compromised; thus, sleep, by promoting social withdrawal, may serve to reduce environmental risk. Many observations indicate, however, that GH is necessary for the proper functioning of the immune system. Either directly or through insulin-like

growth factor-I, GH stimulates the proliferation and differentiation of lymphoid, myeloid, and erythroid cells, promotes wound healing, activates monocytes, stimulates the production of superoxide anions by macrophages, and promotes the synthesis of various cytokines, including further production of IL-1. The significance of GH in host defense is demonstrated by the severe immune deficiencies caused by hypophysectomy that can be corrected by the administration of GH [for references see 18,22].

INHIBITION OF SLEEP BY IL-1 VIA CRH

The activation of the CRH-ACTH-glucocorticoid axis is regarded as the most potent negative feedback mechanism for the acute phase response [23]. Glucocorticoids inhibit IL-1 production and exert anti-inflammatory and immunosuppressive effects (in contrast to T cells, however, IL-1 receptors on B-cells might be up-regulated). CRH may directly suppress some IL-1 actions in the central nervous system. Although CRH is implicated in the mechanism of IL-1–induced fever [24], it also seems to contribute to defervescence [25]. In addition, the enhanced sleep in response to IL-1 is inhibited by a dose of CRH which in itself does not affect NREMS [25]. Administrations of larger doses of CRH are followed by a suppression of both normal sleep and IL-1 elicited enhancement of NREMS. It has been speculated that proopiomelanocortin derived substances might be involved in the mediation of the central effects of CRH. Icv administration of α-melanocyte stimulating hormone, a proposed antipyretic, suppresses IL-1 induced sleep [26]. There are many other pathways, however, which can potentially be involved in the arousing mechanism activated by CRH. GH secretion is inhibited by CRH [27]. This finding is in agreement with our observation that high doses of IL-1 suppress both sleep and GH release [18]. The inhibitory effect of CRH on GH is mediated in part by somatostatin [27]. Somatostatin in turn inhibits GHRH; CRH therefore not only stimulates arousal mechanisms but also blocks the hypothalamic neurocrine involved in the sleep promoting effect of IL-1. In addition to being activated by CRH, somatostatin is directly and dose-dependently stimulated by IL-1 in hypothalamic fragments [19].

After the discovery by Besedovsky et al. [28] that IL-1 causes a marked increase in plasma ACTH and glucocorticoid levels, extensive studies have been performed to elucidate the mechanism of this endocrine action. As a result, the stimulation of hypothalamic CRH by IL-1 has become the best-documented endocrine action of any cytokine. The IL-1–induced CRH release was demonstrated in vitro as well as in vivo [for reference see 29]. IL-1 also stimulates the expression of mRNA for CRH in the hypothalamus [20,30], though systemic IL-1 might act on CRH-containing nerve terminals in the median eminence instead of directly stimulating CRH synthesis [31]. Involvement of noradrenergic mechanisms was both suggested and dismissed in the mediation of the IL-1 effect on CRH containing neurons [32], whereas prostaglandins were implicated in the stimulation of both CRH and somatostatin by IL-1 [19,33]. There seems to be a difference in the CRH releasing activity of the two forms of IL-1. IL-1β is clearly more potent than IL-1α; the latter is either ineffective or less effective than IL-1β in stimulating the CRH-ACTH axis [see 20]. Interestingly, when compared on a molar base, IL-1α seems to be more potent in enhancing NREMS than IL-1β [34]; this finding might be related to the differences in CRH release. Finally, it is also possible that IL-1 has a delayed stimulatory effect on ACTH directly at the pituitary, but the findings in this respect are less consistent than in the hypothalamus. Some observations also suggest direct actions of IL-1 on the adrenal cortex, whereas others fail to support this [see 4,29].

IS IL-1 INVOLVED IN NORMAL SLEEP REGULATION?

It is tempting to assume that the mechanism of sleep alteration initiated by infection is an exageration of a process which is involved in normal sleep regulation. IL-1β is indeed found in the normal brain [e.g., 5], it is produced by glial cells, and neurons containing IL-1–like immunoreactivity were also described in the hypothalamus [reviewed in 4]. The mRNAs for IL-1, the IL-1 receptor, and the IL-1RA [6] are expressed in the normal brain [reviewed in 4]. Inhibition of IL-1 by the IL-1RA or by antibodies suppresses spontaneous sleep [reviewed in 2]. Finally, IL-1 concentration in the cerebrospinal fluid varies with the sleep-wake cycle [7]. Collectively, these observations suggest that intracerebral IL-1 is, in fact, a physiological sleep factor. As described above, GHRH is also a physiological sleep substance. A reciprocal interaction

between GHRH and CRH in sleep regulation has been suggested by Ehlers and Kupfer [35]. If this mechanism indeed exists, then IL-1 is one of the likely controllers regulating sleep-wake activity. The relationships between IL-1, GHRH, and CRH in regards to sleep regulation shown in Figure 1 are part of a large system involving many more sleep factors and neuronal structures.

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