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Somnogenic Cytokines and Models Concerning Their Effects on Sleep

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All the sleep-promoting substances currently identified also have other biological activities. Despite years of effort, a single specific central nervous system sleep center has not been described. These observations led us to propose a biochemical model of a sleep activational system in which the effects of several sleep factors are integrated into a regulatory scheme. These sleep factors interact by altering the metabolism, production, or activity of each other and thereby result in multiple feedback loops. This web of interactions leads to sleep stability in that minor challenges to the system will not greatly alter sleep. The system, however, is responsive to strong perturbations, such as sleep deprivation and infectious disease. The sleep-promoting effects of cytokines and their interactions with prostaglandins and the neuroendocrine system are used to illustrate the functioning of a part of the sleep activational system under normal conditions and during infectious disease. Although the actions of individual sleep factors are not specific to sleep, their interactions at various levels of the neuraxis can mediate a specific sleep response. Such a system would also be responsive to the autonomic and environmental parameters that alter sleep.

INTRODUCTION

The concept that sleep is regulated in part by humoral mechanisms is supported by experimental demonstrations of somnogenic substances in tissue fluids (reviewed, [1–4]). These experiments began at the turn of the century with Legendre and Pieron [5] and Ishimori [6], who described the accumulation during prolonged wakefulness of substances in cerebrospinal fluid (CSF) that induce excess sleep when transferred to recipient animals. Although the chemical identity of these substances was never established, today over 30 putative sleep factors (SFs) have been identified (reviewed, [2]). Most of these putative SFs are hormones, immunomodulators, and/or substances involved in endocrine and/or immune regulation.

Abbreviations: ACTH: adrenocorticotropic hormone α-MSH: alpha-melanocyte-stimulating hormone CNS: central nervous system CRF: corticotropin-releasing factor CSF: cerebrospinal fluid DSIP: delta sleep-inducing peptide EEG: electroencephalogram GH: growth hormone GRF: growth hormone-releasing factor icv:intracerebroventricular $IFN_{\alpha 2}$: interferon alpha$_2$ IL-1: interleukin 1 IL-6: interleukin 6 MP: muramyl peptide NREMS: non-rapid-eye-movement sleep PG:prostaglandin PHI: peptide histidine-isoleucine poly I:C: polyriboinosinic:polyribocytidylic acid REMS: rapid-eye-movement sleep TNF: tumor necrosis factor SF: sleep factor VIP: vasoactive intestinal peptide

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Until recently, it was postulated that a SF, herein defined as any substance found within the body that alters sleep, would have biological actions specific to sleep and would act on central nervous system (CNS) executive sleep centers, which were also assumed to be concerned primarily with sleep regulation. A single CNS center necessary for sleep has not, however, been demonstrated. Furthermore, all SFs identified to date have multiple biological activities. Thus, a revision of the original assumptions is necessary. This review describes a model that links the sleep effects of many putative SFs in a sleep activational system.

The sleep activational system presented is fundamentally a biochemical model and, like all models, is provisional; the cellular localization of many of the specific components that are germane to sleep regulation is not known. Nevertheless, it is assumed that specific components of the model ultimately interact with either glia and/or neurons at various levels of the CNS and that such interactions lead to altered sleep. We propose that such a system would be responsive to the many autonomic and environmental parameters that influence sleep, yet would retain the capacity to regulate sleep selectively.

Rapid-eye-movement sleep (REMS) and non-rapid-eye-movement sleep (NREMS) are the two major types of sleep, although subdivisions of each of these classes have been made. To identify these states of vigilance, the electroencephalogram (EEG) and other physiological measurements, e.g., electromyogram, brain temperature, and motor activity, are recorded. REMS and NREMS states exist in most mammals. Sleep in animals, however, is slightly different from that of humans. Thus, species often used in sleep research, such as rats, cats, and rabbits, have sleep episodes that are relatively short, typically lasting only for a few minutes. These bouts of sleep occur sporadically throughout the 24-hour day, alternating with episodes of wakefulness, although the percentage of any given hour spent in sleep is strongly influenced by circadian rhythms.

PROMOTION OF SLEEP BY CYTOKINES

Attempts to identify a sleep-promoting substance accumulating in CSF during sleep deprivation (Factor S) [7] resulted in the discovery of the somnogenic activity of muramyl peptides [8]. The sleep-promoting muramyl peptide isolated from rabbit brain and from human urine has biochemical characteristics similar to those of Factor S obtained from CSF [9].

Muramyl peptides are monomeric building blocks of bacterial peptidoglycans and are released during processing of bacterial cell walls by mammalian macrophages [10,11]. Muramyl peptides, however, are not the only sleep-promoting substances that can be obtained from microorganisms. Endotoxin and its lipid A moiety, components of the cell wall of gram-negative bacteria, also promote NREMS [12,13]. In addition, recent experiments show that a synthetic double-stranded RNA, polyriboinosinic: polyribocytidylic acid (poly I:C) [14], and RNA extracted from influenza-infected lungs are somnogenic [15].

Although the structure and nature of these sleep-promoting agents of microbial origin are widely different, they have an important common feature: all of them stimulate a set of systemic host defense reactions collectively termed the acute-phase response. Manifestations of the acute-phase response include activation of the immune system, changes in hormone secretion and hepatic synthesis of plasma proteins, alterations in metabolism, and fever [16,17]. These changes are observed after infections or tissue damage. Increased lassitude or sleepiness is a common experience

during infectious diseases; these symptoms are regarded as part of the acute-phase response. Recent studies, in fact, have produced experimental evidence for enhancement of sleep during bacterial [18] and fungal [19] infections. It seems, therefore, that the somnogenic activities of muramyl peptides, endotoxin, or double-stranded RNA are associated with the capacity of these substances to stimulate the acute-phase response. This notion suggests that the mechanisms of the acute-phase response may provide clues for understanding sleep regulation.

The acute-phase response is under humoral regulation. The bioactive substances released from cells affected by infection, inflammation, or tissue damage reach a wide range of target organs, including the CNS. Classical examples of inflammatory mediators include histamine, prostaglandins, neuropeptides like substance P, hormones (cortisol, growth hormone [GH], and the like), and well-known neuronal transmitters like noradrenaline [16,17,20]. A special group of polypeptides, the cytokines, has, however, fundamental importance in the mediation of the acute-phase response. Muramyl peptides, endotoxin, and poly I:C are all well known for their ability to induce cytokine production. Although production of cytokines was formerly attributed to leukocytes, it has now been established that at least some cytokines can be released from a wide variety of cells [16] and that cytokines may act as general intercellular communication signals. The number of identified cytokines increases continuously, and interactions among cytokines are complicated and poorly understood. Some seem to act in parallel, whereas others may be involved in a cascade-like process or may inhibit each other [17,21]. The amount of individual cytokines released varies with the specific noxious agent [22], and this fact may be reflected by differences of the clinical symptoms of the acute-phase response. Nevertheless, one of the cytokines, interleukin 1 (IL-1), seems to have an essential role in the mediation of the acute-phase response. Administration of IL-1 elicits all of the studied clinical and laboratory changes characteristic of the acute-phase response, indicating that IL-1 either directly or through other cytokines can activate the complete machinery of this syndrome [16]. Indeed, IL-1 was even found to promote sleep [23].

Rabbits spend about 45–50 percent of daylight hours in NREMS and about 5–10 percent of the time in REMS (Fig. 1). When they are given IL-1, either intravenously or intracerebroventricularly (icv), the amount of time spent in NREMS increases to 60–70 percent or more [23]. The enhancement of NREMS occurs at the expense of both REMS and wakefulness (Fig. 1) [24]. These effects on sleep are observed within the first hour after administration of IL-1; in contrast, the increases in sleep after muramyl peptide (MP) administration appear only after a delay of one to two hours. IL-1-enhanced NREMS persists for three to 12 hours, depending on the dose. The animals continue to awaken spontaneously and maintain normal postures; thus, the excess NREMS seems to be physiologically normal. Another characteristic of NREMS induced by IL-1 is that it appears to be more intense than spontaneous sleep; EEG slow waves (0.5–4.0 Hz) of supranormal amplitudes are observed [23,24]. Similarly, the deep sleep that follows sleep deprivation is also characterized by EEG slow waves of very high amplitude [25]: these supranormal EEG slow waves are thought to be a measure of the intensity (or depth) of NREMS [26]. Thus, after either sleep deprivation or IL-1 treatment, enhanced NREMS seems to result from an exaggerated activation of physiological sleep mechanisms.

The term IL-1 refers to two polypeptides distinguished as IL-1α and IL-1β, which have some structural homologies, act on the same receptors, and have practically

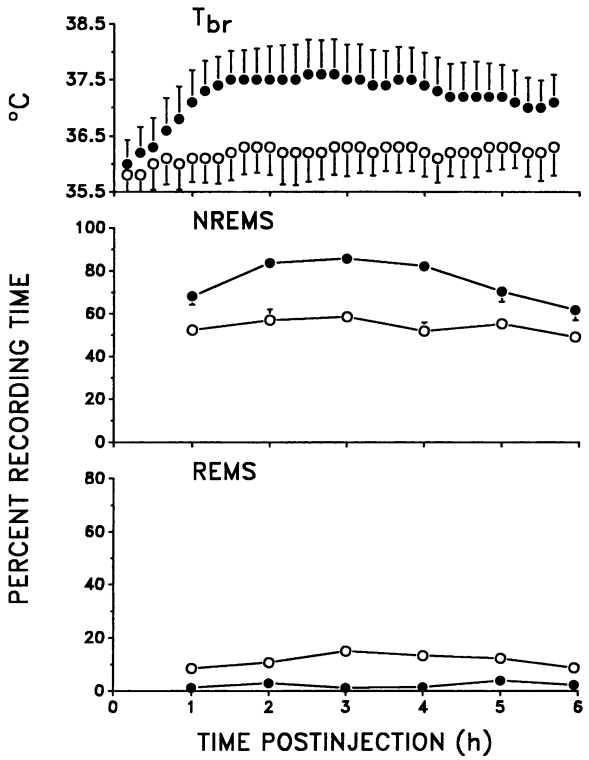

FIG. 1. Effects of intracerebroventricular injection of 5 ng interleukin 1β (IL-1β) on rabbit brain temperature (T_{br}), non-rapid-eye-movement sleep (NREMS), and rapid-eye-movement sleep (REMS). Values are means ± SE for six animals (except T_{br}, $n = 5$). Symbols are as follows: control recordings (artificial cerebrospinal fluid, *open circles*), IL-1β (*closed circles*).

identical biological actions when studied in various *in vitro* and *in vivo* tests [27]. The sleep effects of IL-1α and IL-1β are also very similar [28]. Increases in NREMS were also observed after administration of two other cytokines, tumor necrosis factor (TNF) [24] and interferon α_2 ($IFN_{\alpha 2}$) [29]. The somnogenic actions of these cytokines could be mediated through IL-1 (both TNF [30] and IFN can release IL-1, though this effect of $IFN_{\alpha 2}$ is relatively weak [31]), or they could act independent of IL-1. TNF, for example, is known to share many of the biological actions of IL-1, although the cellular receptors for TNF and IL-1 (α or β) are different [32]. Similarly, the pyrogenic action of IFN is probably not mediated through IL-1 [33].

In considering the sleep-promoting effects of cytokines, particularly IL-1, our starting point was a pathological condition: the acute-phase response. When IL-1 is injected into an animal, increased sleep appears as part of the acute-phase response, accompanied by other symptoms like fever, elevated serum copper, and so on [16]. It is therefore important to determine whether the IL-1 mediation of sleep only functions under special conditions or also contributes to normal sleep regulation. Theoretical considerations and indirect evidence suggest that IL-1 can be involved in physiological sleep regulation [34].

It is reasonable to suppose that the various aspects of the acute-phase response are mediated at different sites and therefore can be separated. Thus, antipyretics inhibit IL-1-induced fever without attenuating the increases in NREMS [23]. Interleukin 6 (IL-6), a recently discovered cytokine, has been implicated in the mediation of certain IL-1 effects, such as synthesis of acute-phase proteins and fever [35]; icv administration of IL-6, in fact, elicits fever in rabbits. This response, however, is not coupled with

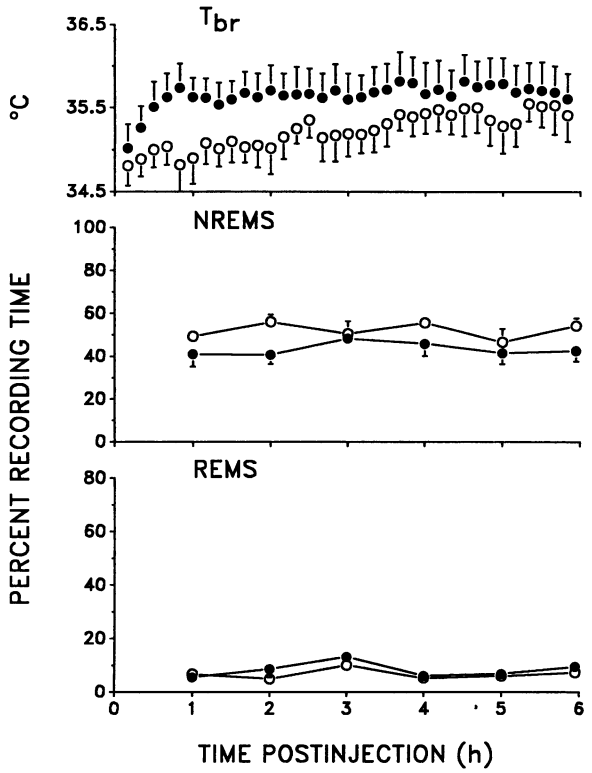

FIG. 2. Effects of intracerebroventricular injection of 80 ng interleukin 6 (IL-6) on rabbit brain temperature (T_{br}), non-rapid-eye-movement sleep (NREMS), and rapid-eye-movement sleep (REMS). Values are means ± SE for six animals (except T_{br}, $n = 5$). Symbols are as follows: control recordings (artificial cerebrospinal fluid, *open circles*), IL-6 (*closed circles*).

increased sleep (Fig. 2) [36]. It has been suggested, therefore, that endogenous IL-1 released in optimal concentrations at the proper effector site(s) may promote sleep without evoking the complete pattern of the acute-phase response [34].

Various cells can produce IL-1; however, macrophages are the primary source of blood-borne IL-1, which mediates various symptoms of the acute-phase response. Although plasma IL-1 activity reportedly peaks at the onset of NREMS in man [37], it is likely that IL-1 involved in physiological sleep regulation is of CNS origin. IL-1-like activity in the CSF varies with the sleep-wake cycle [38]. Receptors for IL-1 have been demonstrated in various structures in the CNS [39]. IL-1β mRNA is constituently expressed in the brain [40]; glial cells are known to produce IL-1 [41]. Recently, IL-1-immunoreactive hypothalamic neurons were described [42]. These findings clearly indicate that IL-1 is not only a mediator of the acute-phase response but has physiological functions in the CNS.

MULTIPLE SLEEP FACTORS: A SLEEP ACTIVATIONAL SYSTEM

Based on various considerations, including their sleep-promoting effects, a great number of substances have been proposed as physiological SFs. Table 1 provides a summary of putative SFs. Note, however, that this list is probably far from complete. None of these substances are specific for sleep; most of them are well-known neuropeptides, transmitters, hormones, or immunomodulators. As a result of testing in various *in vitro* and *in vivo* systems, these substances have also been shown to interact; they might promote, stimulate, or inhibit the production or action of one another. If these

TABLE 1
Substances That Have Been Identified as Sleep Factors

	References
A. Substances that enhance non-rapid-eye-movement sleep (NREMS):	
cholecystokinin (CCK)	[43,44]
insulin	[45,46]
desacetyl-alpha-melanocyte-stimulating hormone (desacetyl-α-MSH)	[47]
interleukin 1 (IL-1)	[23,24]
interferon α_2 ($IFN_{\alpha 2}$)	[29]
tumor necrosis factor (TNF)	[24]
muramyl peptides (MPs)	[8,9]
double-stranded RNA (dsRNA)	[14,15]
endotoxin/lipid A	[12,13]
B. Substances that enhance REMS:	
somatostatin	[46,48]
growth hormone (GH)	[49–51]
corticotropin-like intermediate lobe peptide (CLIP)	[47]
vasoactive intestinal polypeptide (VIP)	[52–56]
peptide histidine-isoleucine (PHI)	[56]
prolactin (PRL)	[56,57]
gamma-Br	[58]
C. Substances that enhance both NREMS and REMS:	
growth hormone-releasing factor (GRF)	[59–62]
delta sleep-inducing peptide (DSIP)	[63–65]
arginine vasotocin (AVT)	[66,67]
prostaglandin D_2 (PGD_2)	[68,69]
uridine	[70]
adenosine	[71]
serotonin (5HT)	[72]
D. Substances that inhibit sleep:	
α-MSH/adrenocorticotropic hormone (ACTH)	[73,74]
corticotropin-releasing factor (CRF)	[59,75]
endogenous opioids	[76]
glucocorticoids	[77]
thyrotropin-releasing hormone (TRH)	[78]
prostaglandin E_2 (PGE_2)	[69,79]
neuropeptide Y	[80]

substances are in fact SFs, the interaction between them can be regarded as sleep regulation itself. We call the SFs linked through their interactions the sleep activational system. In this model, sleep is regulated through cascades of biochemical events; however, many of the pathways can also work in relative independence, and a wealth of feedback loops is involved. It is important to emphasize that at present we do not know the relative contribution of the individual substances to physiological sleep regulation. Furthermore, the interactions are derived from experiments in which sleep was not monitored; therefore, the role of these interactions in sleep regulation remains to be evaluated. With these considerations in mind, a part of the sleep activational system is depicted in Fig. 3; there is reasonable evidence to suppose that the substances and interactions shown are involved in sleep regulation [81,82].

Stimuli associated with duration of prior wakefulness and the circadian clock are generally assumed to be inputs for sleep regulation [26]. Although tissue fluid levels of

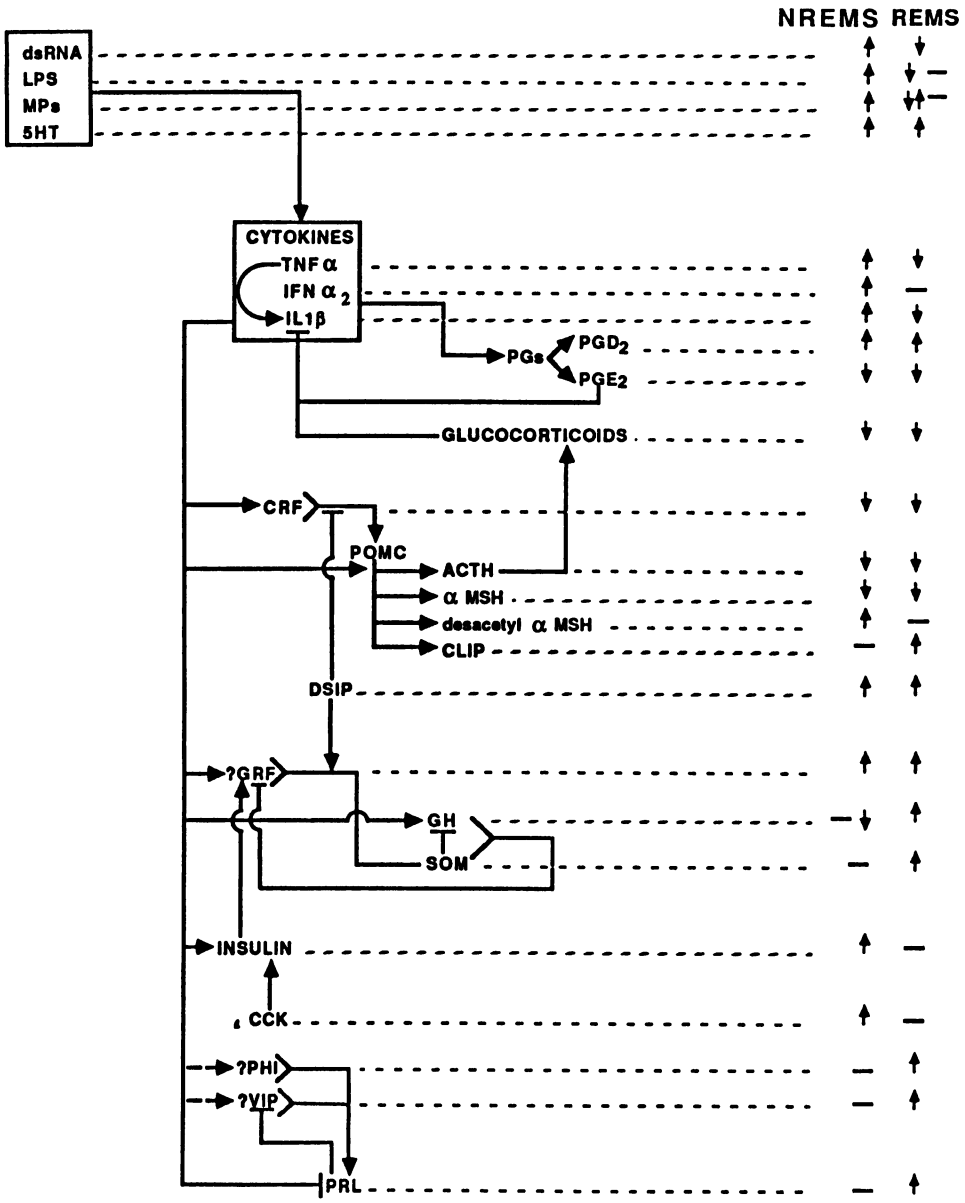

FIG. 3. Sleep activational system showing possible interaction between putative sleep factors and effects of those sleep factors on non-rapid-eye-movement sleep (NREMS) and rapid-eye-movement sleep (REMS). The usefulness of this model is that it provides concrete examples for testing experimentally. For example, one would predict that during bacterial infection, when the supply of MPs and/or LPS is increased, that NREMS should be enhanced because cytokine production is enhanced; this hypothesis, indeed, seems to be the case (see [18,19]). Another prediction, not yet tested, would be that if one lesioned the arcuate nucleus, thereby removing neurons containing CRF and alpha MSH, one would remove a negative feedback signal for IL-1: this procedure should result in a "right shifted" IL-1 dose-sleep response curve. dsRNA, double-stranded ribonucleic acid; LPS, lipopolysaccharide; MPs, muramyl peptides; 5HT, serotonin; TNF, tumor necrosis factor; IFN, interferon; IL-1, interleukin 1; PG, prostaglandin; CRF, corticotropin-releasing factor; POMC, proopiomelanocorticotropin; ACTH, adrenocorticotropic hormone; α-MSH, alpha melanocyte-stimulating hormone; CLIP, corticotropin-like intermediate lobe peptide; DSIP, delta sleep-inducing peptide; GRF, growth hormone-releasing factor; GH, growth hormone; SOM, somatostatin; CCK, cholecystokinin; PHI, peptide histidine isoleucine; VIP, vasoactive intestinal peptide; PRL, prolactin. Refer to Table 1 for original references concerning the sleep effects of these compounds. *Left,* lines; → indicates stimulation and ⊣ indicates inhibition. *Arrows,* right, indicate sleep effects: ↑ indicates increases, ↓ decreases, — no effect.

most of the substances depicted in Fig. 3 have circadian rhythms, the mechanisms responsible for these variations are not known. The effect of normal wakefulness on the turnover and release of SFs has not been studied, although the effects of sleep deprivation were tested on some of the substances. Sleep deprivation, however, is not a physiological condition; many functions might be affected by this stressor, and the specificity of the changes observed is difficult to determine. IL-1 activity in blood [83] and vasoactive intestinal peptide (VIP) immunoreactivity in the CSF [84] increase during sleep deprivation. GH secretion is inhibited during sleep deprivation, whereas recovery sleep is accompanied by greater GH release than normal [85–87]. This finding may indicate an activation of the hypothalamo-pituitary growth hormone-releasing factor (GRF)-GH axis. It is likely, however, that both wakefulness and the circadian clock act on many sites of the sleep activational system.

The body is continuously exposed to bacterial invasion from mucous surfaces, especially from the gut. Bacterial products may therefore have tonic stimulatory activity on the sleep activational system and may be of primary importance as inputs for sleep in infectious diseases [2]. As mentioned above, muramyl peptides from bacteria and endotoxin from gram-negative bacteria stimulate the release of cytokines. IL-1 and other cytokines, in turn, stimulate the prostaglandin (PG) metabolism [16,88]. Some PGs, e.g., PGD_2, enhance sleep [68], while others, e.g., PGE_2 [79], inhibit sleep; thus it is possible that IL-1 and/or other cytokines alter sleep through their effects on PGs. Furthermore, PGE_2 inhibits IL-1 production and induces IL-1 receptor synthesis [89], thereby providing a somewhat complicated short-loop feedback system. The timing of these events *in vivo* remains unknown.

Association of NREMS and GH secretion has been documented in several species [90–92], suggesting a link between the two phenomena. It has recently been shown that icv administration of GRF, a hypothalamic peptide that stimulates pituitary GH secretion, also promotes sleep, especially NREMS [59–62]. GRF therefore is another probable input for sleep regulation, and the various stimuli which affect GRF release all possibly modulate sleep-wake activity. GRF may also be involved in IL-1 effects. IL-1 increases GH secretion through a hypothalamic effector(s) [93] that is (are) likely to be GRF. Although promotion of sleep and stimulation of GH secretion are regarded as two separate outputs of the hypothalamic GRF mechanism [62] (the actions on sleep are assumed to be mediated through basal forebrain projections of the GRF-containing neurons), the hormonal effects of GRF might contribute to sleep regulation. GH may provide negative feedback for NREMS [50], and there are indications that both GH [49–51] and somatostatin [48] (a hypothalamic factor inhibiting GH secretion; somatostatin release is stimulated by rising GH secretion and also by GRF) may promote REMS. VIP and peptide histidine-isoleucine (PHI) are CNS neuropeptides, and, among other functions, they act as hypothalamic releasing factors for pituitary prolactin secretion [94]. VIP, PHI, and prolactin all stimulate REMS [52–57]. Although IL-1 stimulates prolactin release via the hypothalamus [93], it inhibits prolactin secretion from the pituitary [95]. This latter mechanism might be involved in suppression of REMS after high doses of IL-1.

The function of the corticotropin-releasing factor (CRF)-adrenocorticotropic hormone (ACTH)-glucocorticoids hypothalamo-pituitary adrenal axis is largely under circadian control, independent of sleep-wake activity; however, sleep-related inhibition of this system can also be demonstrated for a short period after sleep onset [96,97]. CRF and ACTH-alpha-melanocyte-stimulating hormone (α-MSH), in turn, inhibit

sleep [59,73–75], and CRF also inhibits GH secretion in rats through a hypothalamic mechanism [98]. The CRF-ACTH/α-MSH-glucocorticoid system is likely to act as a major feedback loop for IL-1 [99]. Hypothalamic CRF secretion is stimulated by IL-1 [100,101]. CRF attenuates IL-1-induced enhancement of NREMS (and fever) [75]; the effects may be mediated, at least in part, by stimulation of central opiomelanocortinergic neurons resulting in α-MSH release. Activation of pituitary ACTH secretion results in glucocorticoid release. Glucocorticoids inhibit IL-1 production and various IL-1 actions [99], though IL-1 receptor synthesis is enhanced [89].

Stability is a major characteristic of the proposed sleep activational system. This feature stems from the multiplicity of SFs, the wealth of sleep-promoting pathways which often act in parallel, providing alternative mechanisms, and from the numerous feedback loops. In such a system, manipulation of a single SF is not detrimental, though the extent of changes may vary with the importance of the factor involved. Therefore, removal of a SF or blockade of a part of the sleep activational system per se does not necessarily result in sleep loss (and certainly not in total insomnia), but rather in decreased sleep stability. Because of the reduced stability, however, the system becomes vulnerable; for example, exogenous or endogenous stimuli which are normally ineffective may produce impairment of sleep. For example, increased sensitivity to environmental stimuli is a frequent complaint of patients suffering from sleep disturbances.

Due to the stability of sleep regulation, manipulation of a single SF does not have a great influence on sleep. In fact, all the experimental manipulations that reliably produce increases in sleep, i.e., prolonged sleep deprivation, infectious disease, excessive exercise, and prolonged starvation, are not physiologic. In these cases, enhancement of sleep is likely to be mediated at various sites of action. After less aggressive sleep-promoting manipulations (slight acute increases in ambient temperature above thermoneutrality, food intake), the occurrence of sleep is a statistical rather than an obligate phenomenon, indicating that these stimuli affect the sleep activational system within normal circadian limits.

The effects of many of the putative SFs vary when tested under different experimental conditions (species, timing of the administration with respect to the circadian rhythm, habituation of the animals, and so on) [102]. The variation of the sleep-promoting actions of these substances might also result from the stability of the system. The effects of a sleep substance depend on the function, availability, and simultaneous actions of many other substances, and if all conditions are not met, the exogenous administration of a sleep factor might be ineffective. As discussed above, the circadian pacemaker provides input(s) to the sleep activational system and is therefore an important stabilizing factor. It has been recognized that some of the proposed SFs (uridine, PGD_2) are more effective when administered during the active cycle than in the rest cycle [102]. It is assumed that the exogenously applied substance competes with a high concentration of endogenously produced SFs for the same receptors in the rest period, whereas the majority of the receptors are free and available for the exogenous substance in the active cycle. Other SFs, like delta sleep-inducing factor (DSIP), seem to be more effective if there already exists a spontaneous sleep pressure, presumably because their actions require prior activation of some component of the sleep regulation system [103]. Since the CRF-ACTH-glucocorticoid axis is a negative feedback mechanism for the sleep-promoting and pyrogenic actions of cytokines, it is possible that the effects of exogenous IL-1 are attenuated when the endogenous

corticoid level is high. Indeed, although circadian variations in rabbits are relatively small, we found that the sleep-promoting effect of MP was slightly reduced (the pyrogenic action was blocked) when the substance was injected at night [104]. Finally, if the mechanism of the circadian regulation is a stabilizing factor for the sleep activational system, it can be assumed that attenuation or removal of this factor increases the responsiveness of sleep regulation to exogenous stimuli. In this context, it is worth noting that many of the putative sleep substances (GRF, DSIP, IL-1, MPs) are more effective in rabbits with little circadian rhythm than in rats with a pronounced circadian variation (e.g., [62]).

MEDIATION OF SPECIFIC SLEEP RESPONSES BY NONSPECIFIC SUBSTANCES

The sleep activational system illustrated in Fig. 3 shows possible interactions between many SFs. All of the putative SFs included have other biological activities, however, some of which are not associated with normal sleep. For example, IL-1 and some PGs are pyrogenic, yet body temperatures decrease upon entry into NREMS [105,106]. How can substances not specific to sleep mediate specific sleep responses?

Electrical or chemical stimulation of many brain structures elicits sleep or sleep-like EEG activity. Lesions in various brain regions result in hypersomnia or insomnia, followed by partial or complete recovery of sleep. Furthermore, sleep itself involves changes in many behavioral, psychological, and physiological variables. These variables, in turn, probably alter the activity of many brain areas implicated in sleep regulation. Such considerations led McGinty to conclude that sleep is regulated via numerous independent neuronal networks at all levels of the neuraxis [107]. Figure 4 depicts three such neuronal sets (A–C), each contributing to a propensity to sleep, operating in parallel and interconnecting with each other [81]. Any substance acting on these neuronal sets to alter sleep/wake activity is considered a SF (W–Z, Fig. 4).

We envision that a single neuronal set will interact with one or more SFs (two in the case of Fig. 4) and that the magnitude of stimulation of a neuronal set is dependent upon the concentrations of the SFs interacting with it. Similarly, a single SF may interact with more than one neuronal set with various affinities, and the effects of a SF on one neuronal set may differ from its effects on another neuronal set. For the purpose of illustration, we have assigned hypothetical numerical values to the outputs of each neuronal set in terms of two different biological activities. These values represent relative contributions of individual neuronal sets to the variable shown. It is emphasized that if one chooses different neuronal sets, the relevant biological variables would be different; e.g., another neuronal set may influence sleep, osmotic balance, and blood glucose levels. It is assumed that if the combined value of the outputs from the three neuronal sets shown for an individual activity reaches 9, then an increase in that activity will occur.[1] The output from any individual neuronal set is variable, although limited to the range shown, and depends on the degree of SF stimulation. Thus, the effect of SFs on sleep can be described as follows.

[1]This model is formally set up as a threshold system; i.e., a certain level of activation must be reached before effects are observed. This method was used for ease of illustration. Similar models in which each neuronal set continuously provides some degree of activation/inhibition for each biological activity that it affects can also be constructed. The same conclusions are reached, although the quantitative description of the process is more lengthy and is unnecessary for this discussion.

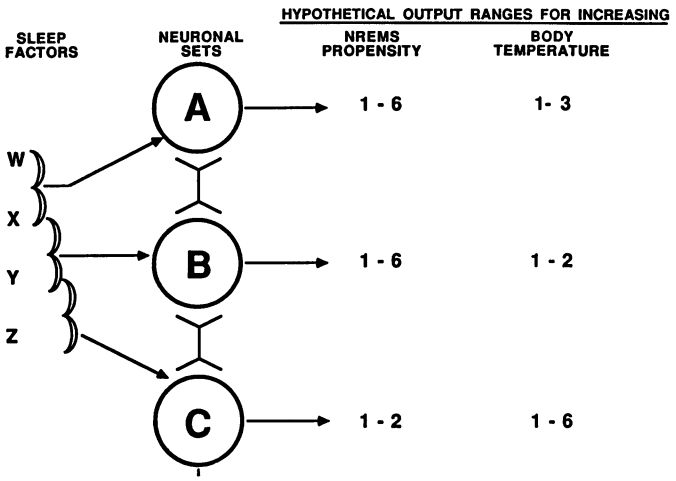

FIG. 4. Illustration of how sleep factors with multiple biological activities may selectively alter sleep.

1. Some neuronal sets contribute more (have a larger output value; e.g., Fig. 4, A, B > C) to sleep propensity than others; thus, some SFs are more important for normal sleep than others (e.g., SF-X has a greater potential for enhancing sleep than does SF-Z, Fig. 4).
2. If the output of two neuronal sets remains constant, maximal stimulation of a third neuronal set could permit the sleep threshold to be reached; that is, the exogenous administration of a SF may induce excess sleep.
3. In contrast, if sets B and C are at minimal output levels, maximal stimulation of set A alone will not initiate sleep.
4. Total sleep propensity would be reduced if one set were lesioned, although sleep would be possible if the remaining sets were driven to a greater degree. Thus, an inherent feature of this model is that no individual neuronal set causes sleep, but all individual sets contribute to overall sleep propensity.

Another concept depicted in Fig. 4 is that neuronal sets are involved in physiological functions other than sleep. To illustrate how responses specific to sleep could result from such a construction, we have included one additional physiological parameter in Fig. 4, body temperature, and, as in the case of sleep propensity, assigned hypothetical numerical values for the outputs from each neuronal set for that function. Again, we assume that a collective value of 9 (from all three sets) must be reached before an increase in body temperature occurs. If the concentrations of SFs W–Z are such that the output for A is 6, for B, 2, and for C, 1, then the combined outputs of sets A–C for sleep would be 9, thus increasing sleep propensity. In contrast, the combined outputs for body temperature would be 6 (because neural set A cannot contribute more than 3 to this activity); thus, body temperature would not be affected by this particular combination of SF concentrations; thereby a specific effect on sleep would be observed. In contrast, if we choose a scenario such that the concentrations of SFs permit an output of 3 for A, 1 for B, and 5 for C, then the combined outputs from the three sets for sleep would be 6, and that for body temperature 9. Thus, body temperature, but not sleep, would be enhanced under this particular combination of SF concentrations.

The data presented in Figs. 1 and 2 can be used as concrete examples to illustrate these ideas further. Thus, IL-1β (Fig. 1) may be considered sleep factor X (Fig. 4)

having the ability to interact strongly with both neuronal sets A and B to enhance NREMS propensity and also to interact with these sets to enhance body temperature. In contrast, IL-6 (Fig. 2) may be considered to be an additional factor (not illustrated and not a sleep factor in Fig. 4) that has the capacity to increase the output of neuronal set C for body temperature and, perhaps, other neuronal sets involved in temperature, but not sleep, regulation. It could not add significantly to NREMS propensity because it cannot interact with neuronal sets A and B and neuronal set C has only a limited capacity to alter NREMS.

It is possible that there are multiple sites in the brain hierarchically arranged to regulate sleep. At each level, something similar to Fig. 4 could be developed; however, the complexity may be different at each level of the hierarchy. At some levels, it is possible that no set would be specific for any physiological function, such as sleep, and all would be involved in regulation of two or more variables. We consider such a brain construction likely for any behavior as complex as sleep.

CONCLUSION

From the discussions presented here, it is clear that cytokines and many other substances alter sleep. We have presented a model of how the regulation of many SFs may be interrelated and another model illustrating how SFs may interact with various neuronal sets to produce specific sleep responses. Ten years ago, it would have been unrealistic to present such models because the roster of putative SFs was much smaller, and there was very little information concerning how SFs might affect each other; however, despite the great number of advances within the field of SFs, many questions remain unanswered. Major challenges that need to be addressed include: *(1)* How do SF concentrations change with sleep/wake cycles and under pathological conditions? *(2)* What is the timing of these changes? *(3)* Where do these changes take place? *(4)* Is one change linked directly to another?

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