Molecular mechanisms in allergy and clinical immunology

Series editors: William T. Shearer, MD, PhD, Lanny J. Rosenwasser, MD, and Bruce S. Bochner, MD

Links between the innate immune system and sleep

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Sleep is a fundamental physiologic process with unknown functions. It is divided into 2 distinct states: non–rapid-eye-movement sleep and rapid-eye-movement sleep. After acute infection with nonneurotropic agents, there are stereotypic changes in non–rapid-eye-movement sleep, particularly increased time spent in slow-wave sleep, and often a reduction of time spent in rapid-eye-movement sleep. It is now recognized that both infection-associated sleep and spontaneous sleep are regulated, in part, by immune mediators called cytokines. This review provides brief tutorials on the elements of the innate immune system that detect infection, how sleep is characterized in the laboratory, issues regarding the interpretation of sleep effects on immune function, the interaction of sleep with circadian rhythms and stress, and some of the microbial products, cytokines, and neuropeptides associated with sleep regulation. We also summarize our current understanding of the role of sleep in host defense and asthma exacerbation. (J Allergy Clin Immunol 2005;116:1188-98.)

Key words: *Sleep, infection, innate immunity, virus, bacteria, toll-like receptors, cytokines, circadian rhythms, stress, asthma*

Abbreviations used

APR:	Acute-phase response
dsRNA:	Double-stranded RNA
EEG:	Electroencephalographic
GHRH:	Growth hormone–releasing hormone
NK cells:	Natural killer cells
NLR:	NACHT–leucine-rich repeat bearing proteins
NOD:	Nucleotide-binding oligomerization domain
NREMS:	Non–rapid-eye-movement sleep
PAMP:	Pathogen-associated molecular pattern
PGD_2:	Prostaglandin D_2
REMS:	Rapid-eye-movement sleep
SWS:	Slow-wave sleep
TLR:	Toll-like receptor

The innate immune system of mammals comprises numerous antimicrobial mechanisms,[1] some of which can be traced back to the first multicellular organisms. Until recently, study of the innate immune system has taken a back seat to the more evolutionarily advanced acquired immune system. In the last decade, however, the emphasis in immunology has shifted to innate immune mechanisms with the discovery of certain key concepts and molecular classes described below.[2] The innate immune system appears to have 2 primary functions: rapid isolation and destruction of invading pathogens (or foreign cells, such as tumors or transplants) through inflammatory processes and antigen recognition and processing for the acquired immune system. The acquired immune system, in turn, uses antibodies and cytotoxic cellular mechanisms that help clear residual microorganisms and, through immunologic memory, speed up their detection and removal in future reinfections.

In the context of infection, both of these innate immune functions require distinguishing pathogenic microorganisms from the self. In recent years, microbiologists have characterized an evolutionarily conserved receptor system that appears to be the major cell membrane–bound system for pathogen recognition. This receptor system has been named the Toll-like receptor (TLR) system after the Toll system of fruit flies,[3] where this class of pathogen-associated molecular pattern (PAMP) recognition receptors was first identified. Currently, TLRs comprise 13 receptors (some found in mice, some found in human subjects, and most shared by both species[4]) that recognize a range of PAMPs unique to microorganisms. These PAMPs include the LPS on the surface of gram-negative bacteria (TLR4), lipopeptides on gram-positive bacteria and mycoplasma (TLR2, TLR1, and TLR6),[5,6] fungal polysaccharides (TLR2), bacterial flagellae (TLR5 and TLR11),[6] unmethylated bacterial and viral DNA (TLR9), guanosine-uridine–rich viral RNA (TLR7 and TLR8),[7]

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Supported solely by National Institute of Health grants NS25378, NS31453, and HD36520.

Received for publication May 24, 2005; revised August 1, 2005; accepted for publication August 3, 2005.

Available online October 4, 2005.

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0091-6749/$30.00

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doi:10.1016/j.jaci.2005.08.005

or the double-stranded RNA (dsRNA) induced during viral replication (TLR3).[3] TLRs all possess amino-terminal leucine-rich repeats that are responsible for PAMP recognition, as well as a carboxy-terminal TLR1 receptor domain required for intracellular signaling.[6] Most TLRs are expressed on the cell surface, but those that recognize nucleic acids are all expressed in endosomal compartments.[6] Soluble factors are also involved in pathogen recognition and can work in association with TLRs and with more generic scavenger, complement, and lectin receptors on phagocytes.[1]

Selected bacterial PAMPs, the peptidoglycans, are also sensed by a family of cytoplasmic proteins, termed the nucleotide-binding site/leucine-rich repeat proteins.[8] This family of pathogen recognition receptors has recently been dubbed NLRs (NACHT–leucine-rich repeat bearing proteins) for convenience.[9] The best studied members of this cytoplasmic system are the nucleotide-binding oligomerization domain (NOD) proteins NOD1 and NOD2.[6] Peptidoglycans are a major structural component of all bacterial cell walls, and NODs can distinguish gram-negative and gram-positive peptidoglycans.[10] There is controversy as to whether peptidoglycans are recognized by TLR2 on the cell surface, as well as intracellular NLRs.[11] Elucidation of the PAMPS for TLRs and related proteins have provided valuable insights into the cause of such human diseases as Crohn's bowel disease and recurrent bladder infections.[6]

Major effector cells in the innate immune system are the circulating phagocytic leukocytes (neutrophils and monocytes), natural killer cells (NK cells), natural killer T lymphocytes (NK T cells), and γδ T lymphocytes. Fixed macrophages and dendritic cells are widely distributed throughout tissues. All of these cells express TLRs that recognize pathogens. TLRs have only recently been found on NK cells[12] and γδ T cells.[13] A central function of phagocytes is to recognize, engulf, and (ideally) destroy pathogens through several mechanisms, often involving oxygen and nitrogen free radicals. NK cells and cytotoxic NK T cells also play a key role in eliminating infected or otherwise altered cells, such as tumor cells.[2,14] Dendritic cells are key antigen-processing cells and form a central link between innate and acquired immunity.[2] Tissue mast cells (which also express TLRs[15]) and enterochromaffin cells[16] also play a role in innate immunity through release of vasoactive factors, such as histamine and serotonin. All of these cells release cytokines when invaded by microbes or when stimulated by other cytokines or mediators released in the course of inflammation.

Cytokines are an enormously complex network of peptide-signaling molecules that are synthesized by immune cells activated by PAMP recognition.[17] Cytokines are also made by infected epithelial cells, endothelial cells, and virtually any other cell when appropriately stimulated, although the specific types made[18] and quantities produced per cell might differ from phagocytes. More than 100 cytokines have been identified, several of which are key regulators of allergy and asthma responses.[19] The cytokines are generally classified as proinflammatory (type I) or anti-inflammatory (type II) and include classical endocrine hormones, such as prolactin and growth hormone, as well as chemotactic chemokines and immunomodulatory type I IFNs as subsets.[14]

The release of cytokines from infected cells alerts neighboring cells through paracrine mechanisms that the host is under attack. This cytokine signaling induces protective cytokines (eg, IFNs) in those neighboring cells and stimulates chemotaxis of inflammatory cells, such as neutrophils, to supplement local defenses. In sufficient concentrations cytokines spill into the lymph and blood to act on the brain, liver, and bone marrow. Circulating cytokines act on brain capillary endothelium to induce pyrogenic prostaglandins and enter the brain parenchyma through specific transporters and at sites lacking a blood-brain barrier, such as the organum vasculosum of lamina terminalis and the median eminence of the hypothalamus.[20] Once in the brain, proinflammatory cytokines induce themselves, as well as prostaglandins and anti-inflammatory cytokines.[21] Extensive evidence indicates that cytokines also signal the brain through the vagus nerve (although this has recently been questioned[22]) and can thereby induce cytokine synthesis in selected regions of the brain.[20] The accumulated systemic and brain proinflammatory cytokines initiate a complex and protective physiologic response termed the acute-phase response (APR).[23] The most commonly studied physiologic APR is fever. Our laboratory has characterized one of the even more complex APRs, excess slow-wave sleep (SWS). Several recent reviews[17,24-32] have discussed the humoral regulation of physiologic and pathologic sleep by microbial products, cytokines, and hormones. This article will summarize and update these reviews with respect to selected microbial products, infective organisms, cytokines, and neuropeptides. In addition, we will discuss our limited knowledge of the host defense role of sleep. Finally, we will discuss the relationship of sleep to asthma.

BASICS OF SLEEP

We spend a third of our lives asleep, but despite a century of study,[30] we have very little understanding of why we sleep. All mammals sleep, although in radically different amounts and patterns. For example, aquatic mammals sleep on one side of the brain at a time to avoid drowning.[33] In an effort to better understand physiologic sleep, our studies have focused on sleep alterations that occur after challenge with microbial products of the type detected by TLRs and NODs or after actual infection.

Whether physiologic or pathologic, sleep is divided into 2 states: non–rapid-eye-movement sleep (NREMS; quiet sleep) and rapid-eye-movement sleep (REMS; paradoxical sleep or dream sleep). These 2 states manifest very differently and appear to be regulated by different regions of the brain.[34] NREMS and REMS are defined by electroencephalographic (EEG) brain wave patterns, the amount of eye movement, and brain temperature by using EEG

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