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List of Abbreviations

- 5 HT : Serotonin
- Ach : Acetyl Choline
- ACTH : Adrenocorticotropic Hormone
- AD : Autoimmune Disease
- ARAS : Ascending reticular activating system
- AS : Ankylosing Spondylitis
- BF : Basal forebrain
- BZD : Benzodiazipine
- CAP : Cyclic Alternating Pattern
- CCL4 : Chemokine (C-C motif) ligand 4
- CHF : Chronic Heart Failure
- CNS : Central Nervous System
- CSA : Central Sleep Apnea
- CSF : Cerebro Spinal Fluid
- CSR : Chynes Stokes Respiration
- CVO : Circum ventricular Organs
- CWP : Chronic Wide spread Pain
- DA : Dopamine
- DNA : Deoxy-ribonucleic acid
- EDS : Excessive Daytime Somnolence
- EEG : Electro Encephalo graphy

- EOG : Electro Oculogram
- FM : Fibromyalgia
- GABA : Gamma aminobutyric acid
- GH : Growth Hormone
- Glut : glutamate
- HA : Histamine
- Hcrt : Hypocretin
- HLA : Human Leukocyte Antigen
- HPA : Hypothalamic Pituitary Axis
- ICAM -1 : Intercellular adhesion molecule 1
- IFN : Interferon
- IkB : Inhibitory Kappa B
- IL : Interleukin
- IVIg : Intravenous Immunoglobulins
- LAK : Lymphokine Activated Killer
- LH : Lateral Hypothalamus
- MnPo : Median preoptic nucleus
- MRF : Midbrain Reticular Formation
- MSLT : Multiple Sleep Latency Test
- MSU : Monosodium Urate
- NE : Norepinephrine
- NF-kB : Nuclear factor – kappa B
- NK : Natural Killer

- NREM : Non Rapid Eye Movement
- NRS : Non Restorative Sleep
- OHS : Obesity Hypoventilation Syndrome
- OSA : Obstructive Sleep Apnea
- OVLT : Organum Vasculosum Lamina Terminalis
- PBMC : Peripheral Blood Mononuclear Cells
- PH : Posterior hypothalamus
- PLMS : Periodic Limb Movements of Sleep
- PNS : Peripheral Nervous System
- PPT : Pedunculo pontine tegmentum
- PSD : partial Sleep deprivation
- PSG : Polysomnography
- PSQI : Pittsburgh Sleep Quality Index
- RA : Rheumatoid Arthritis
- RDI : Respiratory Distress Index
- REM : Rapid Eye Movement
- RLS : Restless Leg Syndrome
- RN : Raphe nucleus
- RNA : Ribonucleic acid
- SAS : Sleep Apnea Syndrome
- SCN : Supra chiasmatic Nucleus
- SD : Sleep deprivation
- SDB : Sleep Disordered Breathing

- SFO : Subfornical Organ
- SIBO : Small intestinal Bacterial Overgrowth
- sICAM : soluble Intercellular adhesion molecule
- SLE : Systemic Lupus Erythematosus
- SNc : Substantia Nigra compacta
- SNS : Sympathetic Nervous System
- SR : Sleep Restriction
- SS : Sjogren's Syndrome
- SSc : Systemic Sclerosis
- SWS : Slow wave sleep
- SWSD : Shift Work Sleep Disorder
- TCA : Tricyclic Antidepressants
- Th 1 : T Helper 1
- Th 2 : T helper 2
- TMJ : Tempro Mandibular Joint
- TMN : Tubero mammilary nuclei
- TNF : Tumor Necrosis Factor
- TSD : Total sleep deprivation
- vLPO : Ventro lateral preoptic area
- VTA : Ventral Tegmental Area
- WASO : Wake- time After Sleep Onset
- WBC : White Blood Cells

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Sleep and Immunology

Essay
Submitted for Partial Fulfillment of
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النوم و المناعة

رسالة

توطئة للحصول على درجة الماجيستير في المخ والأعصاب والطب النفسي

مقدمة من

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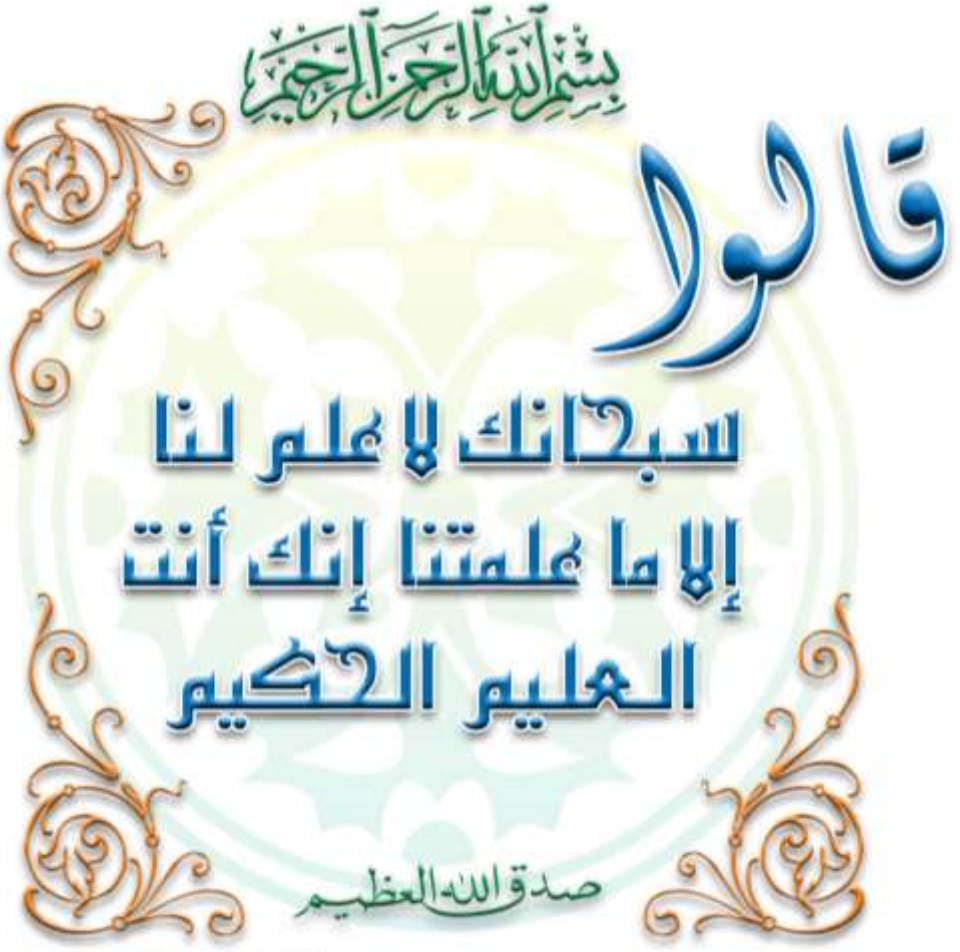

سورة البقرة الآية: ٣٢

Introduction

Sleep is a recurrent state of reduced consciousness and body rest that is intimately associated with the circadian system, characterized by physiological oscillations within a period of approximately 24-h. The combined effect of such cycles has been shown to affect interactions between the central nervous, the endocrine and the immune systems ***(Hastings et al., 2008).***

Recent studies in animals and humans have shown that the immune-neuroendocrine and thermal systems of the body are intimately linked to the sleep-wake system ***(Moldofsky, 1995).*** 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 ***(Majde, 2005).***

Sleep deeply impacts adaptive immune functions as adaptive immune response is initiated by antigen presenting cells and naïve T cells that meet in secondary lymphoid organs,

with the number of naïve T cells recruited to lymphoid organs essentially determining the size of the adaptive response, i.e., the number of effector T cells formed after vaccination . Therefore, sleep might support the formation of adaptive immunity by increasing migration of T lymphocytes to lymph nodes. Hence, sleep on the night after vaccination leads to a long lasting enhancement of antigen-specific antibody and T-helper cell responses ***(Besedovsky et al., 2012).***

The initiation and development of an adaptive immune response depends, among others, critically on the balance between type1 (IL-2, IL-12, IFN-γ) and type2 (IL-4, IL-10) cytokines. Multiple influences like the prevailing cytokine milieu and hormonal mediators can bias cytokine production towards type 1 or type 2 dominance, thereby supporting inflammation and autoimmunity on one hand or enhancing susceptibility to infections and allergy on the other hand. Slow wave sleep (SWS) is characterized by maximum release of growth hormone (GH) and minimum release of cortisol, release of GH by increasing particularly production of IFN-γ can contribute to the shift in type1/type2 balance towards type1 activity characterizing SWS ***(Lange et al., 2005).***

Sleep deprivation from medical and psychiatric conditions, as well as from life style is endemic in modern society, affecting millions of persons daily ***(Report of the National Commission on Sleep Disorders Research, 1993).***

Studies of leukocyte population changes and cytokine levels in various sleep deprivation models have been performed in human volunteers. Different deprivation schedules result in different immune outcomes, particularly in terms of leukocyte numbers and cell types ***(Dinges et al., 1995)***

An inflammatory response begins when macrophages are activated by pathogens or tissue damage to release the pro-inflammatory cytokines, IL-6, IL-1β, and TNF-α. Pro-inflammatory cytokines, in turn, stimulate the local recruitment and activation of leukocytes, and the systemic release of acute phase proteins, such as C-reactive protein (CRP) and fibrinogen cytokine response to immune activation is critical and insufficient response may leave the organism vulnerable to infection, whereas excessive response can increase risk for inflammatory diseases ***(Pavlov and Tracey, 2004***).

Thus, it has been proposed that early pro-inflammatory responses may provide a physiologic mechanism linking sleep disruption to risk of inflammatory disease ***(Opp et al., 2007).***

In contrast, Excessive sleepiness is typical in inflammation and infection. Experimental host defense activation with bacterial endotoxin may influence sleep–wake behavior. The activation of the hypothalamic–pituitary–adrenal (HPA) axis and the presence of fever disturb sleep, while when a lesser amount of endotoxin stimulates the production of

proinflammatory cytokines, the amount of NREM sleep increases ***(Schuld et al., 2005)***. There is increasing evidence showing that cytokines play an important role in alerting the brain to ongoing inflammation in the peripheral tissues ***(Krueger and Majide, 2003).***

Cytokines such as TNF-α and IL-1β have been regarded as the mediators of increased somnolence and symptoms of malaise and loss of appetite in the early stages of acute phase response to viral and bacterial infections. Increased sleep observed in these situations may be mediated through these cytokines ***(Kapsimalis et al., 2008).*** Moreover, abnormal cytokine levels have been described in different rheumatologic diseases. RA patients demonstrate elevated levels of IL-12, IL-15, and IL-18 in synovial fluid and these induce interferon (IFN)–γ production. Juvenile RA patients have increased serum levels of IL-1, IL-6, TNF-α, IL-8, and IL-18. SLE patients have increased levels of serum IL-4, IL-6, IL-10, and IL-18, and disease activity correlates with IL-18 levels ***(Arend and Gabay, 2004)***.

Patients with spondyloarthritis show high levels of TNF-α and lower amounts of transforming growth factor (TGF)β in sacroiliac joints. IL-1, TNF-α, and IL-6 are increased in joints of patients with osteoarthritis. Sjogren's syndrome is associated with cytokines IL-1β, TNF-α, IL-2, and IL-6 in minor salivary glands. Patients with central nervous

system (CNS) lupus have increased levels of TNF-alpha, IL-6, and IL-10 in cerebrospinal fluid (CSF) ***(Harris et al., 2005).***

The increased IL-6 levels in patients with RA, SLE, Sjogren's syndrome, and osteoarthritis is hypothesized to be partially responsible for some of the sleep difficulties seen in these disorders and abnormalities in circadian secretion of IL-6 and TNF-α could contribute to the insomnia seen in rheumatologic diseases. On the other hand, data show that immune response molecules may be potentially involved in the pathogenesis of narcolepsy, but their nature has still to be identified **(*Bentivoglio and Kristensson, 2007)***. The disease is usually sporadic, with an almost complete association with HLA (Human Leukocyte Antigen) genes. The cause of narcolepsy is unknown yet mmune-mediated mechanisms have been suggested because of its HLA association (***Dauvilliers and Tafti, 2006)*** and interestingly, treatment with immunoglobulins early after disease onset results in positive effects in some patients tentatively by downregulation of T-cell function and reduced cytokine release (***Dauvilliers et al., 2004)*.**

Moreover, the high prevalence of autoimmune disease among women with REM sleep Behaviour Disorder (RBD) suggests an intriguing link between immune dysfunction and RBD ***(Ju et al., 2011)***. In addition to the fact that 95% of the 38 highly-associated Restless Legs Syndrome (RLS) conditions are also associated with inflammatory/ immune changes which