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Effects of sleep deprivation on immune function via cortisol and catecholamines

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SCHOOL OF MEDICINE

Thesis

**EFFECTS OF SLEEP DEPRIVATION ON IMMUNE FUNCTION VIA
CORTISOL AND CATECHOLAMINES**

by

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ABSTRACT

Sleep loss alters both the concentration and activity of various aspects of the immune system. These alterations lead to increased susceptibility to infection and the progression of pathologies such as insulin resistance and atherosclerosis. Two proposed mechanisms of this alteration in immune function are the changes in both cortisol and sympathetic nervous system activity that accompany sleep deprivation. This work reviewed literature that measured the effects of periods of sleep restriction upon both cortisol and catecholamine concentrations within human subjects. Furthermore, studies which measured the effects of sleep loss upon these hormone levels and the associated changes in immune parameters were included. This thesis asserts that there is no defined pattern in reference to alterations of cortisol levels as a result of sleep deprivation. Furthermore, more evidence must be collected before implementing cortisol as a main effector of sleep loss upon immune system function. This dissertation, although repeatedly noting increased levels of norepinephrine following periods of sleep restriction, similarly argues that more research must be completed in order to declare that altered catecholamine concentrations as a result of sleep loss is a mechanism for altered immune function.

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LIST OF ABBREVIATIONS

B cells/ B lymphocytes.....	Bursa Lymphocytes
IFN- γ	Interferon-gamma
IL.....	Interleukin
NK cells.....	Natural Killer Cells
NKT cells.....	Natural Killer Thymus Cells
T cells/ T lymphocytes.....	Thymus Lymphocytes
T helper cell.....	CD4+ thymus helper cell
Th1.....	Thymus helper cell type 1
Th2.....	Thymus helper cell type 2
TNF- α	Tumor necrosis factor-alpha
β_2 AR.....	beta type two adrenergic receptors
β AR.....	beta type adrenergic receptors
γ/δ T cells.....	gamma delta T lymphocytes

INTRODUCTION

The relationship between sleep and the immune system was first uncovered by Krueger et al. in 1982 with the discovery of the sleep-inducing muramyl peptide Factor S. (Krueger et al., 1984; Cardinali et al., 2006) Krueger discovered that Factor S induced the release of interleukin-1, a highly inflammatory cytokine prominent in the acute phase response of the innate immune system. (Cardinali et al., 2006; Mak et al., 2006) Since Krueger's revelation, there has been immense interest in the interplay between sleep and the immune system function.

Understanding this relationship is of critical importance, as studies have shown an increasing prevalence of sleeping disorders within the general population (Schlaepfer et al., 2012; Ram et al., 2010). In addition to the high prevalence of sleep deprivation caused by sleeping disorders, there is also evidence that an increased occurrence of sleep deprivation is, in part, a result of modern society's demands in school and the workplace. (Andersen et al., 2015; Basner et al., 2014) Much of the literature published in this field has asserted that a lack of sleep is directly correlated to the development of numerous pathologies, although the mechanisms of this observation are still under debate (Nakao, 2014; Christofferson et al., 2014). Many of these articles have implicated altered cortisol levels and sympathetic nervous system activity as possible mechanisms of immune parameter changes that occur with sleep deprivation (Carroll et al., 2015; Irwin et al., 2015; Irwin et al., 2015; Wright et al., 2015; Christofferson et al., 2014; Axelsson et al., 2013; Faraut et al., 2011; Boudjeltia et al., 2008; Kerkhofs et al., 2007; Matsumoto et al., 2001). Other researchers, however, have denied any association between the effects of

sleep deprivation upon the immune system and altered cortisol or catecholamine concentrations within their own studies (Ruiz et al., 2012; Guariniello et al., 2012; Fondell et al., 2011).

Despite these differing viewpoints, it is well understood that the functional characteristics of the immune system are profoundly intertwined with those of the human endocrine system and sympathetic nervous system. In particular, varying levels of cortisol and catecholamines have differing effects upon the activities of leukocytes and cytokines. Therefore, in order to holistically comprehend the mechanisms by which sleep deprivation exerts its adverse effects upon the immune system, it is necessary to understand the ways in which sleep deprivation affects these aforementioned physiological systems.

Firstly, the ramifications that sleep deprivation has on the various components of the immune system will be examined. Then, the interplay between the hypothalamic-pituitary-adrenal axis and the immune system in healthy, non-sleep deprived subjects will be explored. Following this discussion, the consequences of sympathetic nervous system activity upon immune function will be examined in similar subjects. Finally, this work will inspect the response of glucocorticoid and catecholamine levels within sleep deprived populations and any associated changes in immune function. This thesis will demonstrate that there is insufficient evidence to link sleep loss-induced alterations in cortisol and catecholamine levels to altered immune function.

BACKGROUND

A. Sleep Deprivation and the Immune System

Sleep deprivation has been shown to alter the functionality of the immune system by altering the concentrations of various leukocytes and cytokines throughout the normal twenty-four hour sleep-wake cycle (Opp et al., 2015). Although the effects on some specific parameters of the immune system have not been agreed upon by different groups of researchers, it has been commonly accepted that acute and chronic sleep loss lead to inflammation and increased susceptibility to infection or disease (Besedovsky et al., 2011). Literature in this topic of study has elucidated the effect of sleep restriction upon the various subsets of leukocytes within the human body, including granulocytes, natural killer (NK) cells, monocytes, bursa lymphocytes (B cells or B lymphocytes), and thymus lymphocytes (T cells or T lymphocytes).

Christoffersson et al. 2014 conducted a study to investigate the effects that acute total sleep deprivation holds upon circulating concentrations of neutrophils. The experiment was conducted upon a population of healthy, young men and revealed that a twenty-four hour period of total sleep deprivation caused a significantly raised plasma concentration of neutrophils the following morning as compared to the levels seen in non-sleep deprived subjects. Despite concurring evidence from other research groups (Dinges et al., 1994; Born et al., 1997; Faraut et al., 2011; Boudjeltia et al., 2008; Kerkhofs et al., 2007; Lasselin et al., 2015), Christoffersson et al. also recognized that an experiment conducted by Irwin et al. in 2006 showed a decrease in neutrophil cell count following a period of acute sleep loss (Irwin et al., 2006).

Similar to Christoffersson's findings, Ruiz et al. 2012 discovered an increase in neutrophil cell count following a period of acute sleep deprivation in healthy, young men. Furthermore, Ruiz et al. 2012 uncovered the effects of sleep loss on the populations of eosinophils and basophils. Unlike neutrophils, these granulocytes were not significantly affected following periods of reduced sleep (Kerkhofs et al., 2007). Similar to granulocytes, NK cell counts have also been shown to vary following periods of sleep loss.

According to De Lorenzo et al. 2014, periods of prolonged sleep loss in adult mice not only caused a decline in the plasma concentration of NK cells and natural killer thymus cells (NKT cells), but also in their cytotoxicity. Findings of lower NK cell concentrations following periods of sleep loss have only been supported by studies conducted in animal models. However, the results indicating curtailed cytotoxic activity in NK cells as a result of sleep loss has been supported in both animal (Guariniello et al., 2011) and human models (Dinges et al., 1994; Irwin et al., 1996; Fondell et al., 2011; Heiser et al., 2000). However, within healthy, young men, and other animal models it has also been demonstrated that NK cell and NKT cell counts increase during periods of sustained wakefulness (Born et al., 1997; Dimitrov et al., 2007; Velazquez-Moctezume et al., 2004). Furthermore, there has also been testimony to the notion that acute sleep loss can actually induce cytotoxic NK cell activity within healthy, young men (Matsumoto et al., 2001). Similar to NK cells, monocyte concentration and activity within the sleep deprived are an area of focus in this field of study due to their prominent role in the innate inflammatory response.

The general consensus in regards to monocytes within sleep deprived subjects is an increase in both cytotoxicity and concentration (Irwin et al., 2006; Irwin et al. 2015; Born et al., 1997; Carroll et al., 2015; Dimitrov et al., 2009; Lasselin et al., 2015). In particular, monocytes have been identified in producing large quantities of the proinflammatory cytokines interleukin (IL)-6 and tumor necrosis factor-alpha (TNF- α) during sleep loss conditions (Carroll et al., 2015; Irwin et al., 2015; Dimitrov et al., 2015). Although sleep loss has been indicted in altering the concentrations of innate immunity components, research has also associated it with modified concentrations of lymphocytes.

Although B lymphocytes do not appear to be affected by sleep deprivation, subsets of T lymphocytes have been shown to be influenced by the restriction of sleep in various ways (Ruiz et al., 2012; Boudjeltia et al., 2008). Many accounts have asserted that the only subset of T lymphocyte to be influenced by sleep loss is the CD4+ thymus helper cell (T helper cell) (Ruiz et al., 2012; Dinges et al., 1994; Zager et al., 2007). These cells have been shown to increase in population size under sleep loss conditions (Heiser et al., 2000; Ruiz et al., 2012). Akin to affecting leukocyte populations, both total sleep loss and partial sleep loss have also been proven to alter the circulating plasma concentrations of cytokines within subjects.

It is hypothesized by many investigators that sleep deprivation, whether it be acute or chronic, transitions the affected body from a state of immune balance to one favoring the inflammatory immune response. Despite this allegation, however, there is

conflicting evidence on how sleep deprivation affects both pro- and anti- inflammatory cytokines and other mediators of immunity.

Most studies have focused their efforts in determining the effect of sleep deprivation upon the two most notable pro-inflammatory cytokines, IL-6 and TNF- α . Many studies have associated sleep loss with an increase in plasma concentration of the pro-inflammatory cytokine TNF- α in healthy, young men (Dimitrov et al., 2014; Vgontzas et al., 2004; Chennaoui et al., 2011; Irwin et al., 2006; Irwin et al., 2010). Similarly, many published articles have correlated sleep loss with increased plasma levels of IL-6 (Irwin et al., 2006; Irwin et al., 2010; Burgos et al., 2006; Haack et al., 2007; Vgontzas et al., 2004). However, some literature indicated a decrease in IL-6 levels (Frey et al., 2007), while other works have denied any significant effect of sleep loss on either cytokine (Ruiz et al., 2012; Lekander et al., 2013).

In addition to these discoveries, much of the published literature in this field of study has identified sleep loss with a shift from thymus helper cell type 1 (Th1) activity to thymus helper cell type 2 (Th2) activity. In accordance with this observation, it has been reported that sleep reduction is correlated with decreases in IL-2 production and increases in production of IL-4 and IL-10 (Axelsson et al., 2013; Irwin et al., 1996; Lange et al., 2006; Dimitrov et al., 2004).

B. Normal Circadian Rhythms of Cortisol, Epinephrine, and Norepinephrine

It was discovered that hormone and catecholamine release are principally controlled by either the homeostatic mechanisms or circadian mechanisms.

Norepinephrine, epinephrine, and cortisol release, however, are prevailingly under the control of circadian measures (Cardinali et al., 2005). In humans, plasma levels of cortisol have been shown to peak in the early hours of the morning and to steadily decline throughout the day. Cortisol levels steadily begin to rise in the second half of an individual's sleeping period until again peaking in the early hours of the morning (See Figure 1) (Nicolaidis et al., 2014; Dimitrov et al., 2009).

Norepinephrine and epinephrine levels throughout a 24 hour wake-sleep cycle are comparable to those of cortisol. Norepinephrine and epinephrine concentrations in an individual's plasma spike in the early hours of the morning and then decline. However, unlike cortisol, the levels of norepinephrine and epinephrine do not decrease throughout the day, but rather remain constant until late evening. At this point, the norepinephrine and epinephrine concentrations plummet and do not rise again until their peak in the early hours of the morning (See Figure 1) (Lechin et al., 2004; Dimitrov et al., 2009).

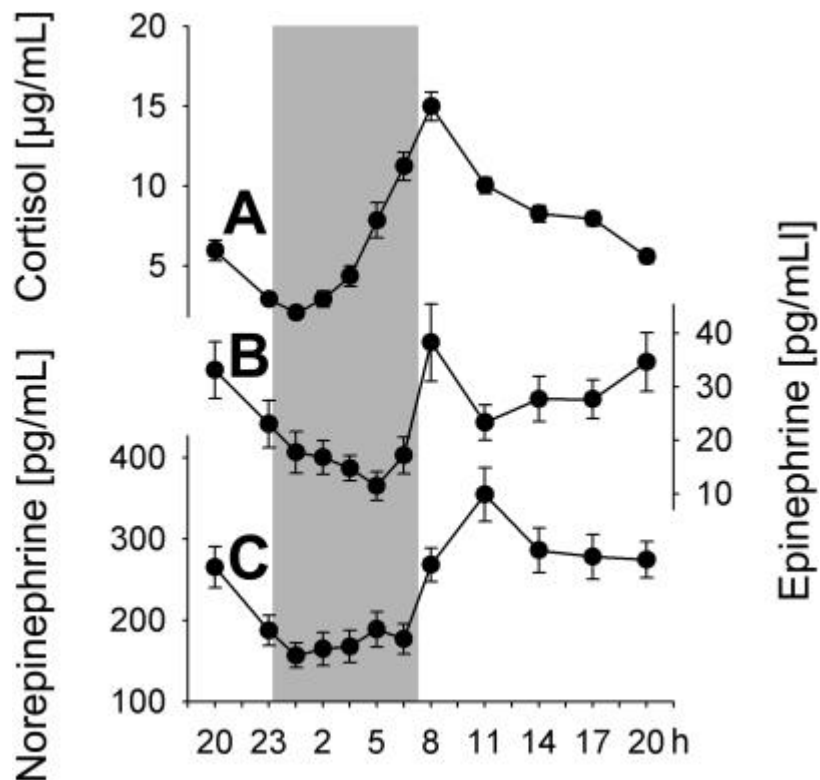


Figure 1. Circadian variations in stress hormone concentrations. The mean plasma concentrations in pictograms per milliliter of cortisol (A), epinephrine (B), and norepinephrine (C) in fourteen healthy, young men across a twenty-four hour time frame. Figure reproduced from *Cortisol and epinephrine control opposing circadian rhythms in T cell subsets* by Dimitrov et al. 2009

C. The Hypothalamic-pituitary-adrenal Axis, Sympathetic Nervous System, and T lymphocytes

Studies have shown a particular correlation between activation of the two major stress systems of the human body, the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system, and levels of circulating T cells (Okutsu et al., 2005; Tønnesen et al., 1987). In their publication *Effects of sleep and circadian rhythm on the*

human immune system Lange et al. 2010 hypothesized that certain subsets of T cell populations are under direct control of either cortisol or epinephrine and norepinephrine. This hypothesis was based on an experiment in which the plasma concentrations of CD4+ and CD8+ T cells and the plasma concentrations of cortisol, epinephrine, and norepinephrine were measured at regular intervals throughout the 24 hour sleep-wake cycle. The team discovered that total CD4+ and total CD8+ concentrations were indirectly proportional to cortisol concentrations, with a three hour delay, and that total CD4+ and CD8+ concentrations were indirectly proportional to epinephrine and norepinephrine with no time delay (Dimitrov et al., 2009).

Furthermore, the same investigators discovered that although total numbers of T lymphocytes were reduced when cortisol, epinephrine, and norepinephrine concentrations were high, concentrations of different subsets of T cell populations showed varying circadian rhythms. Administration of epinephrine in subjects only showed an increase in the concentration of effector CD8+ T lymphocytes, gamma delta T lymphocytes (γ/δ T cells), and natural killer thymus lymphocytes (NKT cells), and did not show any effects on other T cell subpopulations (Dimitrov et al., 2010). Cortisol administration, on the other hand, was directly correlated with suppressed naïve T cell, central memory T cell, and effector memory T cell concentrations (Dimitrov et al., 2009)(See Figure 2).

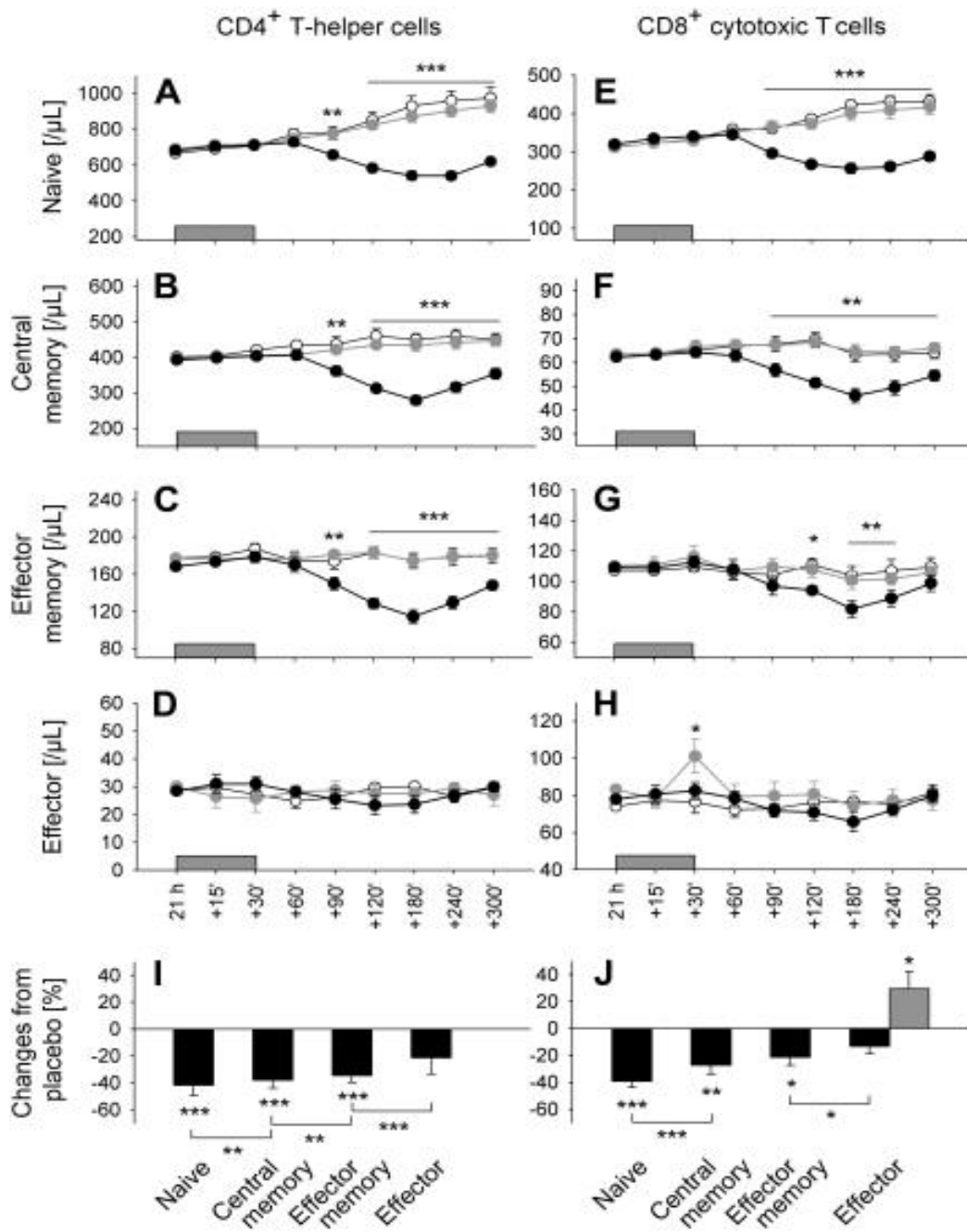


Figure 2. Cortisol and epinephrine differentially influence T cell subpopulations.

Administration of epinephrine (grey circles) only showed an increase in the concentration of CD8⁺ effector cells in test subjects in comparison to placebo administration (white circles) and cortisol administration (black circles) (H). On the other hand, cortisol administration effectively suppressed naïve (A), central memory (B), and effector memory (C) T-helper cells concentrations, while also suppressing naïve (E), central

memory (F), and effector memory (G) cytotoxic T cells in comparison to placebo and epinephrine administration. The relative changes in concentrations of CD4+ T helper cells subpopulations (I) and CD8+ cytotoxic T cells (J) in comparison to the placebo. Figure reproduced from *Cortisol and epinephrine control opposing circadian rhythms in T cell subsets* by Dimitrov et al. 2009

D. Catecholamines and the Immune System in Healthy, Non-sleep Deprived

Individuals

In addition to the effects of increased catecholamine concentrations upon the subsets of T lymphocytes within the human body, these hormones have also been implicated in altering the amount and activity of other immune cells. These molecules exert their influence via binding to beta type adrenergic receptors (β AR), which are present upon all of the aforementioned subsets of T lymphocytes, B lymphocytes, NK cells, and monocytes (Kin et al., 2006; Sarkar et al., 2012). Although epinephrine and norepinephrine have been identified in mobilizing certain subsets of immune cells by inducing differential expression of adhesion molecules (Dimitrov et al., 2009; Wahle et al., 2005), their general effect is to downregulate cytotoxic activity (Inbar et al., 2011; Wenisch et al., 1996). In regards to lymphocytes, it has not only been demonstrated that catecholamines have a great influence on circulating concentrations of subset populations of T cells, but also on the activities of these cells (Elenkov et al., 2000).

Many investigators have asserted that sympathetic nervous system activity causes a shift from Th1 activity to Th2 activity. For instance, researchers have observed in both animal and human subjects that increased concentrations of norepinephrine and subsequent activation of beta type two adrenergic receptors (β_2 AR) decreases production

of Th1 associated cytokines such as IL-2, IL-12, interferon-gamma, and TNF- α in CD4+ T helper lymphocytes (Ramer-Quinn et al., 2000; Elenkov et al., 2000; Swanson et al., 2001; Kin et al., 2006; Takayanagi et al., 2012). However, because Th2 cells do not have any adrenergic receptors, concentrations of catecholamine do not affect their expression of cytokine genes (Nance et al., 2007). Although of importance, T helper cells are not the only subset of lymphocytes to be associated with altered function as a result of sympathetic nervous system activity.

According to Marino et al. 2013, adrenergic stimulation of β_2 AR reduces proliferation of cytotoxic CD8+ T lymphocytes and their production of the pro-inflammatory cytokines IL-2, interferon-gamma, and IL-3. Although the results of adrenergic receptor activation upon T cell activity are fairly well-defined, the influence of the sympathetic nervous system upon B cell is still ambiguous and in need of further investigation (Webster Marketon et al., 2008; Pongratz et al., 2009). In addition to exerting effects upon lymphocytes, epinephrine and norepinephrine have also been exposed in affecting NK cell function.

Activation of adrenergic receptors upon NK cells induces both a decrease in cytotoxic activity and an increase in plasma concentration (Marino et al., 2013). In animal models, NK cell cytotoxicity and production of cytokines is markedly decreased by administration of catecholamines (Sarkar et al., 2012; Dokur et al., 2004; Inbar et al., 2011). In human subjects, it has similarly been demonstrated that increased catecholamine concentrations lead to increased NK cell plasma levels though alterations in adhesion molecules (Dimitrov et al., 2009; Benschop et al., 1996). Similar to their

effects upon the population size of NK cells, epinephrine and norepinephrine have been known to increase the total number of circulating granulocytes (Benschop et al., 1996).

Epinephrine and norepinephrine can exert their effects upon granulocyte populations due to the presence of β AR. The concentration of neutrophils has been proven to increase upon administration of epinephrine or norepinephrine due to a downregulation of adhesion molecules (Kasprisin et al., 1979; Wahle et al., 2005). However, neutrophils have been observed to have decreased cytotoxic activity in the presence of sympathetic nervous system activity. Evidence has indicated that upon sympathetic activation, the anti-inflammatory cytokine IL-8 is upregulated (Wahle et al., 2005) within neutrophilic populations. Research has also disclosed that the phagocytic ability of human neutrophils is greatly reduced under similar conditions (Wenisch et al., 1996).

Similar to neutrophils, activation of adrenergic receptors by catecholamines was exhibited to cause an increase in peripheral monocyte concentration (Steppich et al., 2000; Dimitrov et al., 2009; Parks et al., 2012), and a decrease in cytotoxic activity (Röntgen et al., 2004). Monocyte populations under sympathetic influence have demonstrated downregulation of production of the pro-inflammatory cytokines IL-6 and TNF- α , with no effect upon production of the anti-inflammatory cytokines IL-8 and IL-10 (Röntgen et al., 2004; Platzer et al., 2000).

In summary, the sympathetic nervous system works to suppress the inflammatory actions of the immune system. In fact, catecholamines have been directly correlated with a decrease in the production of pro-inflammatory Th1 cytokines along with those

produced by cytotoxic T cells. Most evidence supports the notion that NK cells lose cytotoxic activity upon exposure to catecholamines, while also suffering decreased plasma concentrations. Similarly, granulocytes, and in particular neutrophils, have been shown to dramatically increase in population size upon adrenergic stimulation. The activity of these cells was characterized by decreased phagocytic activity and, in some research, the production of an anti-inflammatory cytokine. Likewise, monocyte activity was deterred from production of pro-inflammatory cytokines in the presence of elevated cortisol, although peripheral concentrations of these cells were shown to rise.

E. Cortisol and the Immune System in Non-sleep Deprived Subjects

Cortisol has been implemented in causing anti-inflammatory responses within various components of the immune system. For example, cortisol is known to decrease the production of the pro-inflammatory cytokines IL-1, IL-6, and TNF- α by downregulating the activity of the transcription factor nuclear factor kappa B. In addition to inhibiting the production of these and many other pro-inflammatory cytokines, release of this hormone causes the reduction of concentration and function of many immune cells (Marik, 2016; McEwen et al., 1997). This work will focus on cortisol's particular effects upon T lymphocytes (discussed previously), natural killer cells, monocytes, and granulocytes.

Substantial research has been conducted in regards to the suppressive effects that cortisol has upon NK cell activity. In studies conducted upon the effects of increased cortisol levels in the presence of NK cells, investigators discovered reduced cytotoxic

activity expressed by these cells (Gatti et al., 1987; Callewaert et al., 1991; Masera et al., 1989; Gatti et al., 1986; Zhou et al., 1997). Evidence contrary to these findings was presented by Bodner et al. 1998, who did not note any change in NK cell activity upon exposure to increased cortisol concentrations. Despite changes in activity, none of the aforementioned research groups were able to determine a significant effect of cortisol levels upon NK cell proliferation and concentration. Similar to its influence upon NK cell populations, cortisol is known to suppress the activity of granulocytes.

Granulocytes in peripheral circulation, and particularly those of neutrophils, were observed to increase in number in response to increased cortisol concentrations (Davis et al., 1991; Toft et al., 2004; Yeager et al., 2016; Tuckermann et al., 2005). However, akin to its effects upon NK cells, cortisol has been shown to decrease the cytotoxic activity of neutrophils by impeding superoxide production (Békési et al., 2000; Khanfer et al., 2011). Cortisol also impacts the function of the immune system by influencing the activity of monocytes.

Recent evidence has indicated that cortisol can either suppress or enhance the immune function of monocytes. Many researchers discovered that low levels of cortisol can actually induce a pro-inflammatory response, while higher levels within the body led to reduced cytotoxicity of monocytes (Yeager et al., 2016; Yeager et al., 2008; Okutsu et al., 2008; Lim et al., 2007). These investigators revealed increased migration to sites of inflammation by enhanced expression of chemokine receptors (Okutsu et al., 2008; Yeager et al., 2016; Lim et al., 2007), along with decreased expression of the anti-inflammatory cytokine IL-10 (Yeager et al., 2008) within monocytes upon exposure to

low levels of plasma cortisol. Despite these findings, the prevailing evidence surrounding monocytes and cortisol is an overwhelmingly suppressive effect upon inflammatory responses (Coutinho et al., 2011; Tuckermann et al., 2005). Monocytic production of IL-6 and interferon-gamma (INF- γ) along with the expression of major histocompatibility complex II (MHC II) after exposure to the pathogen *Brucella abortus* was severely reduced in the presence of elevated cortisol concentration (Gentilini et al., 2015). In addition, Bagheri et al. 2014 not only demonstrated reduced secretion of IL-1 β and TNF- α , but also diminished expression of human Toll-like receptor 4. Other researchers have even identified the production of anti-inflammatory cytokine IL-4 and IL-10 within monocytes as a result of raised cortisol levels (Tuckermann et al., 2005).

In summary, at increased levels, cortisol acts to suppress the actions of the immune system. The majority of research investigating the effects of increased cortisol levels upon NK cell function asserted that while the concentration of this cell type within the circulation was largely unaffected, its activity was greatly curtailed. Although substantial evidence has been put forth exhibiting a similar decrease in activity among granulocyte populations, granulocyte levels, and particularly those of neutrophils, have been demonstrated to rise significantly under the same conditions. Despite published literature reporting increased monocyte migration to sites of inflammation as a result of low concentrations of cortisol, an overwhelming body of work has demonstrated decreased inflammatory activity within monocytes exposed to increased cortisol levels. In addition, evidence has indicated the decreased production of inflammatory cytokines and the production of anti-inflammatory cytokines within these monocytes.

F. Cortisol and Catecholamines Act Synergistically to Downregulate Inflammation

Both cortisol and sympathetic nervous system activity cause a shift from pro-inflammatory Th1 activity to anti-inflammatory Th2 actions. Although catecholamines directly downregulate the production of cytokines by Th1 cells via β AR, as previously noted, cortisol indirectly contributes to the shift from Th1 immunity to Th2 immunity. Cortisol downregulates the production of monocyte and macrophage-derived Th1 cytokines such as IL-12, IL-2, and INF- γ , while promoting the production and secretion of the anti-inflammatory Th2 cytokines IL-4 and IL-10 (Tuckermann et al., 2005; Ramírez et al., 1996; Blotta et al., 1997). Interestingly enough, cortisol has been associated with an increase in expression of adrenergic receptors within immune cells of mice (De Lorenzo et al., 2015) and humans (Cotecchia et al., 1994; McEwen et al., 1997). The two major stress systems also act in a similar manner in regards to regulation of NK cells, granulocytes, and monocytes.

As documented earlier, both increased cortisol and catecholamine concentrations cause reduced cytotoxicity within NK cells, although only sympathetic stimulation has been shown to cause a significant increase in peripheral NK cell populations. It was also noted previously in this work that both adrenergic activation and increased cortisol concentrations can lead to dramatically boosted levels of neutrophils within the human body's circulation, in addition to greatly reduced cytotoxic activity within these cells. Finally, in accordance with their effects upon neutrophils, these molecules cause increased plasma concentrations of monocytes, yet decreased inflammatory activity.

G. Significance

It is estimated that ten percent of the general population suffers from a sleeping disorder that is clinically significant (Partinen et al., 2011). Specifically, in 2006 it was surveyed that between fifty and seventy million Americans suffer from a sleeping disorder (Colten et al., 2006). Among others, obstructive sleep apnea is believed to affect at least nine to fifteen percent of all middle-aged adults (Ferini-Strombi et al., 2006), while insomnia, as defined by the Fourth Edition of the Diagnostic and Statistical Manual of Mental Disorders, is believed to affect between four and seven percent of the general population (Grewal et al., 2010). Furthermore, another of the most prevalent sleeping disorders, restless leg syndrome, has been reported to be present within populations of European descent at a rate of five to fifteen percent (Chaudhuri et al., 2009). Researchers have also discovered trends of shorter sleeping times that correlate to the demands of modern society.

Knutson et al. 2010 discovered a significant increase in the number of full-time workers whom regularly slept less than six hours per night from 1975 until 2006. In addition, a survey of 74,571 American adults conducted by the Centers for Disease Control and Prevention in 2009 showed that 35.3% of participants slept for less than seven hours each night. Furthermore, the National Health Interview Survey from 2008-2010 showed that twenty-eight percent of adults slept, on average, six hours or less per night. Restricted sleep has been directly correlated to abnormal immune function and the subsequent development of numerous illnesses.

The first study to disclose compromised immune function following a period of sleep loss was conducted by Spiegel et al. 2002. Experimental evidence between sleep deprived and normal sleep groups exhibited a dramatic deficiency in the ability of sleep deprived subjects to produce comparable amounts of antibodies in response to influenza vaccination. A similar experiment modeled the same way found that human antibody production in response to the hepatitis A vaccination was also significantly reduced among the sleep-deprived group. In 2009, Cohen et al. 2009 discovered that workers who slept less than seven hours each night were three times more likely to develop a cold in comparison to those subjects who slept for eight or more hours per night. Similarly, a study conducted on athletes discovered that reduced sleep quantity and quality led to a significantly increased prevalence of upper respiratory tract infections (Hauswirth et al., 2014). Immune alterations caused by sleep loss have even been implicated in the development of insulin resistance (Lasselin et al., 2015) and atherosclerosis (Axelsson et al., 2013).

SPECIFIC AIMS AND OBJECTIVES

This dissertation will investigate the viability of altered cortisol and catecholamine concentrations as a possible mechanism of sleep deprivation to exert its effects upon the immune system within human subjects. In order to accomplish this goal, it will be necessary to determine whether sleep restricted conditions hold any measurable influence over the circulating levels of these substances. A comprehensive collection of literature which investigated the effects of sleep loss upon circulating cortisol and catecholamine concentrations was reviewed to this end. Furthermore, investigations which measured both sleep deprived alterations in hormone levels and immune parameters were included. These studies were used not only to determine the effects of sleep loss upon hormone and catecholamine levels, but also to evaluate whether sleep deprived alterations in immune parameters could be attributed to the observed hormone concentrations.

REVIEW OF PUBLISHED LITERATURE

A. Cortisol Levels in Sleep-Deprived Subjects

i. Influence of sleep deprivation and circadian misalignment on cortisol, inflammatory markers, and cytokine balance

Wright et al. 2015 investigated the possible effect of acute sleep deprivation and chronic circadian misalignment on circulating cortisol levels, as well as the effects of circadian misalignment upon circulating cytokine levels. As circadian misalignment is not relevant to this particular dissertation, it will not be discussed. Seventeen healthy, young individuals (fourteen men and three women) were evaluated during six days of normal sleep-wake cycles and then a forty hour period of wakefulness. Blood was sampled for cortisol levels every thirty minutes throughout the last day of the normal sleep-wake routine and throughout the entire day of sleep deprivation.

The study demonstrated that acute periods of sleep loss result in generally increased plasma cortisol levels throughout the day compared to healthy non-sleep deprived individuals. Blood samples taken throughout the normal twenty-four hour sleep-wake cycle and during the forty hours of constant wakefulness revealed specific times in which this disparity was most obvious. Cortisol levels in the blood were notably greater in the sleep-deprived subjects in the early hours of the resting phase (when they would have normally been sleeping) and the early hours of the active phase in the morning (See Figure 3).

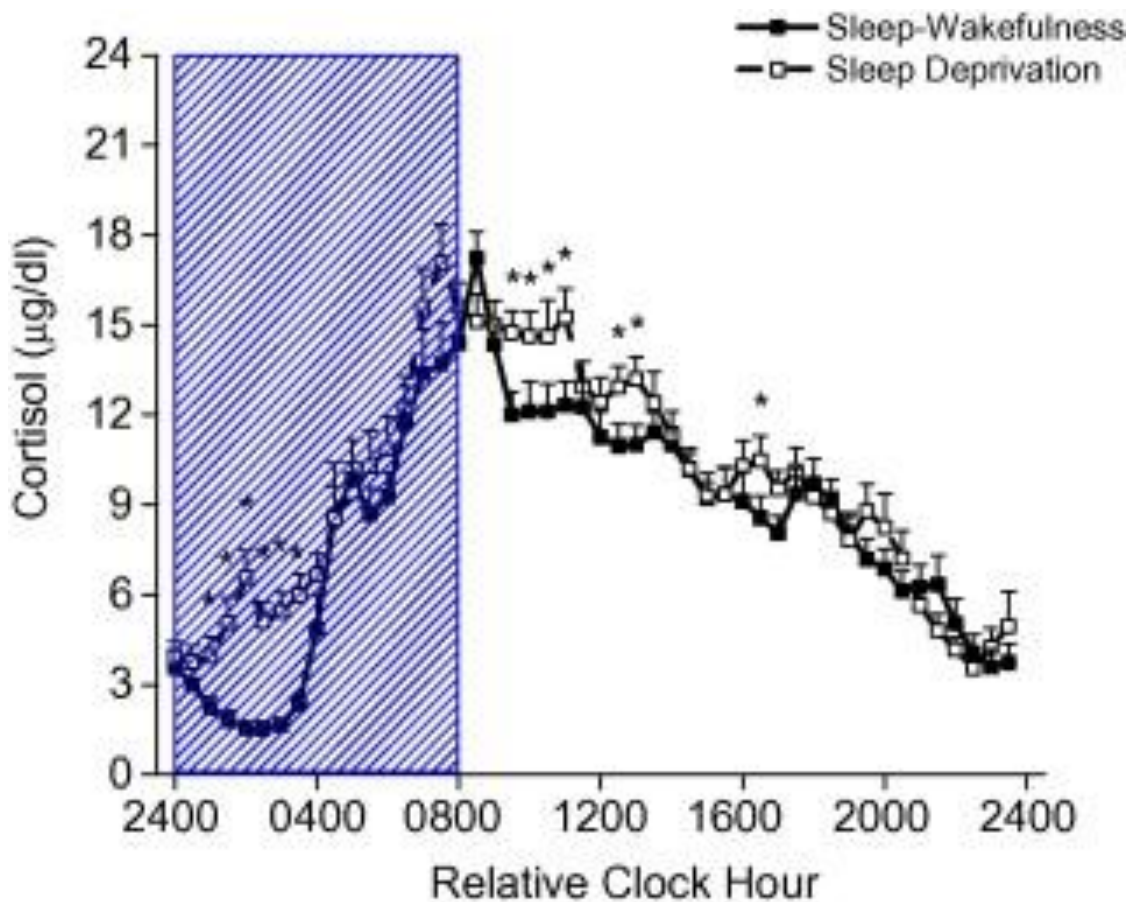


Figure 3. Plasma cortisol measurements between normal and sleep deprived conditions. Plasma levels of cortisol were assessed every thirty minutes throughout a day of normal sleep-wake conditions (filled squares) and a day of total sleep deprivation (open squares). The shaded area indicates time spent sleeping during normal conditions. Figure reproduced from *Influence of sleep deprivation and circadian misalignment on cortisol, inflammatory markers, and cytokine balance* by Wright et al. 2015

ii. Effects of Sustained Sleep Restriction on Mitogen-Stimulated Cytokines, Chemokines and T Helper 1/T Helper 2 Balance in Humans

Axelsson et al. 2013 studied the possible correlation between sleep-deprived cortisol concentrations and levels of circulating leukocytes and cytokines within nine healthy, young men. In the control experiment, test subjects were allowed to sleep from

23:00 hours until 7:00 hours. Under sleep-deprived conditions, the individuals partaking in the experiment were able to sleep from 3:00 hours to 7:00 hours for five sequential nights. Plasma samples were taken at regular intervals throughout the day prior to sleep-deprived conditions and during sleep-deprived conditions.

In regards to cortisol concentrations, the researchers discovered that total cortisol release was very comparable between the sleep-deprived and normal sleep trials. However, the levels of cortisol within the blood of the sleep-deprived individuals were significantly suppressed in the first two hours of restricted sleep as compared to those found in the non-sleep deprived subjects.

Similarly, levels of circulating monocytes and lymphocytes did not vary greatly between the two trials. During both trials, lymphocyte numbers peaked at 2:00 hours, while monocyte levels peaked at 24:00 hours and 1:00 hours during the control and sleep-deprived conditions, respectively. The only significant difference noted between concentrations of immune cells was found at 3:00 hours when the number of circulating monocytes was significantly greater in the sleep-deprived group as compared to the control.

TNF- α levels were shown to be significantly increased in the sleep-deprived subjects in the early rest phase (23:00 hours-2:00 hours), and significantly decreased in the late evening hours in comparison to the non-sleep deprived recordings. Other notable findings regarding cytokines involved the balance of Th1 and Th2 activity as measured by concentrations of IL-2 and IL-4, respectively. The sleep-deprived subjects displayed dramatically reduced ratios of IL-2/IL-4, especially during the active phase of the day.

Monocyte chemoattractant protein-1 and IL-1 β did not show any considerable variations in concentration between the two trials.

iii. Effects of Sleep and Sleep Deprivation on Interleukin-6, Growth Hormone, Cortisol, and Melatonin Levels in Humans

Redwine et al. 2000 worked to uncover the associations between sleep deprivation, interleukin-6, and circulating hormone concentrations. The examination included thirty-one healthy, young male participants subjected to both one night of seven hours of sleep (23:30 hours until 6:30 hours) and one night of restricted sleep (3:00 hours until 6:30 hours). Blood samples were taken every thirty minutes between 21:00 hours and 6:00 hours.

During the early stages of the night, (12:30 hours until 3:00 hours), there were no drastic changes in cortisol concentrations across the two trials. However, the measurements taken in the latter half of the night (3:00 hours until 6:00 hours) exhibited significantly lower levels of cortisol within the reduced sleep trial. Peak and nadir times were comparable between the two trials. Similar to cortisol, interleukin-6 levels were reduced in the sleep loss trial compared to normal sleep.

In the seven hours of sleep trial, interleukin-6 levels increased significantly from awake measurements just thirty minutes after sleep (24:00 hours) onset. Interleukin-6 concentrations peaked two and a half hours after sleep onset (2:30 hours), and remained elevated compared to awake values for the remainder of the night. In contrast, the measurements taken during the early part of the night (12:30 hours until 3:00 hours) in

the reduced sleep trial displayed levels of interleukin-6 that mirrored those taken while the subjects were awake. Interleukin-6 only significantly increased in concentration after the participants engaged in sleep, at which point the values were comparable to those found in the normal sleep phase.

iv. Adverse Effects of Two Nights of Sleep Restriction on the Hypothalamic-Pituitary-Adrenal Axis in Healthy Men

Guyon et al. 2014 studied the effects of two nights of sleep deprivation on cortisol and adrenocorticotrophic releasing hormone (ACTH) levels within thirteen healthy, young men. The participants were subjected to both conditions of regular sleep and insufficient sleep. Blood and salivary measurements of ACTH and cortisol were taken after both two nights of normal sleep (22:00 hours to 8:00 hours) and two nights of shortened sleep (1:00 hours to 5:00 hours). The investigation recorded plasma ACTH and serum cortisol levels every twenty minutes from 9:00 hours until 24:00 hours, while salivary cortisol levels were measured from 2:00 hours until 24:00 hours.

Both ACTH plasma levels and cortisol serum levels were found to be elevated during the sampling period in the restricted sleep trial as compared to the control. ACTH measurements were found to be 19% greater during sleep-deprivation throughout the entire sampling phase. More specifically, morning concentrations of ACTH were markedly increased while evening levels were more comparable to those of the control group. Serum cortisol levels were discovered to have increased by 21% in the reduced sleep group. However, contrary to the pattern shown by ACTH, levels of cortisol in the

morning were comparable between the two trials while concentrations during the evening were markedly raised. Salivary cortisol concentrations were found to mirror those found in serum samples (see Figure 4).

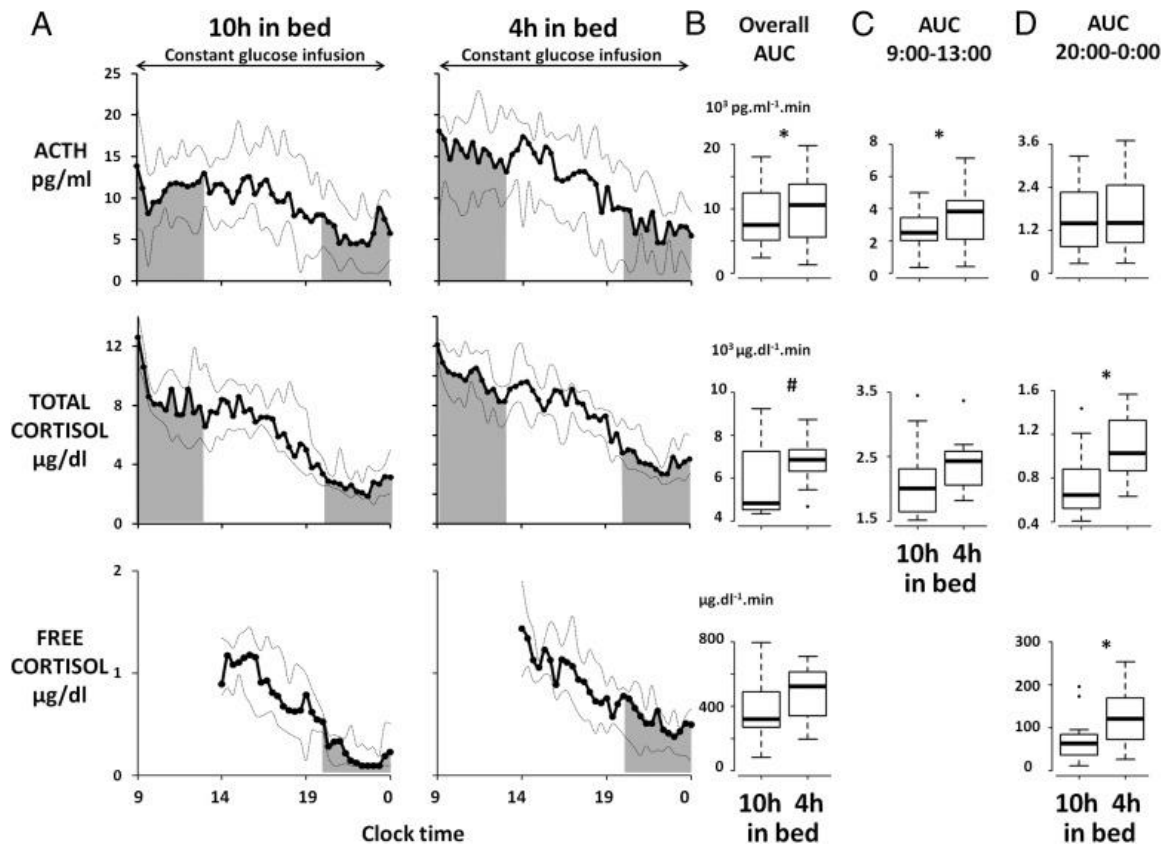


Figure 4. Recorded measurements of ACTH and cortisol from 9:00 hours until 24:00 hours. The values of plasma ACTH, serum cortisol, and salivary cortisol measurements following normal sleep schedules and reduced sleep schedules across the entire experimental time frame (A). Overall area under the curve (AUC) (B), day time area under the curve (C), and evening area under the curve (D) values are also depicted. Figure reproduced from *Adverse Effects of Two Nights of Sleep Restriction on the Hypothalamic-Pituitary-Adrenal Axis in Healthy Men* by Guyon et al. 2014

v. Neurophysiological Effects of Sleep Deprivation in Healthy Adults, a Pilot Study

Klumpers et al. 2015 also conducted an experiment to determine the effects of sleep deprivation upon levels of cortisol within twelve healthy young adults (six male and six female). Measurements were taken on both a baseline day, following a period of normal sleep, and a day characterized by total sleep deprivation. On the baseline day, salivary cortisol concentrations were recorded immediately after waking and then thirty, sixty, and ninety minutes after waking. Additional values were noted at 14:00 hours, 17:00 hours, and 23:00 hours. Evaluations of cortisol levels were made at the exact same times the following day during sleep restriction.

Significant differences in cortisol levels between the two trials were observed at sixty and ninety minutes after awakening and at 14:00 hours. Measurements taken at these times showed markedly suppressed levels of salivary cortisol. Although measurements taken at the time thirty minutes after awakening varied greatly from those observed the following day, the statistical analysis did not reveal significance. Measurements taken at the time of waking and later hours of the evening did not show any marked differences in salivary cortisol concentrations.

vi. Impact of sleep debt on metabolic and endocrine function

A research endeavor, carried out by Spiegel et al. 1999, investigated the effects of six consecutive days of four hours of sleep (1:00 hours to 5:00 hours) in eleven healthy young men in regards to salivary cortisol levels. On the last day of sleep restriction, measurements were made every thirty minutes from 15:00 hours until 21:00 hours and

compared to values obtained during a regular sleep trial involving the same participants. The investigators determined that afternoon cortisol levels (approximately 16:00 hours until 20:00 hours) were significantly elevated in comparison to the control values.

vii. Sleep deprivation effects on the activity of the hypothalamic–pituitary–adrenal and growth axes: potential clinical implications

Vgontzas et al. 1999 also considered the effect that sleep restriction would hold upon the circulating levels of cortisol within the human body. In this endeavor, ten healthy, young male volunteers were assessed for blood cortisol levels during normal sleep conditions and sleep restricted conditions. The participants stayed at the laboratory for seven days. The first four nights were characterized by normal sleep, while the fifth involved no sleep at all. Blood samples were taken every thirty minutes for twenty-four hours on the fourth day (pre-sleep deprivation) and on the sixth day (post-sleep deprivation).

The results indicated that total cortisol secretion was reduced in the post-sleep deprivation trial as compared to the pre-sleep deprivation trial. Secretion during day time hours did not significantly vary between the two conditions, although measurements during the resting phase (22:00 hours until 6:00 hours) did indicate significantly lower cortisol levels in the post-sleep deprived scenario. The authors also noted that both conditions showed the same peaks in cortisol throughout the twenty-four hour testing period. However, the peaks in the sleep restricted phase were always lower than those seen in the non-sleep restricted trial.

viii. White blood cells and cortisol after sleep deprivation and recovery in humans

Heiser et al. 2000 attempted to disclose the relationship between cortisol and white blood cell counts in sleep deprived individuals. Ten healthy, young males underwent one full day of total sleep deprivation following a day constituted of a normal sleep-wake cycle. On the first day, subjects were allowed to sleep from 22:00 hours until 6:00 hours. Blood samples were taken on both days at 7:00 hours, 13:00 hours, and 19:00 hours.

The investigators determined that there was significant variance between NK cell and granulocyte concentrations, respectively, during the two trials. While NK cell populations showed a marked decline after a period of sleep deprivation, granulocyte levels increased dramatically. The researchers failed to find any significant alterations in cortisol levels between the day of normal sleep-wake cycle and sleep deprivation.

ix. The effects of 40 hours of total sleep deprivation on inflammatory markers in healthy young adults

Nineteen healthy, young men and women (nine females and ten males) were subjected to three days of regular sleep-wake cycles followed by forty hours of total sleep loss in a study performed by Frey et al. 2007. Salivary samples were taken every hour beginning at two hours into total sleep loss and ending 38 hours into total sleep deprivation. Blood samples were taken every thirty minutes to determine the plasma concentrations of pro-inflammatory markers and expression of adhesion molecules throughout the forty hours of sleep deprivation.

Statistical analysis revealed significantly lower levels of cortisol in the sleep deprived trial as compared to those of the normal sleep trial at approximately 13:00 hours and 20:00 hours. All measurements taken across other time points showed comparable levels of salivary cortisol. Other measurements taken indicated significantly increased levels of IL-1 β at 9:00 hours and between 14:00 hours and 16:00 hours within the sleep deprived conditions in relation to the normal sleep conditions. However, the same blood drawings also revealed decreased levels of the pro-inflammatory proteins c-reactive protein and IL-6 throughout most of the day in the same total sleep deprived group.

x. Effect of one night of sleep loss on changes in tumor necrosis factor alpha (TNF- α) levels in healthy men

One study, conducted by Chennaoui et al. 2011, inspected the possible relationship between acute sleep deprivation, circulating plasma cortisol concentrations, and levels of TNF- α within twelve healthy, young men. During day one and day two of the experiment, subjects slept for eight hours (from 23:00 hours until 7:00 hours). Total sleep deprivation began on day three at 7:00 hours and ended on day four at 23:00 hours. Blood samples were collected and analyzed during days two and four at 8:00 hours, 11:00 hours, 14:00 hours, 17:00 hours, 20:00 hours, and 23:00 hours.

Statistical analysis of the collected data showed no significant changes in cortisol concentrations between the day of normal sleep-wake conditions and the day following total sleep restriction. Similarly, there were no significant differences in IL-6 and c-reactive protein between the two sets of measurements. The data did exhibit, however,

significant increases in TNF- α within the sleep deprived trial at 17:00 hours and 20:00 hours.

B. Evaluations of Cortisol and Catecholamine Levels in Sleep-Deprived Subjects

i. Sleep restriction increases free fatty acids in healthy men

Broussard et al. 2015 conducted an experiment revealing the levels of norepinephrine and cortisol in sleep-deprived volunteers whilst attempting to disclose the particular mechanism employed by sleep-deprivation on the development of insulin resistance. In this undertaking, nineteen healthy, young men were subjected to four consecutive nights of eight and a half hours of sleep (23:00 hours to 7:30 hours) followed by four consecutive nights of four and a half hours of sleep (1:00 hours to 5:30 hours). Blood samples were taken every fifteen minutes starting at 21:30 hours of the third consecutive night of each trial for twenty-four hours.

In regards to norepinephrine, the authors discovered a thirty percent increase in concentration during the early night (23:00 hours until 1:30 hours) and early hours of the morning (5:30 hours until 7:30 hours) in the sleep-restricted trial as compared to the control. This particular time frame correlated to the specific hours during the shortened sleep phase in which the participants were forced to stay awake rather than slumber. The investigators did not note any significant differences between the two trials in norepinephrine concentrations throughout the rest of the twenty-four hour testing period.

Cortisol concentrations were found to be significantly greater during the evening hours (19:00 hours until 21:30 hours) and the late evening/early morning hours (23:00 hours until 1:30 hours) in the sleep restricted trial as compared to the normal sleep trial. Also of note, the normal cortisol peak associated with waking was evidenced two hours earlier in the volunteers while sleep-deprived.

ii. Exposure to Recurrent Sleep Restriction in the Setting of High Caloric Intake and Physical Inactivity Results in Increased Insulin Resistance and Reduced Glucose Tolerance

Nedeltcheva et al. 2009 also conducted an experiment to investigate the possible mechanism behind sleep deprivation on the development of insulin resistance. The literature produced from this endeavor describes the associated changes in cortisol, epinephrine, and norepinephrine when individuals experience sleep deprivation. Eleven healthy young adults (six females and five males) each underwent two fourteen day trials in which they sustained either eight and a half hours of sleep per night or five and a half hours of sleep per night. During the last twenty-four hours of each trial, blood samples were taken every half hour to analyze cortisol, norepinephrine, and epinephrine concentrations amongst other variables.

Total cortisol release between the two conditions did not vary significantly. In fact, the study showed comparable concentrations of cortisol throughout all hours of the time frame measured. The only significant difference noted was an increase in cortisol between 20:00 hours and 22:00 hours in the sleep restricted conditions. Of notable

difference, yet not of significance, were the shifts in acrophase from 7:49 hours to 7:05 hours and the shift in nadir from 0:27 hours to 1:28 hours in the sleep restricted group. Unlike those of cortisol, the comparative levels of catecholamines did show marked differences in concentrations.

Total epinephrine concentrations throughout the twenty-four hour testing phase were markedly greater in the sleep deprived group. In fact, epinephrine levels were elevated throughout both daytime hours and those of the night. Norepinephrine levels similarly showed significant increases during the evening hours of the study in the sleep restricted trial, although no such observations were made during the daytime hours. Taken together, test subjects were subjected to an approximate twenty-five percent increase in catecholamine concentration during evening hours whilst subjected to restricted sleep conditions.

iii. Number and Function of Circulating Human Antigen Presenting Cells Regulated by Sleep

Dimitrov et al. 2007 aimed to find correlations between concentrations of antigen presenting cells and hormones in sleep deprived volunteers. Twenty-seven healthy, young men were subjected to both one full day with a regular sleep cycle (from 23:00 hours until 7:00 hours) and one full day of no sleep at all. During both conditions, blood was sampled between 23:00 hours and 7:00 hours every one and a half hours, and then every three hours between 7:00 hours and 23:00 hours.

While the incremental samples of norepinephrine showed drastically different patterns throughout the testing period, the results did not indicate any significant changes in cortisol concentrations between the two conditions. In addition, both trials exhibited a peak and nadir in cortisol levels at 0:30 hours and 8:30 hours, respectively.

Norepinephrine assessment during the sleep deprived condition, however, did reveal dramatically inflated values during the normal sleeping period (23:00 hours until 7:00 hours). Assessments taken at all other time points did not indicate any discrepancies. Dimitrov et al. 2007 asserted that the elevated levels of norepinephrine were directly correlated to the elevated levels of NK cells during the same time frame.

The assessment taken during the sleep restricted conditions revealed populations of total NK cells that directly mirrored the varying levels of norepinephrine taken during the same trial. NK cell populations were significantly increased from 23:00 hours until 7:00 hours, yet did not show any marked differences in concentration from the normal sleep trial at any other point in time.

iv. Cortisol and epinephrine control opposing circadian rhythms in T cell subsets

A study was completed by Dimitrov et al. 2009 to disclose the role of sleep, cortisol, norepinephrine, and epinephrine in the expression of T lymphocytes. The experiment included fourteen healthy, young men who underwent a normal sleep-wake cycle and then subsequently a twenty-four hour period of no sleep. During the normal conditions trial, sleep was allotted between 23:00 hours and 7:00 hours. On both days,

blood samples were taken at 20:00 hours, then every one and a half hours between 23:00 hours and 8:00 hours, and finally every three hours from 8:00 hours until 20:00 hours.

The blood analysis did not reveal any significant variations in hormone or catecholamine levels between the two trials. However, the researchers did note a particular rhythmic pattern in different T lymphocyte subset concentrations that correlated to concentrations of cortisol and epinephrine, which was discussed earlier in this work.

v. Acute sleep deprivation reduces energy expenditure in healthy men

Benedict et al. 2011 investigated the effects of one night of acute total sleep restriction upon both circulating cortisol and norepinephrine levels within fourteen healthy, young males. Subjects were monitored through one day of normal sleep-wake conditions (sleep between 23:00 hours and 7:00 hours) and then one subsequent day of total sleep deprivation. Both the normal sleep-wake trial and the sleep restricted trial followed the same schedule for blood drawing and assessment. Blood was first sampled at 18:00 hours and 21:00 hours. Then, blood was taken every one and a half hours between 24:00 hours and 9:00 hours, every one hour between 10:00 hours and 13:00 hours, and finally at 15:00 hours and 18:00 hours once again.

Norepinephrine levels were found to be markedly increased during regular sleep hours (between 24:00 hours and 6:00 hours) in the sleep deprived trial as compared to the normal sleep-wake conditions. Levels of this catecholamine were also discovered to be elevated in the hours following a night of total sleep loss in comparison to the normal

conditions (between 9:00 hours and 13:00 hours). Mean cortisol levels were similarly found to be significantly higher throughout the sleep restricted trial. Concentrations of this hormone were specifically found to be increased between approximately 3:00 hours and 5:00 hours and then again at approximately 12:00 hours and 15:00 hours.

C. Catecholamine Levels in Sleep-Deprived Subjects

i. Nocturnal catecholamines and immune function in insomniacs, depressed patients, and control subjects

Irwin et al. 2003 studied the link between sleep deprivation, catecholamine concentration, and immune function in insomniacs. The researchers studied blood samples of thirty-one healthy, young male volunteers with no sleeping conditions and seventeen healthy, young male volunteers with insomnia. Following two days of sleep adjustment to the laboratory conditions, blood samples were taken every thirty minutes between 22:00 hours and 6:00 hours (assigned sleeping phase) without disturbing sleep in order to determine circulating catecholamine concentrations. The following morning, more blood was drawn to sample for NK cell activity, IL-2 concentration, and T lymphocyte concentration.

Insomniacs showed a significant decrease in total sleep time as well as the amount of time spent in stage 2 and REM sleep as compared with controls. The experiment also exhibited a marked increase in catecholamine concentrations in the subjects suffering insomnia as compared to controls throughout the time frame tested (see Figure 5). In

regards to leukocyte measurements, the insomniacs were shown to have decreased NK cell activity in comparison to the non-sleep deprived control group, but comparable T lymphocyte levels. IL-2 concentrations were similarly comparable between the two groups.

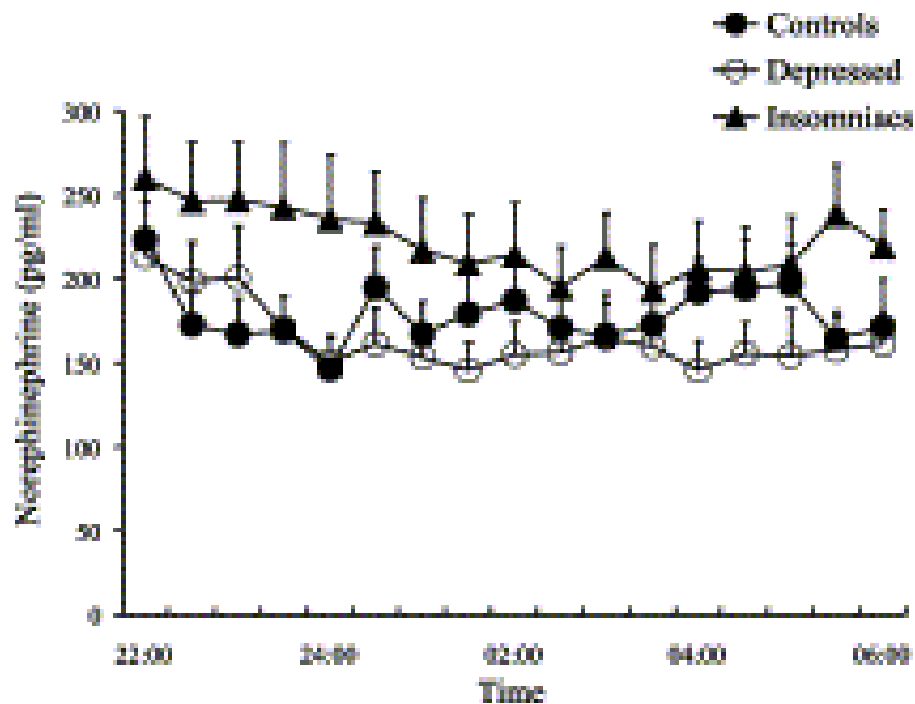


Figure 5. Plasma Levels of Norepinephrine as Measured in Control, Insomnia, and Depression Groups. Subjects suffering from insomnia (triangle) showed increased levels of norepinephrine throughout normal sleeping hours as compared to non-sleep-deprived volunteers (filled circle). Depressed subjects (open circle) were also tested in this experiment, but did not demonstrate significant sleep deprivation compared to controls. For this reason, this experimental group was left out of this thesis's assessment. Figure reproduced from *Nocturnal catecholamines and immune function in insomniacs, depressed patients, and control subjects* by Irwin et al. 2003

ii. Effects of Sleep and Sleep Deprivation on Catecholamine And Interleukin-2 Levels in Humans: Clinical Implications

Another undertaking performed by Irwin et al. 1999 in order to investigate any correlations between sleep deprivation and levels of both catecholamines and interleukin-2. Seventeen healthy, young male individuals partook in this study. During the normal sleep conditions trial, the participants were allotted seven hours of sleep (23:00 hours until 6:00 hours), while during the sleep restricted trial the volunteers slept for about four hours (23:15 hours until 3:00 hours). Blood samples were taken every thirty minutes between 22:00 hours and 6:00 hours.

Catecholamine concentrations showed significant variance between the two trials. Although norepinephrine levels were comparable between 22:00 hours and 3:00 hours in both conditions, values measured between 3:00 hours and 6:00 hours exhibited vast differences. The recordings within the shortened sleep group displayed marked increases in norepinephrine concentrations during this time frame in comparison to the normal sleep trial. Epinephrine levels were similarly increased during the 3:00 hours to 6:00 hour time frame, despite not reaching experimental significance. Concentrations of epinephrine between the two conditions were similar from 22:00 hours until 3:00 hours. On the other hand, IL-2 concentrations did not show any considerable difference in concentration between the two tests.

iii. Effects of chronic sleep deprivation on autonomic activity by examining heart rate variability, plasma catecholamine, and intracellular magnesium levels

Takase et al. 2004 conducted this experiment in order to determine the outcome of chronic sleep loss on the function of the autonomic nervous system. In order to do so, the researchers gathered samples of plasma catecholamine concentrations in thirty healthy, young men after periods of both normal sleep conditions, and chronic sleep deprivation. Each night of the four week restricted sleep trial, participants were only allotted eighty percent of their normal sleeping time.

The mean epinephrine value following the period of chronic sleep loss were fifty-two pictograms per milliliter, while that of the normal sleep conditions was thirty-eight pictograms per milliliter. Although the authors noted this as an important distinction between the two trials, the disparity did not reach statistical significance. Norepinephrine plasma concentrations between the two conditions, however, did reach statistical significance. Those associated with chronic sleep loss were markedly increased as compared to those identified with normal sleeping patterns.

DISCUSSION

A. Cortisol

Many studies have suggested that sleep deprivation may exert its effects upon the immune system by altering cortisol levels within individuals (Carroll et al., 2015; Irwin et al., 2015; Wright et al., 2015; Christofferson et al., 2014; Axelsson et al., 2013; Faraut et al., 2011; Kerkhofs et al., 2007; Matsumoto et al., 2001). Some groups even went so far as to generalize trends that sleep deprivation and cortisol levels share. For example, it has been speculated that among young individuals, sleep deprivation reduces morning cortisol levels (Carroll et al., 2015). Others asserted that their findings of increased cortisol levels within sleep deprived subjects were consistent with prior research (Wright et al., 2015). Christofferson et al. 2014 noted that cortisol measurements taken during acute total sleep deprivation trials may be lower in the second half of the night in comparison to normal sleep-wake trials. Similarly, Irwin et al. 2015 speculated that partial sleep deprivation may lead to decreased levels of cortisol during the second half of the normal sleeping period. Despite citing sources to support these speculations, there exist many more published studies finding the opposite trends. The literature aimed at deciphering the impact of sleep deprivation upon circulating levels of cortisol within young individuals is too inconsistent to make any definitive claims regarding this relationship.

The results noted within this thesis show no homogeneity with respect to cortisol concentrations following periods of sleep deprivation. Conclusions drawn from investigators included significant increases, marked decreases, and no notable changes at

all in cortisol levels within sleep deprived groups of individuals in comparison to normal sleep groups. Even among trials measuring the effects of either total or partial sleep deprivation upon the activity of the hypothalamic-pituitary-adrenal axis, there were no congruent findings.

In fact, a very similar experimental trial conducted by different research groups upon a very similar demographic of people yielded different results (Vgontzas et al., 1999; Heiser et al., 2000; Dimitrov et al., 2007; Dimitrov et al., 2009; Benedict et al., 2011; Chennaoui et al., 2011). All of these experiments measured the levels of cortisol in young, healthy men in both normal sleep conditions and throughout a one day period of total sleep deprivation. Whilst one study found increases in cortisol levels following the sleep restricted trial (Benedict et al., 2011), one found decreased levels (Vgontzas et al., 1999), and others observed no significant changes at all (Heiser et al., 2000; Dimitrov et al., 2007; Dimitrov et al., 2009; Chennaoui et al., 2011).

The three experiments reported which measured the effects of one day of total sleep deprivation upon both young, healthy men and women did not note any significant differences between the two genders. Two of these experiments showed significantly decreased concentrations of cortisol during the sleep restricted day, albeit at completely different points in time (Frey et al., 2007; Klumpers et al., 2015). The other, performed by Wright et al. 2015, showed significant increases in cortisol levels within the sleep deprived trial.

In a similar fashion, experiments which measured cortisol levels throughout periods of partial sleep deprivation did not reveal any consistent patterns. Literature

reporting the values of cortisol after both baseline and short time frames of partial sleep loss indicated both a decrease (Redwine et al., 2000), and an increase (Guyon et al., 2014) in cortisol levels in the sleep restricted trial compared to the normal sleep conditions. Studies conducted to determine the effects of partial sleep loss upon subjects during a longer time frame (four days or longer) also did not disclose any concurring evidence. While some found increased levels of cortisol as a result of decreased sleep time (Spiegel et al., 1999; Broussard et al., 2015), others observed no significant changes at all (Axelsson et al., 2013; Nedeltcheva et al., 2009). In accordance with those experiments involving total sleep restriction, no significant differences were noted between genders in the partially sleep deprived trials.

Even among research groups that similarly found a decrease in cortisol concentrations following periods of acute total sleep deprivation (Vgontzas et al., 1999; Klumpers et al., 2015; Frey et al., 2007), there is no unison in the observed times that these decreases were statistically significant. While Klumpers et al. 2015 discovered the most significant decline in cortisol levels just after normal waking hours and at 14:00 hours, Vgontzas et al. 1999 discovered the most marked decreases in cortisol during normal resting hours. Although Frey et al. 2007 discovered decreased cortisol levels at 13:00 hours, similar to Klumpers et al. 2015, no such differences were noted just after normal waking hours.

Although Wright et al. 2015 and Benedict et al. 2011 found a little congruence between times that cortisol was significantly increased following a night of total sleep deprivation, the consistency is not convincing. Both research groups discovered marked

increases in cortisol concentrations within the sleep deprived during the later hours of the morning and mid-afternoon. However, while Wright et al. 2015 detected significantly increased levels of cortisol within the sleep deprived trial during the early hours of the normal sleeping period, Benedict et al. 2011 discovered increased cortisol levels within the same trial during the later hours of the normal sleeping period. In addition, Wright et al. 2015 also disclosed significantly raised levels of cortisol during the early hours of the morning following a night of total sleep loss, while Benedict et al. 2011 showed no such findings.

Among those undertakings which found increased cortisol levels as a result of partial sleep deprivation, no compliance was established between the times of day that these increased values were measured. Guyon et al. 2014 discovered increased values between 20:00 hours and 0:00 hours while Broussard et al. 2015 only found increased cortisol levels between 19:00 hours and 21:30 hours, and then again between 23:00 hours and 1:30 hours. Spiegel et al. 1999, on the other hand, discovered increased cortisol levels between 16:00 hours and 20:00 hours.

The lack of accordance between these experiments could be attributed to the various methods of cortisol measurements used. For example, some researchers used plasma analysis while others measured salivary cortisol levels. In addition, some investigators only measured cortisol levels a few times throughout the trials while others measured the cortisol concentrations every fifteen or thirty minutes. The time frames of cortisol measurements similarly were often not aligned between the different experiments reviewed.

B. Cortisol Levels and Associated Immune Parameters in Sleep Deprivation

There is a very limited amount of literature that investigated direct correlations between sleep deprivation induced alterations in cortisol concentrations and the associated changes in immune parameters. What research actually aimed to accomplish this goal was presented within this thesis. The results given do not indicate any significant role for cortisol in altering immune function during or following periods of sleep deprivation.

The most compelling evidence indicating a very limited role of cortisol levels in altering immune function was found within those experiments that noted no significant changes in cortisol concentrations between sleep deprived and normal trials, yet also noted significant alterations in immune parameters. For example, Axelsson et al. 2013 and Chennaoui et al. 2011 noted no changes in cortisol levels between the two trials, yet also reported dramatic increases in TNF- α concentration within their respective sleep deprived trials. Furthermore, Axelsson et al. 2013 also noted a marked decline in the IL-2/IL-4 ratio within the sleep restricted conditions.

Redwine et al. 2000 found no increase in IL-6 production following a decrease in cortisol concentration, despite evidence suggesting that increased cortisol concentrations suppress IL-6 production (Marik, 2016; McEwen et al., 1997). Furthermore, Frey et al. 2007 discovered a decrease in IL-6 production in association with suppressed cortisol levels during a sleep restricted trial. The only evidence in accordance with expected immune parameter alterations in response to altered cortisol levels was an increase in IL-1 β concentration following a decrease in cortisol concentration.

Despite existing evidence suggesting that cortisol plays a minor role, if any, in altering immune function during periods of sleep deprivation, there is not enough research investigating this topic to completely refute this notion. More research needs to be completed that measures the effects of sleep deprivation upon circulating cortisol levels and immune parameters within the same experiment.

C. Catecholamines

Increased sympathetic nervous system activity has been suggested as a possible mechanism by which sleep deprivation affects the immune system (Irwin et al., 2015; Irwin et al., 2015; Christofferson et al., 2014; Faraut et al., 2011; Boudjeltia et al., 2008; Kerkhofs et al., 2007; Matsumoto et al., 2001). Some of these suggested models associate increased catecholamine concentrations caused by sleep loss in upregulation of pro-inflammatory proteins and increased leukocyte concentrations within the plasma (Irwin et al., 2015; Christofferson et al., 2014; Faraut et al., 2011; Boudjeltia et al., 2008; Kerkhofs et al., 2007; Matsumoto et al., 2001). The results reviewed within this thesis strongly support the notion that sleep deprivation causes increased sympathetic activity, yet insufficient research has been done to directly correlate this increased activity to increased immune cell and protein concentrations.

With the exception to the experiment conducted by Dimitrov et al. 2009, all of the reviewed literature exhibited increases in norepinephrine levels during periods of sleep deprivation. Both trials of total sleep deprivation and partial sleep restriction showed concurring results. Among research conducted to determine the effects of acute total sleep loss upon circulating norepinephrine concentrations, it was discovered that this

catecholamine's concentration was particularly increased within the sustained wakefulness trials during the hours previously spent sleeping in the normal sleep-wake trial (Dimitrov et al., 2007; Benedict et al., 2011; Irwin et al., 2003). The literature which investigated the effects of partial sleep deprivation upon circulating catecholamine concentrations similarly discovered that norepinephrine was dramatically increased during wakeful nocturnal times previously spent sleeping in the normal sleep-wake conditions (Nedeltcheva et al., 2009; Broussard et al., 2015; Irwin et al., 1999). Studies investigating the effects of sleep deprivation upon circulating concentrations of epinephrine found no significant results (Nedeltcheva et al., 2009; Irwin et al., 1999; Dimitrov et al., 2009).

There is a very limited sample of studies which investigated the possible correlation between sleep loss-induced increases in catecholamine concentrations and altered immune parameters. Those presented here showed a correlation between increased norepinephrine levels and NK cell concentrations (Dimitrov et al., 2007), along with decreased NK cell activity (Irwin et al., 2003). However, studies which showed increased norepinephrine levels as a result of sleep loss did not show any change in IL-2 concentration (Irwin et al., 2003; Irwin et al., 1999).

More research needs to be done investigating the direct correlation between sleep deprivation, altered catecholamine levels, and immune parameters. There is not enough research reported within this dissertation in order to conclusively determine whether or not altered catecholamine levels are a viable mechanism for sleep deprivation to alter immune function.

D. Limitations and Future Directions

This present work is accompanied by many limitations, all of which may contribute to the lack of agreement within the literature presented in this thesis. Firstly, the material presented is focused primarily on young, healthy men. Although the experiments reported which investigated the effects of sleep loss on men and women noted no significant disparities between the two genders, other researchers have noted that both sex and age may be important factors within this field of study (Carroll et al., 2015; Benedict et al., 2012).

Various protocols were employed by the experimenters discussed in order to determine how sleep loss would affect both hormone levels and immune parameters. However, none of the methods used accurately depicted sleep deprivation experienced throughout life. Individuals who suffer from a lack of sleep due to either a sleeping disorder or a stressful schedule are rarely subjected to periods of total sleep restriction. Although partial sleep deprivation is more similar to sleep loss experienced in life, it does not account for all instances. For example, people with sleep apnea or parents of a newborn child are subjected to short intermittent periods of sleep and wakefulness. In addition, the partial sleep loss that most people experience often continues for months or even years.

Another factor that may have attributed to the varied results is the inherent uniqueness of all human individuals. It is not uncommon for humans to have inherently different baseline levels of cortisol throughout different parts of the day (Kudielka et al., 2007). Similarly, baseline sympathetic nervous system activity varies from person to

person (Straznicky et al., 2012). As humans are complex beings, it is also difficult to isolate sleep deprivation as the only variable within these trials. For example, it is known that increased psychosocial stress can induce increased cortisol, epinephrine, and norepinephrine concentrations within humans (Nater et al., 2013).

Interestingly enough, much of the current research investigating the effects of sleep loss upon the immune system is focusing upon circadian misalignment. An altered or disrupted sleep-wake cycle can alter the regular rhythmicity of the master circadian clock of the body (Wright et al., 2015). This master circadian clock is the predominant regulator of cortisol levels and sympathetic nervous system activity throughout the twenty-four hour day (Cardinali et al., 2005). In addition, there is emerging evidence that the circadian rhythm can directly influence the activity of the immune system (Curtis et al., 2014; Logan et al., 2012; Gibbs et al., 2012).

Future investigations need to simulate sleep loss as experienced in the real world. These trials should not be focused on short periods of total or partial sleep deprivation, but should be extended over months. Measurements should be taken at regular and frequent intervals throughout the entire experiment. Studies should be limited to one demographic of the population in order to limit the number of differences between test subjects. The measured baseline values of cortisol and sympathetic nervous system activity should be comparable across all participants. In addition, subjects should be disqualified if they exhibit signs of elevated physical or mental stress as this has been known to affect circulating levels of hormones and catecholamines. Furthermore, future endeavors should measure the effects of sleep deprivation upon cortisol levels,

catecholamine concentrations, and immune parameters together. This will allow for a direct comparison between the sleep loss induced changes in cortisol and catecholamine levels and the affected immune parameters.

CONCLUSIONS

Research has not been able to elucidate any association between sleep deprivation and circulating levels of cortisol within human subjects. Furthermore, there is not sufficient evidence at present to either indict or dismiss cortisol levels as a possible mechanism of sleep deprivation to alter immune function. On the other hand, literature has shown a positive correlation between sleep deprivation and increased catecholamine concentrations within human subjects. However, there is similarly not sufficient evidence to either implement or reject the role of altered catecholamine concentrations as a mechanism of sleep deprivation to alter immune function.

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CURRICULUM VITAE

JAMES MORGAN KENNEDY

Year of Birth: 1992

19 Brigham Road, Worcester, MA, 01609 * (774)-696-5254 * jk1@bu.edu

Education

Boston University School of Medicine, Boston, MA

Masters of Science in Medical Science, Expected Graduation 2016

GPA: 3.62

Providence College, Providence, RI

Bachelor of Science in Biology, May 2014

GPA: 3.12

CEA, PC School of Theology and Religious Studies, Rome, Italy; September-December 2012

Saint John's High School, Shrewsbury, MA

Experience

Medstar Ambulance, Worcester, MA; November, 2015- Current

Emergency Medical Technician- Basic

Job description included forty hours of patient care rendered each week in both emergency and transportation settings.

Marine Biology Lab, Woods Hole, MA; June-September 2013

Researcher

Research was conducted alongside Dr. John Costello in the field of flexible propulsors.

The research consisted of surveying literature in the field of flexible propulsors.

The scientific paper resulting from this research is in its final stages of completion before submission for publication.

Providence College Biology Department, Providence, RI; January, 2013-May 2014

Undergraduate Research Student

Research was conducted alongside Dr. John Costello of the Providence College Biology Department. Research included the study of the movements of animals through mediums.

Vector Marketing Corporation, Worcester, MA; June-August 2012

Sales Representative

Experience included extensive networking and personal skills in order to attain clients through a non-cold-call or door-to-door operation. Clients were then met in their homes and given a brief presentation on the product. Personal sales reached over \$8,000.

Lauring Construction Company, LLC, Worcester, MA; May-August 2011

Laborer

Experience included general labor and operation of simple machinery. 45-55 hours were worked each week.

Leadership and Service

Women and Infant's Hospital, Providence, RI; January-May 2014

Volunteer

Volunteering included close coordination with the nursing staff in order to provide optimum service to all patients. Services included discharge, transportation, stocking rooms, and offering any aid needed by the nursing staff.

Jeanne Jugan Residence-Little Sisters of the Poor, Pawtucket, RI; April-Dec. 2013

Liaison/Vice President of Jeanne Jugan-Providence College Community Service Program

Bring students from Providence College who are interested in doing community service to the residency. Activities can include completing projects for the church in order to raise money for the organization, or spending time with the elderly who reside there.

Skills

Adequate skills with all Microsoft applications (Word, Excel, etc.).

Highly efficient organizational skills.

Quick learner.