Medical Hypotheses 77 (2011) 353–355

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

Does sleep deprivation and morphine influence wound healing?

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ARTICLE INFO

Article history:
Received 28 March 2011
Accepted 11 May 2011

ABSTRACT

The contrast between present-day sleep habits and those of the pre-industrial era are quite evident. One study recent has shown that the amount of sleep has decreased 2 h per night over the past 50 years. Such sleep curtailment, ubiquitous in the modern lifestyle, inflicts adverse repercussions upon health and well being. Investigations examining the relationship between stress and the skin have shown that different types of stress affect the healing process. Morphine is an immunosuppressive drug, and when it is used chronically, it can lead to an increased incidence of infections and a delay in the healing process. Therefore, our hypothesis is that the lack of sleep associated with chronic treatment with morphine is detrimental to the healing of the skin in the animal model we have adopted. Thus, it is important that future studies consider the paradigm of sleep curtailment when investigating the mechanisms involved in the process of skin healing in individuals who are dependent on morphine.

Introduction

The skin is the most extensive organ of the human body and corresponds to 16% of the body's total weight. Skin covers the entirety of the body's surface and exerts innumerable functions to protect tissues against damage, such as dehydration, invasion of foreign bodies, physical injury as well as damage caused by chemical and biological agents.

Damage to the skin triggers mechanisms of repair called healing. This process commences immediately after injury and is composed of three main phases: inflammatory, proliferative, and maturation. The first and second phases involve the release of cellular mediators, such as growth factors, serotonin, prostaglandins and neuropeptides, which are synthesized by fibrocystic elements, thus establishing an inflammatory response. This release produces vasodilatation and increased vascular permeability and stimulates cell migration and proliferation by means of cytokine production [1]. Subsequently, the extracellular matrix is synthesized, resulting in the remodeling of connective tissue and parenchymal components, collagenization and resistance at the site of injury. The maturation phase is characterized by the deposition, grouping and remodeling of collagen in addition to endothelial regression.

Angiogenesis, an essential event in the normal and homeostatic development of tissue, is defined as the formation of new blood vessels from preexisting vessels. Park and Barbul [2] have demonstrated that angiogenesis occurs 7 days after the formation of a skin lesion. Several growth factors are involved in angiogenesis, including vascular endothelial growth factor (VEGF), insulin-like growth factor (IGF) and platelet-derived growth factor (PDGF) [3]. Among these, VEGF plays a key role in neo-vascularization by stimulating the proliferation, migration and survival of endothelial cells [4,5].

Just as the physiological integrity of the skin is essential for the maintenance of the health of living beings, so is sleep. This important biological phenomenon, which consumes up to one-third of our lives, is fundamental to the maintenance of mental, emotional and physical health (for a review, see [6]). The contrast between present-day sleep habits and those of the pre-industrial era are quite evident [7]. One study by Van Cauter et al. [8] has shown that the amount of sleep has decreased 2 h per night over the past 50 years. Indeed, long working hours, increased numbers of daily activities and social obligations are only a few of the reasons that sleep time is becoming ever shorter. To make matters worse, the growing number of around-the-clock services available 7 days a week leads to increased amounts of shift work.

Such sleep curtailment, ubiquitous in the modern lifestyle, inflicts adverse repercussions upon health and well being. Studies have shown that the lack of sleep in rodents causes alterations in several behavioral parameters [9–12], including hormonal [13–15], metabolic [16] and neurochemical factors [17], in addition to detrimental effects to the immunological system [18–22].

Several studies have noted the difficulty in determining whether the physiological alterations observed within a given sleep deprivation (SD) experiment are indeed a consequence of sleep loss or rather of the stress such protocols cause on the subjects [23–25]. This doubt stems from observed alterations in the function of the hypothalamus–pituitary–adrenal (HPA) axis in

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0306-9877
doi:10.1016/j.mehy.2011.05.012

animal subjects [26], characterized by an increase in the production of corticosterone and adrenocorticotropic hormone [13,14,27].

The activation of the HPA axis and the consequent production of glucocorticoids that occur during conditions of stress are among the main mechanisms responsible for the observed alterations of the immunological response [28]. Studies investigating the interaction between the immune and nervous systems have shown that emotional, depressive and stressful states, anxiety [29–31] and medications with central activity influence immunity in animal subjects [32].

Investigations examining the relationship between stress and the skin have shown that psychological stress affects the healing process in women [33]. In addition to promoting several skin disorders, such as psoriasis and dermatitis [34–38], stress adversely affects the barrier function of the skin [39,40].

Using an animal model involving stress by immobilization, Padgett et al. [41] observed retardation of the healing process. That effect was most likely associated with reduced expression of pro-inflammatory cytokines (e.g., IL-1α and IL-1β) and growth factors [42,43] and also with increasing susceptibility to infection with *Staphylococcus aureus* [44].

Despite the relevance of stress-related studies to immunological parameters and skin integrity, Landis and Whitney [1] did not observe any detrimental effects on healing at the cellular level when observing sleep deprived rats for 72 h using the single-platform method. Similarly, those rats did not present a slower healing process when subjected to 5 days of SD with the multiple-platform method [45].

Although these data cannot be construed as evidence that the lack of sleep jeopardizes the healing process, it is nevertheless possible that those effects are mediated by other molecular mechanisms that are currently unidentified. Indeed, there are several factors that can impair wound healing, such as age, emotional state, nutritional state, the existence of diseases including diabetes, cardiocirculatory alterations, clotting, arteriosclerosis, kidney dysfunction, systemic infection and the use of drugs, such as morphine [46].

Morphine, an opiate, is extracted from the sap of the poppy plant (*Papaver somniferum*) and has been used for medicinal purposes for millennia. The importance of opiate compounds in clinical practice and in the development of analgesics is incontestable. Still, the side and toxic effects brought about by the extended use of opiates cannot be ignored. Opiates behave as cytokines, modulating the immunological response by interacting with receptors present in the central and peripheral nervous systems. The immunosuppressant effect caused by opiates can be traced to an increase in the incidence of viral infection in individuals addicted to heroin, leading to AIDS (acquired immunodeficiency syndrome). This increased incidence of infection is related to reduced secretion of chemokines (1α and 1β) and increased expression of the chemoreceptors CCR5 and CCR3 [47]. Others studies have shown that opiates can be used to induce sepsis in laboratory animals [48,49]. Additionally, there are data showing that the abuse of exogenous opiates can lead to DNA damage, specifically damage to DNA in immune cells, causing the proliferation of such cells or even apoptosis [50].

Recently, Martin et al. [51] have investigated the effect of morphine on wound healing in a mouse model, involving immune challenge with an inflammatory inductor (lipopolysaccharide). Chronic treatment with morphine resulted in an accentuated reduction in wound healing and increased bacterial sepsis. In addition, there was a reduction in neutrophil number and a delay in the recruitment of macrophages to the site of the wound. These alterations were due to perturbation of the expression of several cytokines that perform critical roles in the regulation of the immunological and inflammatory response after the occurrence of a lesion.

Another study by Martin et al. [52] have demonstrated that morphine leads to significant suppression of myofibroblasts and deficient angiogenesis in mice, either in the presence or absence of stimulation with lipopolysaccharides, significantly reducing the secretion of VEGF by macrophages in mice.

Final considerations

Sleep is an important biological phenomenon for skin homeostasis, and a shortage of sleep interferes with the barrier function of the skin. Moreover, morphine, a substance widely used in hospital practices, interferes in wound healing. Therefore, our hypothesis is that the lack of sleep caused by chronic treatment with morphine is detrimental to the healing of the skin in the animal model. Thus, it is important that future studies consider the paradigm of sleep curtailment when investigating the mechanisms involved in the process of skin healing in individuals who are dependent on morphine.

Funding sources

Associação Fundo de Incentivo à Pesquisa (AFIP), CNPq, and Fundação de Amparo à Pesquisa do Estado de São Paulo-FAPESP.

Conflict of interest statement

None declared.

Acknowledgments

This work was supported by grants from Associação Fundo de Incentivo à Pesquisa (AFIP), CNPq, and Fundação de Amparo à Pesquisa do Estado de São Paulo-FAPESP (CEPID #98/14303-3 to S.T.). M.L.A. and S.T. are recipients of the CNPq fellowship.

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