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Review

Photoimmunomodulation and melatonin

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ABSTRACT

The seasons, and daily physical rhythms can have a profound effect on the physiology of the living organism, which includes immune status. The immune system can be influenced by a variety of signals and one of them is photic stimulus. Light may regulate the immunity through the neuroendocrine system leading to the most recent branch of research the "Photoimmunomodulation". Mammals perceive visible light (400–700 nm) through some specialized photoreceptors located in retina like retinal ganglion cells (RGC). This photic signal is then delivered to the visual cortex from there to the suprachiasmatic nucleus (SCN) of the hypothalamic region. Melatonin – one of the universally accepted chronobiotic molecule secreted by the pineal gland is now emerging as one of the most effective immunostimulatory compound in rodents and as oncostatic molecule at least in human. Its synthesis decreases with light activation along with norepinephrine and acetylcholine. The changes in level of melatonin may lead to alterations (stimulatory/inhibitory) in immune system. The evidences for the presence of melatonin receptor subtypes on lymphoid tissues heralded the research area about mechanism of action for melatonin. Further, melatonin receptor subtypes-MT1 and MT2 was noted on pars tuberalis, SCN and on lymphatic tissues suggesting a direct action of melatonin in modulation of immunity by photoperiod as well. The nuclear receptors (ROR, RZR etc.) of melatonin are known for its free radical scavenging actions and might be indirectly controlling the immune function.

Contents

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1. Introduction

The demand of good health is of prime importance for all living being and is essential for reproduction as well as to combat with environmental stress. For timed physiological function, almost all the vertebrate groups are dependent on environmental signals (i.e. light, temperature and humidity) [1,2] which help them to achieve high survival rate for their young ones. Among the environmental signals, the photoperiod is one of the most important environmental cues, which has a perfect timing over eons in geographically distributed zones. Further, a set of neuroendocrine mechanism is directly responsible for the timing of seasonal rhythm and ensuring that they are synchronized to the annual geophysical cycles. Till date, the majority of work on the physiological mechanism of the photoperiodic action was focused on annual reproductive regulation among the photoperiodic vertebrates. However, photoperiodic regulation of various neuroendocrine, endocrine function(s) by melatonin – a chemical component of the neuroendocrine pineal gland, released into circulation in response to light/dark cycle is also reported. For example, the neuroendocrine mechanisms that transfer day length information into melatonin secretion patterns are critical for ultimately translating environmental factors into season-specific target organ responses such as immunity [3]. Therefore, it is reasonable to suggest that animals have developed the ability to use photoperiod information to forecast recurrent conditions associated with impending changes in the seasonal environment. Other environment factors, e.g., temperature or nutrients can modulate physiological function but they are of limited value to forecast changes in season.

Adaptations in immune function present one strategy that may promote individual survival in relation to a seasonal incidence of opportunistic diseases or changes in environmental conditions. The annual change in photoperiod is the most reliable proximate cue that predicts seasonal challenges in climate, nutrition and opportunistic pathogens. Not only in mammals seasonal changes in disease prevalence and immune status were noted, but these differences are also well known among humans [4].

2. The immune system

Immune system is a truly amazing constellation of responses to attacks from outside the body. It has many facets, a number of which can change to optimize the response to these unwanted intrusions. The system is remarkably effective, most of the time with a series of dual nature, the most important of which is self/non-self recognition. The others are general/specific, natural/adaptive = innate/acquired, cell-mediated/humoral, active/passive, primary/secondary. Parts of the immune system are antigen-specific (they recognize and act against particular antigens), systemic (not confined to the initial infection site, but work throughout the body) and have memory (recognize and mount an even stronger attack to the same antigen the next time). Self/non-self recognition is achieved by having every cell display a marker based on the major histocompatibility complex. Any cell not displaying this marker is treated as non-self and attacked. The process is so effective that undigested proteins are treated as antigens.

The immune system is composed of many interdependent cell types that collectively protect the body from bacterial, parasitic, fungal, viral infections and from the growth of tumor cells. Many of these cell types have specialized functions. Often, these cells depend on the T helper subset for activation signals in the form of secretions formally known as cytokines, lymphokines or more specifically interleukins. In very simple terms, the immune system involves a variety of white blood cells that work in concert to rid the body of the presence of a foreign pathogen (antigen). The primary cell types involved in an immune response are the macrophages, the T helper/inducer cells $CD4^+$ (T4), natural killer (NK) cells, B cells and the T suppresser/cytotoxic cells $CD8^+$ (T8). The function of the macrophages is to first recognize and interact with antigen. The original antigen can also be recognized by other antigen-presenting cells such as dendritic cells or B lymphocytes. The T4 helper cells, NK cells and B cells attack and destroy the antigen. The T8 suppresser cells turn off (anergize) the immune response.

2.1. Cytokines and immune responses

Cytokines are small secreted proteins which mediate and regulate immunity, inflammation and hematopoiesis. They must be produced *de novo* in response to an immune stimulus. They generally (although not always) act over short distances and short time spans and at very low concentration. They act by binding to specific membrane receptors, which then signal the cell *via* second messengers, often tyrosine kinases to alter its behavior (gene expression). Responses to cytokines include increasing or decreasing expression of membrane proteins (including cytokine receptors), proliferation and secretion of effector molecules.

Cytokine activities are characterized using recombinant cytokines and purified cell populations *in vitro* or with knock-out mice for individual cytokine genes to characterize cytokine functions *in vivo*. Cytokines are secreted by many cell populations, but the predominant producers are helper T cells (Th) and macrophages. The most prevalent group of cytokines are various subtypes of interleukins, IL 1–23 which stimulates immune cell proliferation and differentiation for example, IL-2 stimulates proliferation of antigen-activated T and B cells; IL-4, IL-5 and IL-6 stimulates proliferation and differentiation of B cells; interferon gamma (IFN-γ) activates macrophages, IL-3, IL-7 and granulocyte macrophage colony stimulating factor (GM-CSF) stimulates hematopoiesis. Some cytokines are predominantly inhibitory for example, IL-10 and IL-13 inhibit inflammatory cytokine production by macrophages [5].

Other groups of cytokines include interferons and chemokines. Interferons (IFN-α and IFN-β) inhibit virus replication in infected cells while IFN-γ also stimulates antigen-presenting cell major histocompatibility complex (MHC) expression. Chemokines attract leukocytes to infection sites. Chemokines have conserved cysteine residues that allow them to be assigned to four groups. The groups with representative chemokines are C–C chemokines (RANTES, MCP-1, MIP-1α, and MIP-1β), C–X–C chemokines (IL-8), C chemokines (lymphotactin), and CXXXC chemokines (fractalkine) [5].

Helper T cells have two important functions; (i) to stimulate cellular immunity and inflammation and (ii) to stimulate B cells to produce antibody. Two functionally distinct subsets of T cells secrete cytokines which promote these different activities. Th1 cells produce IL-2, IFN-γ and TNF-β which activate Tc (cytotoxic T cells) and macrophages to stimulate cellular immunity and inflammation. Th1 cells also secrete IL-3 and GM-CSF to stimulate the bone marrow to produce more leukocytes. Th2 cells secrete IL-4, IL-5, IL-6, and IL-10, which stimulate antibody production by B cells. Studies proposed that modulation of cytokines are possible by circulating hormones, neurotransmitters and opioids which generally influences the immune status [6]. Further, we know that fluctuation in photoperiod daily or seasonal is equally responsible for fluctuation in immune status or function which we will deal in the next few pages.

3. Photoimmunomodulation

Light strongly influences life of all living beings on the planet through the stimulation of the visual system and the regulation of the circadian timing system [7]. The vertebrate retina contains