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Introduction: Advances in Neuroimmune Biology: A Comprehensive way to Look at Biology

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Abstract. After a long period of specialization in science it has been gradually realized that the time has come for coordination, integration and interpretation in Biological Sciences. Advances in Neuroimmune Biology (ANIB) will fulfill, in part, this objective. ANIB deals with the immune-neuroendocrine circuitry as it integrates, coordinates and regulates all biological events in animals and men. This constitutes the Neuroimmune Super system (NISS), the ultimate central regulator of biological processes in animals. Homeostasis is discussed with respect to immune function. The role of the autonomic nervous system, immunological memory, Pavlovian conditioning of immunity, immune deficiency, stress, mast cells and neuroinflammation are included. Therapeutical application of the new knowledge is also considered.

INTRODUCTION

In the beginning Aristotle and Leonardo da Vinci could deal with all areas of science and art as so little was known that they could venture into virtually any field of science or art and investigate, draw conclusions or produce masterpieces. Later individual scientists dealt with one major discipline, such as Biology, Medicine, Natural sciences, Arts, History, and Social Sciences. The distinctions of Faculty of Arts and of Sciences reflect this specialization today at Universities. This specialization continues to grow, as knowledge is extending, and new disciplines occur such as Nuclear Medicine and Computer based Medicine, etc.

For a long time the reductionist approach was followed in Science, which involved the reduction of a problem as much as possible and then the clarification of details could be resolved with ease and with confidence that the findings are correct. This was necessary in order to understand the details of various problems in biology and in other disciplines. The creation of scientific disciplines reflects this specialization. However, now it is necessary to organize, evaluate and integrate the accumulated knowledge. It is necessary to analyze the current knowledge and try to understand the Biology of entire macro-organisms, especially of higher animals and of men. The facilitation of data storage and analysis by computers help us greatly to do this job.

Neuroimmune Biology (NIB) is one area of Comprehensive Biology, which aims to understand the organization, integration and coordinative regulation of higher animals and of men. Over the past 3 decades NIB has evolved into an exact science with rapidly increasing impact and the time is right to initiate a review journal, which helps to follow and understand this new multidisciplinary area of Biology. Here we present Advances in Neuroimmune Biology (ANIB), which is produced in order to make up for the gap of not having a review journal so far for this area of research.

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An important principle what is followed in NIB is the multidisciplinary approach. Bring everything together what we know and look for new mechanisms, new regulatory pathways, new rules and laws by which the entire organism is regulated. These efforts led already to major discoveries as summarized briefly below.

THE IMMUNE NEUROENDOCRINE CIRCUITRY (INEC)

Initially it was recognized that the central nervous system (CNS), the endocrine system (ES) and immune system (IMS) form a dynamic regulating circuitry, which integrates, coordinates and regulates bodily functions. Classical hormones, neurotransmitters, neuropeptides and cytokines are the soluble mediators of INEC. In addition innervations, recirculating leukocytes, blood and lymph circulation are important for systemic regulation. Cell to cell contact via adhesion molecules play important role in the regulation of individual cells, according to their functional differentiation in the body [1].

Initially feedback regulation by cytokines from the immune system to the brain (hypothalamus) was described [2]. Now it is apparent that the mediators are *shared widely* by numerous organs and tissues in the body. Communication is possible with the entire organism [3]. Recently it has been discovered that neurons in the brain expresses the innate antigen receptors, toll-like receptors (TLRs), and therefore the CNS is able to recognize directly infection and insults and is able to respond instantaneously to infection and injury. Numerous other organs and tissues, such as the pituitary gland, the adrenals, gonads, mucous membranes, endothelium, smooth muscle, cornea etc. express TLRs. This implicates that the entire body responds to infectious and other noxious insults. Sensory nerves pick up signals via mast cells and directly about inflammation (via bradykinin), infection, immunization, immune complexes, complement activation (by C3a, C5a) and inflammatory cytokines such as TNF-α, IL-1, IL-6, and GM-CSF. Environmental factors, especially antigens, but also circadian and circannual factors have immunoregulatory role [3–5].

Neuroimmune regulation in homeostasis

During health every parameter in the body is balanced physiologically (homeostasis). The serum levels of cytokines are extremely low, so they serve the regulation of tissues and organs locally, and have no systemic function. Sensory nerves will detect directly and via mast cell, immune activation, inflammation, complement activation and injury caused by diverse noxious agents. In addition the innate immune receptors (INIR) of the lymphoid elements of innate immunity (INIM) and of other tissues are capable of recognizing the noxious agents and produce cytokines, which alert the CNS. This CNS ruled INIR exerts an instantaneous host defense reaction by causing inflammation and activating leucocytes for phagocytosis and cytotoxicity, etc. Phagocytes, especially macrophages, engulf infectious microbes and other foreign material, digest (process) it and present peptides via surface MHC molecules to thymus derived (T) cells of adaptive immunity (ADIM). Helper T (Th1,-2) cells will be generated which will start up cell mediated and humoral ADIM reactions. Once these responses are generated, suppressor/regulatory T cells (Ts/r) emerge from the thymus in order to control the response. So that immune reactions will arise, perform their defensive function and subside. However, memory cells will remain which will initiate a faster and more powerful response if the same agent/infection occurs again [3].

The hypothalamic immunoregulatory hormone is *vasopressin* (VP) during homeostasis. VP regulates both prolactin (PRL) and the hypothalamic-pituitary-adrenal (HPA) axis in a balanced way so that cell-mediated and humoral immunity of ADIM and INIM will coexist in harmony. The hypothalamic hormones, growth hormone (GH) and PRL maintain adaptive immune function. These hormones stimulate cell growth, and B and T lymphocytes have to grow in order to go through clonal expansion before the development of a population of effector cells. GH and type I cytokines are able to stimulate lymphocyte growth, as they share signal transduction pathways. During debilitating conditions such as radiation disease, or immunodeficiency caused by cytotoxic chemotherapy, where cytokine production is impaired, pituitary hormones will stimulate immune regeneration. The HPA axis stimulates INIM, along with catecholamines (CAT). These hormones also stimulate Ts/r, which suppress ADIM function. This fact indicates that Ts/r is an innate immune cell as it is stimulated by the same hormones as INIM is. Thus the innate immune system can activate and suppress adaptive immunity. Gonadotropins, sex hormones, and vitamin D are modulators of ADIM [1, 6].

INIM is able to work autonomously, but responds to pituitary hormones for boosting and inhibition. INIM protects against pathogenic agents, injury and

various noxious agents. Polyspecific immunity and general protection against diverse pathogenic agents are characteristic of INIM. Germ line gene coded receptors recognize evolutionarily preserved cross reactive (homologous) epitopes, *homotopes,* or *patterns* [7, 8]. For example the lipid A is one such homotope of lipopolysaccharide (LPS) from Gram negative bacteria. This homotope is present in all Gram negative organisms, and TLR 4 has evolved in the INIM system to recognize this homotope. This way the INIM system can fight the entire class of Gram negative organisms, while using a single antigen receptor, [7]. In addition, it has been shown that heat exposure-induced expression of IL-1β and cyclooxygenase-2 in the brain is caused by LPS/lipid A through bacterial translocation from the gut in aged animals [9].

We are born with the INIM system and it is with us for life. The cells performing INIM are able to function autonomously, if necessary, without any systemic regulatory input. However, during homeostasis GH stimulates and the HPA axis inhibits the cytokine output of the INIM system [3].

In addition to host defense, immune mechanisms are involved in physiological regulation of the body. Thus the cytokines in the CNS perform physiological regulatory function [10], and during experimental allergic encephalomyelitis (EAE), T lymphocytes producing neuroprotective hormones (such as nerve growth factor (NGF)) which will infiltrate and protect the brain [11]. Immune mechanisms regulate the endocrine system, play a role in the mucosal and epithelial tissues, affect behavior and play a role in reproduction [12]. Immunological tolerance must be developed to food antigens in the gut so that excessive stimulation would not deplete immunological resource of the host [13]. On the other hand in the reproductive tract the semiallogeneic fetus must be tolerated by the mother's immune system [12].

AUTONOMIC MODULATION OF IMMUNITY

Since 1980s, anatomical studies have revealed the compartmentalization of noradrenergic innervation in lymphoid tissues and the direct contact between tyrosine hydroxylase-positive sympathetic nerve terminals and lymphocytes in the spleen and thymus [14]. Functional significance of the sympathetic innervation to the spleen was shown by the suppressive effects of sympathetic activation on splenic natural killer (NK) cell activity through β-adrenergic receptors [15] and inhibition of perforin and granzyme B expression by β-adrenergic agonists [16]. Furthermore, involvement of brain cytokines such as IFN-α and IL-1β in the suppression of NK cell activity through the hypothalamo-sympathetic and –pituitary-adrenals has also been demonstrated [17–19].

On the other hand, acetylcholine (ACh) released from parasympathetic (vagal) nerve has been demonstrated to inhibit macrophage cytokine production. It has been proposed that peripheral inflammatory stimuli activate afferent vagal nerve to transmit inflammatory signal to the brain, which in turn causes vagal reflex to suppress production of proinflammatory cytokines such as TNF-α and IL-1β through the activation of α7 subunit of nicotinic ACh receptor of macrophages [20]. This response to inflammation is termed cholinergic anti-inflammatory pathway. It has been shown that ACh derived from T lymphocyte also contributes to the regulation of immune functions [21].

IMMUNOLOGICAL MEMORY

Traditionally it has been assumed that immunocompetence is gradually lost with ageing. The age-related regression of the thymus was the main argument for the validity of this hypothesis. However, lately "successful ageing" has been described, whereby individuals with advanced age maintained normal immune and endocrine parameters [22]. It is certain that innate immune function is never lost. Now it is also known that memory cells of adaptive immunity survive major disasters and regenerate normal adaptive immunity, once the disaster is over [3]. Memory cells are generated continuously with advancing age and will maintain immune function, so the thymus has little if anything to do; this is the reason for regression. Our immune system has an incredible ability to defend us. The doom and gloom theory about age related immunodeficiency can now be discredited.

PAVLOVIAN CONDITIONING OF ADAPTIVE IMMUNE REACTIONS

The immune responses may be conditioned according to the classical method of Pavlov [23, 24]. This phenomenon is firmly established and it has been proposed that that INEC can anticipate danger and is able to mount a preemptive immune response. The mechanisms involved in conditioning are complex and poorly understood [25].

IMMUNODEFICIENCY

Hypohysectomy (Hypox) and neurointermediate lobectomy (NIL) lead to adaptive immunodeficiency [1]. However, in long surviving Hypox animals PRL is regenerated up to ~50% of normal levels and this PRL will maintain vital bodily functions, including normal immunocompetence. If this residual PRL is neutralized with specific antibodies all the animals die within 4 weeks [26]. Hypox and adrenalectomized (ADX) animals lack HPA axis function and will die after stimulating with immunological adjuvants, which is due to excess cytokine production. Such animals also die easily after LPS, TNF or IL-1 administration [27, 28]. In Hypox animals the excess cytokines are produced by the innate immune system after adjuvant stimulation, in ADX animals both the INIM and ADIM systems respond with excess cytokine production to stimulation.

Sex hormone deficiency also leads to immunological problems. There is estradiol (E2) deficiency in women after menopause. This deficiency results in enhanced T cell activity, which leads excess IL-7 production and these cytokine, together with T cells, over stimulate osteoclast activity. The result is osteoporosis. Females are also known to be more sensitive to autoimmune disease than are males. Sex hormones and PRL play a role in the pathogenesis of autoimmune disease. Autoimmunity may be regarded as the result of deficient immunoregulation [29].

PRL has a beneficial effect on radiation-induced immunodeficiency [29]. Recently some AIDS patients have been treated with growth hormone with encouraging results [30].

Glucocorticoids (GCs) are immunosuppressive and anti-inflammatory and have long been used as therapeutic agents in inflammatory diseases [26]. GH, PRL and type I cytokines, share signal transduction and are able to substitute for each other in immunoregulation [31].

STRESS, ACUTE ILLNESS AND INNATE IMMUNITY (ALLOSTASIS)

Hans Selye gave a detailed description of the stress syndrome in 1938 [32]. His outline of the neuroendocrine and immunological events during stress are actually analogous to the major symptoms of acute febrile illness or *acute phase response (APR)*. APR is an emergency defense reaction to infection, trauma and other noxious insults to the body [3, 33].

APR occurs when there is no sufficient time to develop an adaptive immune defense, which takes 7–10 days. Therefore, ADIM is suppressed, and INIM, which responds instantaneously, is rapidly amplified by INIM derived cytokines (e.g. IL-1β, IL-6, TNF-α and GM-CSF), and hormones (of the HPA axis and CAT) (immunoconversion). GCs and CAT enhance INIM and stimulate the generation of Ts/r, which in turn suppress ADIM function. The bone marrow will produce excess leukocytes, the liver will convert to the production of acute phase proteins (APP), which are defense molecules, such as C-reactive protein, endotoxin binding protein, mannose binding protein; other proteins are enzyme inhibitors or have anti-inflammatory function. Fibrinogen is also an APP, so are complement components and are elevated during APR. Natural antibodies are also increased and fulfill important roles in host defense [3, 33].

Fever and catabolism prevail during APR. The nutrient and energy demands are so high during APR, which can only be obtained by rapid degradation of bodily resources. If catabolism is inhibited, by giving an anabolic agent, such as GH, the result will be catastrophic and may lead to the death of the host organism [3, 33].

During APR the entire organism is mobilized to defend the body. The CNS and most other tissues express INIR to recognize homotopes, and get activated by the insult directly. Once activated, the cells will perform their physiological function to amplify host resistance, which will go on without the necessity of central regulatory input. Normally INEC coordinates and integrates the defense response. The HPA axis is a major regulator during APR. It regulates inflammation, cytokine production and makes sure that the defense response does not get out of hand. CAT supports this function via β_2-adrenergic receptors [3].

APR is a powerful defense response and we never loose it. All of us suffered from febrile illness numerous times during our lifetime and recovered. This indicates the incredible power of APR to defend the host. The INIM system is the first and last to exert host defense [34].

Mast cells and neurogenic inflammation

Mast cells are closely associated with sensory nerve fibers and serve as sensory organs for the penetration of antigen, which are recognized by IgE and IgG antibodies fixed to specific Fc receptors on the surface of mast cells. Antigen will react with the surface antibodies and trigger must cells to discharge their contents

of biological mediators (histamine, serotonin (5-HT), heparin, cytokines etc.) that act on sensory nerves. In turn sensory nerves trigger *neurogenic inflammation* and also transmit signals to the CNS [35]. The proinflammatory mediators of sensory nerves are substance P (P), calcitonin gene related peptide (CGRP), and vasoactive intestinal peptide (VIP). Anti inflammatory neuropeptides are somatostatin and galanin [36]. The vagus nerve also has sympathetic fibers and these fibers regulate neurogenic inflammation in visceral organs [37].

NEUROINFLAMMATION

Polyinosinic:polycytidylic acid (poly I:C), synthetic double-stranded RNAs, are ligands of TLR 3 and are used for mimicking viral infection in experimental animals. It has been shown that peripheral infection models produced by systemic administration of poly I:C, as well as LPS, demonstrate neuroinflammation in the CNS, which is characterized by activation of glial cells and increased expression of cytokines and their related substances, resulting in neurodegeneration and depression-like behavior [38–40]. Neuroinflammation induced by systemic injection of LPS, a TLR 4 ligand, results in cognitive impairment accompanied by enhanced production of β-amyloid protein [39], while TLR 3 signaling is suggested to be a suppressor of adult hippocampal neurogenesis [41].

Furthermore, intraperitoneal injection of poly I:C induced sustained suppression of running wheel activity, which was accompanied by enhanced expression of IFN-α and IL-1β, as well as 5-HT transporter (5-HTT), and was attenuated by 5-HT_{1A} receptor agonist [42–44]. The decrease in running wheel activity lasted several days after an abolishment of acute phase responses such as fever, HPA axis activation and sickness. This model is considered to be useful for studying pathogenesis of chronic fatigue syndrome that shows increased amount of IFN-α in the cerebrospinal fluid and polymorphism of 5-HT promoter region, which has an enhanced transcription activity [45].

It is unknown how peripheral LPS/poly I:C signals the brain to induce neuroinflammation. However, the following cells in the multiple routes have been suggested so far; (1) cerebral endothelial cells and perivascular microglial cells that have TLRs (2) glial cells in circumventricular organs, which lack a functional blood-brain barrier, and (3) visceral vagal afferent nerves. Furthermore, it has been shown that peripheral poly I:C administration leads to a breakdown of the blood-brain barrier depending on TLR 3 [46]

NEUROENDOCINE REGULATION OF HEALING

Once APR subsides and the inflammation becomes chronic, CRH will subside and VP takes over the regulation of the HPA axis, and also of PRL. VP is capable of regenerating normal immune function as well as it will regulate the healing of the host. This process has been coined as immunoreversion. During homeostasis VP remains the hypothalamic regulator of immunocompetence [6].

THE NEUROIMMUNE SUPER SYSTEM (NISS)

As already mentioned, during APR the entire host organism battles for survival. Even if there is extensive injury, the innate immune system will continue to defend the host. In case of lesioning the paraventricular nucleus, which synthesize pituitary hormone releasing hormones, the pituitary gland can be signaled directly by the TLR present, if the pituitary is gone, signaling may go through the adrenals. If no central regulatory pathway is active, the cells mediating INIM will be signaled via TLRs and INIM function will be still activated. Therefore the NISS is regulated by superimposed regulatory circuits as follows: 1) the CNS; 2) the pituitary gland; 3) adrenals, glands, thyroid, etc; 4) signaling may be delivered at the cellular level to activate INIM. This system is capable of exerting a massive resistance to infection and to other insults. Shared mediators allow for coordination, integration and dynamic regulation of the entire host organism [3, 47].

THERAPEUTIC APPLICATION OF NIB

GCs have been used for therapy of autoimmune disease, since Hench discovered their beneficial effect [48]. That GCs are important immunomodulators has been revealed much later [49]. Today the pharmacological industry attempts to produce GC analogues that regulate immune function but has no side effects. The hope is that such agents would suit better for therapy.

Sex hormones and their analogs may be useful in the treatment of inflammatory disease [29].

Currently GH is used for the treatment of short stature in GH deficient children. Some immune alteration was described in such children, but pituitary dwarf individuals have normal PRL levels and therefore, they also have normal immune function [49]. It is no wonder that not much have been seen in GH treated individuals. In animal experiments PRL treatment is effective against radiation disease [29] and GH therapy was used in AIDS patients with beneficial effects [30].

PRL promotes autoimmune disease and the dopamine antagonist agent, bromocriptine, which inhibits PRL secretion, has been employed in animals and in patient against systemic lupus erythematosus [49–51].

Bacterial LPS may be used as an immunological adjuvant. The lipid-A moiety of LPS is recognized by TLR 4, and therefore, LPS activates the innate immune system, which in tern exerts a therapeutic effect on diseases, restores bone marrow function and in general brings about recovery from disease. Detoxified LPS, especially radiodetoxified LPS, has similar beneficial properties [34].

Hormonal replacement therapy (HRT) is given to post-menopausal woman. Such therapy affect immune function, and may influence autoimmune disease and blood coagulation [29].

Estrogen antagonist agents used for the treatment of estrogen receptor positive breast cancer and of some other tumors are immunomodulators [29, 52–54]. This feature may contribute to the therapeutic effects of anti-estrogens.

CONCLUSIONS

The time has come when it is necessary to evaluate comprehensively the enormous amount of data accumulated in the scientific literature. ANIB will collect, organize and interpret the literature on the subject of central regulation of biological processes in higher organisms. Organization and interpretation make it possible to use the newly acquired knowledge in practice in Biology and in Medicine.

In the first issue we discuss the nomenclature and significance of innate/natural immunity and of species-specific resistance. Innate immunity is the first to defend the host and it is there serving host defense and other bodily functions until the last moment of existence. We never loose our innate immune competence, it is with us for life [37].

Innate immunity includes *polyspecifc immune mechanisms* with germ line gene based antigen receptors (INIR/NIR) that recognize phylogenetically preserved, highly cross-reactive (homologous) epitopes, or *homotopes.* Because both the antigen receptors (e.g., TLRs) and the homotopes (e.g., lipid A in bacterial LPS) are constant, and fully differentiated immune (monocyte/macrophages and other leucocytes) and somatic cells express TLRs, the entire organism is capable of responding instantaneously to infection or injury. Innate phagocytes, primarily monocyte/macrophages, support the development of adaptive immunity, by presenting antigen and by contributing cytokines for cell activation. If natural immunity is depressed, ADIM will be deficient. The natural immune system provides continuous protection for the host animals or men against the effects of stress, treatment of cytostatic drugs, septic shock, infectious diseases, and numerous other noxious agents [37].

Neuroendocrine, nutritional and environmental factors regulate natural immunity. The maintenance of good NIM defense is most important in modern medicine. Radiodetoxified endotoxin (RD-LPS) stimulates NIM, and activates the bone marrow. Animal experiments and human studies showed that RD-LPS is a promising preparation for the elevation of natural immune defense. RD-LPS is a potent immunological adjuvant in the case of inactivated virus vaccines (e.g. influenza) [37].

Antigenic stimulation elicits reactions taking place in the CNS. Brain cells in the hypothalamus are stimulated to express c-fos mRNA and protein in response to stimulation. Noradrenergic, cholinergic, serotonergic, dopaminergic and neuropetide Y containing neurons, vasopressin neurons, histaminergic neurons and orexinergic neurons are all involved in the brain response to antigenic stimulation. Although much remains to be established it is very clear that the brain is responding strongly to antigenic stimulation [55]. As a matter of fact, neurons express TLRs of innate immunity, so the brain may be considered to be an immunocompetent organ [4].

Recent research indicates that fetal/neonatal developmental phases are sensitive for many well-documented developmental deficits, amongst which are subtle immune-related disorders. In addition, a growing body of literature now exists to show that changes in the neurohormonal milieu of both mother/infant during pregnancy and weaning can itself produce profound changes in immune potential of the offspring, and, perhaps even more provocative, that immune changes in the pregnant mother can in turn modify behavior in offspring [56].

Immune cells (lymphocytes, monocytes and macrophages, granulocytes and mast cells) produce numerous hormones, store and secrete them. These cells have receptors for hormones and possess signal transduction pathways. These functions are under the control of the central nervous system (neuroimmune regulation), and there is a dynamic multi-directional interaction within the neuroimmune circuitry. The hormone production of immune cells rivals the production of "classical" endocrine glands [57].

Immune cells are poly-producers and poly-receivers, having receptors for different hormones. Immune cells are mobile and can transport the hormones in a packaged form, even though they are able to synthesize and secrete the hormones locally. Immune cells recognize the sites where their hormones are needed.

It is proposed that under the control of the CNS immune cells produce hormones for general regulation, for intra-system regulation and for remote, local regulation [57].

Hormone production is gender dependent. Receptors are affected by hormonal imprinting during the critical developmental periods of target cells and the imprinting influences also the hormone synthesis of immune cells for life. Some hormones can be demonstrated in the nucleus of mast cells, however their function is not known. Knocking-out of genes of relevant hormones disturbs hormone balance in immune cells [57].

Microglia are housekeepers in the adult brain. The primary candidate as a chemoattractant for microglia at damaged sites is adenosine triphosphate (ATP). However, many other substances can induce immediate change of microglia. Some neuropeptides such as angiotensin II, bradykinin (BK), endothelin, galanin (GAL), and neurotensin are also chemoattractants for microglia [58].

The central administration of IL-1β and IFN-α suppresses splenic NK cell activity in rats, which is mediated by, at least in part, the sympathetic nerves that innervate the spleen. The central administration of IL-1β and IFN-α increases splenic sympathetic nerve activity, and an electrical stimulation of the nerve results in a suppression of splenic NK cell activity through a β-adrenergic receptor-mediated process. Furthermore, immobilization (IMB) stress produced an elevation of extracellular concentration of noradrenaline in the spleen, and IMB-induced reduction of splenic NK activity was partially blocked by splenic denervation. Central injection of neutralizing anti-IL-1β antibody attenuated the IMB-induced NK suppression, and hypothalamic IL-1β and IFN-α mRNA was increased after 1 hr IMB. Therefore, IL-1β and IFN-α produced in the brain are key substances mediating IMB stress-induced immunosuppression [59].

Recent data indicate that NK cells play an important immunoregulatory role in the pathogenesis of autoimmune diseases, such as multiple sclerosis (MS) and EAE. NK cells eliminate harmful self-reactive T cells and thus inhibit the autoimmune process [60].

The hormone produced by the pineal gland, melatonin is involved in the innate immune response, and in inflammatory responses. The pineal gland is affected by antigens that stimulate innate immunity and produce melatonin. Melatonin is also produced by activated immune cells.

Nocturnal melatonin surge is suppressed at the beginning of an inflammatory reaction in order to allow full development of an innate immune response. Melatonin produced at the site of a lesion by activated immunocompetent cells favors phagocytosis and reduces inflammatory reactions that could cause tissue damage [61].

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