MLT AND THE IMMUNE-HEMATOPOIETIC SYSTEM

Georges J. M. Maestroni

Istituto Cantonale di Patologia, Center for Experimental Pathology, 6601 Locarno, Switzerland

1. ABSTRACT

It is now well recognized that a main actor in the continuous interaction between the nervous and immune systems is the pineal hormone MLT. T-helper cells bear G-protein coupled MLT cell membrane receptors and, perhaps, MLT nuclear receptors. Activation of MLT receptors enhances the release of T-helper cell type 1 (Th1) cytokines, such as gamma-interferon and interleukin-2 (IL-2), as well as of novel opioid cytokines which crossreact immunologically with both interleukin-4 (IL-4) and dynorphin B. MLT has been reported also to enhance the production of interleukin-1 (IL-1), interleukin-6 (IL-6) and interleukin-12 (IL-12) in human monocytes. These mediators may counteract stress-induced immunodepression and other secondary immunodeficiencies, protect mice against lethal viral and bacterial diseases, synergize with IL-2 in cancer patients and influence hematopoiesis. In cancer patients, MLT seems to be required for the effectiveness of low dose IL-2 in those neoplasias that are generally resistant to IL-2 alone. Hematopoiesis is apparently influenced by the action of the MLT-induced-opioids (MIO) on kappa-opioid receptors present on stromal bone marrow macrophages. Most interestingly, gamma-interferon and colony stimulating factors (CSFs) may modulate the production of MLT in the pineal gland. A hypothetical pineal-immune-hematopoietic network is, therefore, taking shape. From the immunopharmacological and ethical point of view, clinical studies on the effect of MLT in combination with IL-2 or other cytokines in viral disease including human immunodeficiency virus-infected patients and cancer patients are needed. In conclusion, MLT seems to play a crucial role in the homeostatic interactions between the brain and the immune-hematopoietic system and deserves to be further studied to identify its therapeutic indications and its adverse effects.

Melatonin after Four Decades, edited by James Olcese.
2. NEUROIMMUNOMODULATION

Maintenance of health depends to a significant extent on the ability of the exposed host to respond appropriately and, eventually, to adapt to environmental stressors. It is now well established that inappropriate or maladaptative response to such stressors weaken the body’s resistance to other stimuli from the environment such as pathogenic organisms or cancer cells. It is fair to consider the social environment as part of the general environment which has an impact on the body via redundant and reciprocal interactions between the body and the brain. These are linked by the nervous, endocrine, and immune systems and utilize a large array of chemical messengers including hormones, cytokines and neurotransmitters (72). There is abundant evidence that there are functional afferent nerve endings in the tissue of the immune and hematopoietic systems arising from both the sympathetic and parasympathetic systems (1,2). It is also clear that many neurotransmitters, neuroendocrine factors and hormones can drastically change immune functions and that, on the contrary, cytokines derived from immunocompetent cells can profoundly affect the central nervous system (1,2). As a consequence, any environmental stimulus to the nervous system will affect the immune system and vice versa essentially via the endocrine system. On this conceptual basis, it should not be surprising that the day/night photoperiod, which constitutes a basic environmental cue for any organism, can also influence the immune-hematopoietic system. As for many other adaptative responses, a major mediator of this influence seems to be the pineal gland which transduces the light/dark rhythm into the circadian synthesis and release of MLT (78).

3. MLT EFFECTS

Early studies about a possible link between the pineal gland and the immune system claimed that absence of the pineal gland stimulated the proliferation of immunocompetent cells (11,21,70) and others just the opposite (6,32,73). However, most studies agreed that pinealectomy is associated with a precocious involution and histological disorganization of the thymus (6,20,21,73). The mechanism of this effect was postulated to depend on increased steroid gonadal hormones. By various pharmacological interventions aimed at inhibiting MLT synthesis, we provided a first evidence about a possible involvement of endogenous MLT on humoral and T cell immune reactions, as well as on spleen and thymus cellularity in mice (59,63). In another report we show that pinealectomy inhibits leukemogenesis in a radiation leukemia virus murine model and that MLT has a promoting effect on the disease (18). A number of other authors have then further extended this type of evidence. Pinealectomized mice were reported to have depressed humoral immunity (7). In another report, inhibition of endogenous MLT in hamster produced a decrease of spleen weight and reduced T cell blastogenesis. MLT administration counteracted this effect (16). IL-2 production and antibody-dependent cellular cytotoxicity were inhibited in pinealectomized mice and exogenous MLT restored these important functions (22,67). Endogenous MLT has been also reported to influence the concentration of bone marrow granulocyte/macrophage colony-forming unity (GM-CFU) (28). An interesting finding which might be associated with and explained by the immunoenhancing action of endogenous MLT, is the widely documented oncostatic role of the pineal gland and of MLT (12). From the pharmacological point of view, MLT can augment the immune response and correct