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Role of Pineal and Pituitary in Immunomodulation: A Systematic Review

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Abstract: *The neuroendocrine-immune axis represents a highly coordinated, bidirectional communication network crucial for maintaining physiological homeostasis. Within this network, the pineal and pituitary glands serve as central orchestrators. This systematic review synthesises the current literature exploring the immunomodulatory roles of pineal melatonin and pituitary hormones, with a specific focus on findings derived from murine models. Evidence consistently demonstrates that pineal melatonin acts as a potent pleiotropic immune enhancer. By exerting anti-apoptotic and antioxidant effects, melatonin protects critical lymphoid organs specifically the thymus and spleen against stress-induced involution and cellular depletion. Concurrently, the pituitary gland exerts a multifaceted regulatory influence; while pituitary prolactin acts as a vital survival factor that stimulates lymphocyte proliferation and cellular immunity, the hypothalamic-pituitary-adrenal (HPA) axis counterbalances this by mediating immunosuppressive pathways to prevent auto-reactivity. Ultimately, murine research delineates a precise immunological balance governed by these neuroendocrine components. Deciphering the exact intracellular signalling mechanisms of melatonin and prolactin in mice provides a critical foundational framework for the future development of targeted neuro-immunomodulatory therapies aimed at managing stress-induced immune-deficiency and autoimmune disoreders*

Keywords: Glucocorticoids (GCs), Pineal, Pituitary, Melatonin, Lymphoid organ, Thymus, Spleen, Leukocytes, Immunomodulation, Immunosuppressive, Mice

I. INTRODUCTION

The relationship between neuroendocrine and the immune system has been analyzed since the 1980s, and is now well established that there is a bidirectional communication between these two systems. The neuroendocrine system can both directly and indirectly influence the developmental and functional activity of the immune system. On the other hand, the immune system can affect and regulate the endocrine activity. The network of connections is mediated by nerve pathways, hormonal circuits, cytokines, neuropeptides and chemokines acting in an autocrine, paracrine and endocrine manner (Besedovsky and del Rey, 1996; Szyper-Kravitz et al., 2005).

A large body of literature is available stating the role of neuroendocrine components on modulation of immune functioning. Three of the major neuroendocrine systems linked to immunomodulation are hypothalmo-pituitary-adrenal, hypothalmo-pituitary-gonadal (HPG) and hypothalmo-pituitary-thyroid (HPT) axes. The hormones of these three axes: ACTH and glucocorticoids of HPA axis, gonadal steroids of HPG axis and TSH and thyroxine of HPT axis have varied effects on immune system. Besides the hormones of these three axes other pituitary hormones playing roles in immune regulation are PRL and GH. Another neuroendocrine gland playing major role in immunomodulation is pineal through its hormone melatonin. Both immune enhancing and immune suppressive roles of neuroendocrine hormones have been reported depending on the kind, dose and the timing of their administration. In view of the major focus of the present investigation which aimed at reviewing the literature that explores the immunomodulatory roles of pineal melatonin and pituitary prolactin, a detailed review of available literature on immune regulation by these two hormones is given below.

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ROLE OF PINEAL MELATONIN IN IMMUNOMODULTION

Melatonin (N-acetyl-5-methoxytryptamine) is synthesized mainly in pineal gland. Pineal product melatonin is involved in reciprocal relationships between neuroendocrine and immune systems, responsible for keeping internal homeostasis in vertebrate animals. In recent years, much attention has been devoted to explore the possible interaction between MEL and the immune system (Maestroni, 2001; Guerrero and Reiter, 2002; Esquifino et al., 2004). Melatonin has a defined immunomodulatory role both in animals and humans (Maestroni, 2001; Esquifino et al., 2004). The diurnal and seasonal changes in the immune system have been shown to correlate with MEL synthesis and secretion (Skwarlo-Sonta, 2002). Melatonin receptors have been identified directly on circulating lymphocytes, splenocytes, and thymocytes (Lopez-Gonzales et al 1992; Calvo et al., 1995; Rafii-el-idrissi et al., 1995). The cells and organs of immune system using membrane receptors as well as nuclear orphan receptors perceive MEL message. Effects exerted by MEL on immune parameters are different, and depend on several factors, including dose and way of MEL application, species, sex, age of animal, immune system maturation and stressful conditions etc. Maestroni and coworkers first showed that inhibition of MEL synthesis causes inhibition of cellular and humoral responses in mice (Maestroni et al., 1986). Mice kept under constant light, or receiving injections of beta-adrenergic blockers (propranolol) to inhibit MEL synthesis, exhibited an inability to mount a primary antibody response to sheep red blood cells, a decreased cellularity in thymus and spleen and a depressed autologous mixed lymphocyte reaction; all these were reversed by MEL administration at the late afternoon (Maestroni et al., 1986). Hamsters exposed to short photoperiods had increased spleen weight and number of splenic lymphocytes and macrophages (Peters et al., 1989). A number of studies reported that MEL stimulates the production of progenitor cells for granulocytes and macrophages and has a general stimulatory action on hemopoiesis (Maestroni and Conti, 1996; Maestroni, 1998). Exogenous MEL augments NK cells and monocytes in both the bone marrow and the spleen (Currier et al., 2000). An increased activation of monocytes/ macrophages by MEL has been reported in yet another study in rodents (Kaur and Ling, 1999). Melatonin treatment restores the decreased total leukocyte count in peripheral blood and bone marrow of pinealectomized and GC treated squirrels (Haldar and Singh, 2001; Haldar et al., 2004). Besides its stimulatory action on the production of several cytokines that regulate immune function, melatonin's immunoenhancing properties have been attributed to a direct action on the immunocompetent cells (e.g. granulocyte-macrophage cells, NK cells and lymphocytes). Earlier studies demonstrated that the thymus is a primary target of melatonin's action. Studies have revealed that pinealectomized young mice underwent accelerated involution of the thymus (Csaba and Barath, 1975). The severe loss of thymocytes with age is the main cause of structural thymic atrophy and thymic weight loss. It is reported that melatonin administration increased the total number of thymocytes in old mice (Tian et al., 2003). Both *in vivo* and *in vitro* studies have shown that the administration of MEL inhibits programmed cell death in main lymphoid organs (Csaba and Barath, 1975; Sianz et al., 1995; Provinciali et al., 1996).

Besides its immune enhancing property, the anti-glucocorticoid (GC) effect of MEL has also been studied. It is reported that MEL counteracts the negative impact of GC on immune system (Maestroni et al., 1993). Melatonin counteracts the GC-induced suppression of lymphoid organs has been demonstrated through the histological study of thymus and spleen in different vertebrates (Maestroni et al., 1993; Haldar et al., 2004). Studies are there stating that MEL down-regulates the GC receptors in lymphoid organs and prevents the GC-induced apoptosis (Persengiev et al., 1991, 1992; Sainz et al., 1999). Melatonin antagonization of the effects of exogenous GC and seasonal stress on circulating immune cells has also been reported (Maestroni and Conti, 1990; Conti and Maestroni, 1993; Haldar et al., 2004).

ROLE OF PITUITARY HORMONES IN IMMUNOMODULTION

The pituitary gland is the major endocrine gland playing a key role in the regulation of growth, differentiation, and function of all cells in the body including cells and organs of the immune system through its various tropic hormones. Both suppressive and enhancing effects have been elucidated. ACTH is reported to depress the immune response where as other pituitary hormones like growth hormone, prolactin, and thyroid stimulating hormone are reported to exert immunostimulatory effects. Recently much attention has been paid to understand role of GH and PRL in immune regulation. A literature survey on immunomodulatory roles of various pituitary hormones is given below:

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Adrenocorticotropic Hormone (ACTH)

Specific, high affinity receptors for ACTH have been identified on T and B lymphocytes of rats (Clarke and Bost, 1989). It is reported that ACTH has suppressive effect on the immune system *in vivo* (Bernton et al., 1991; Berczi, 1994). ACTH inhibits antibody production and modulates many aspects of immune cells (Johnson et al., 1992). ACTH has also been shown to suppress major histocompatibity complex (II) expression by murine peritoneal macrophage, stimulate NK cell activity, suppress the production of IFN-γ, function as a late-acting B-lymphocyte growth factor and stimulate the growth and differentiation of human tonsillar B cells (Johnson et al., 1992). Several reports have appeared that strongly point to an important immunoregulatory role for other POMC peptides in lymphocytes *in vivo* (Carr, 1992).

Thyroid Stimulating Hormone (TSH)

Pituitary thyrotropin (TSH) was one of the neuroendocrine hormone that was recognized to play an important role in immunologic regulation *in vivo* (Pierpaoli et al., 1969). Thyrotropin enhanced the *in vitro* antibody response at physiological concentrations (Kruger, 1986). TSH has been shown to have a variety of immune-regulating cytokine-like activities that can affect the magnitude of antibody and cell-mediated responses of peripheral lymphocytes (Wang and Klein, 2001). TSH-mediated upregulation of the mouse lymphocyte proliferative response to both Con A and PHA has been reported (Provinciali et al., 1992). Interactions between pituitary–thyroid hormones and the immune system are mainly based on the existence of receptors for thyrotropic and thyroid hormones on lymphocytes or on the frequent immune alterations observed in physiological and pathological fluctuations of thyroid hormones (**Klecha et al., 2006**). Participation of thyroid hormone in primary and secondary lymphopoiesis has been described (Fabris et al., 1995). Hypothyroidism in humans has been shown to diminish thymic activity (Stagia et al., 2005). Experimentally induced hypothyroidism in rodents has been associated with involution of thymus, spleen and lymph nodes (Fabris et al., 1995) and was reported to depress humoral and cell-mediated immune responses (Klecha et al., 2006).

Conversely, contradictory results exist in the literature on the effect of experimental hyperthyroidism on the humoral and cellular immunity (Fabris et al., 1995; Klecha et al., 2006). Either an enhancing or suppressing effect of primary antibody responses or of T- and B-lymphocyte proliferation (Chatterjee and Chandel, 1983; Klecha et al., 2006) was demonstrated in hyperthyroid conditions.

Growth Hormone (GH)

Growth hormone is classically defined as a peptide hormone that is synthesized and secreted primarily by somatotrophic cells in the anterior pituitary. Growth hormone has wide ranging effects on the immune system. Several *in vitro* or *in vivo* studies have suggested that GH could play a role in immune function, inducing the survival and/or the proliferation of lymphoid cells. Mice with the dwarf mutation and ablation of the pituitary gland exhibit diminished immune functions and thymic atrophy (Redelman et al., 2008). Similarly, hypophysectomized rats or Snell dwarf mice (both defective in the production of GH) display deficiencies in lymphocyte development and function. Moreover, administration of GH was found to enhance development of the thymus in aged mice (Redelman et al., 2008). It has now been clearly demonstrated that lymphoid cells also contain receptors for GH (Weigent et al., 1994). The potential role of GH in immunoregulation has also been demonstrated *in vitro* including stimulation of DNA and RNA synthesis in the spleen and thymus of normal and hypophysectomized rats. Evidences are there that GH affects hemopoiesis by stimulating neutrophil differentiation, augment erythropoiesis, increases proliferation of bone marrow cells, and influences thymic development (Fu et al., 1992). In other *in vivo* studies it has been shown that GH can stimulate the production of IL-I, IL-2, TNF- α, thymulin; induce the cytotoxic activity of NK cells; and restore the normal architecture of the thymus in aged animals (Kelley, 1989).

Prolactin (PRL)

Numerous review articles have summarized the literature indicating that PRL can have effects on the immune system (Kooijman et al., 1996; Yu-Lee, 1997; Bole-Feysot et al., 1998; **Dorshkind and Horseman, 2000**). Clinical, animal, and *in vitro* studies combine to suggest that PRL exhibits immunostimulatory properties (Yu-Lee, 1997). Although actions of PRL on the hemopoietic system were suggested in early studies involving treatment of hypophysectomized rats with PRL (Vollmer et al., 1942), it was not until much later that a clear role of PRL in the immune system was established. Multiple effects of PRL in the regulation of immune function have been reported. PRL has been shown to

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stimulate T cells, B cells, NK cells, macrophages, neutrophils and antigen-presenting dendritic cells (Kooijman et al., 1996; Dogusan et al., 2001; Matera et al., 2001). Pharmacologic suppression of PRL secretion in rodents has been reported to affect normal lymphocyte function and impair lymphocyte-dependent immune host defenses (Bernton, 1989). Furthermore, studies have shown that the stimulation of PRL release by the administration of dopamine antagonists such as metoclopramide reverses many aspects of immunosuppression brought about by cyclosporine, glucocorticoids, or chronic morphine treatment in mice (Holaday et al., 1993). In accordance with its immunoenhancing effect, PRL administration restored the depressed splenocyte proliferative capacity and cytokine release following trauma hemorrhage (Zellweger et al., 1996b). Injection of PRL into hypophysectomized rats causes an increase in the weight of the spleen and thymus (Berczi et al., 1991). In addition, PRL activates an immunostimulatory action of the submandibular gland (Nagy et al., 1992) and augments the production of a thymic hormone, thymulin (Dardenne et al., 1989).

Prolactin receptor is ubiquitously expressed by cells of the immune system and certain subpopulations of lymphocytes synthesize and secrete biologically active PRL. This suggests that PRL can act as an autocrine and/or paracrine factor to modulate the activities of immune cells (Russell et al., 1985; Matera et al., 1988; Yu-Lee, 1997). In lymphocytes, PRL is known to increase hurmoral and cellular immunity to reverse anemia, leukopenia, and thrombocytopenia induced by hypophysectomy (Nagy and Berczi, 1989). Role of PRL in increase antibody formation (Berczi et al., 1981; McMurray et al., 1991; Lahat et al., 1993) and lymphocyte proliferation (Mukherjee et al., 1990; Sabharwal et al., 1992; Murphy et al., 1993) has also been reported. Evidences also support the role of PRL in the mitogenesis of T lymphocytes (Montgomery et al., 1987). Prolactin has been shown to enhance the release of thymocytes from lymphoepithelial complexes in the thymus (De Mello-Cuelho et al., 1997), and to act as growth factor for T cells (Mukherjee et al., 1990). PRL has also been reported to increase receptor levels for IL-2 (Mukherjee et al., 1990; Gala and Shevach, 1993). In addition to stimulating proliferation, PRL has been shown to inhibit apoptosis of lymphocytes (Fletcher-Chiappini et al., 1993). Administration of PRL is also associated with increased graft rejection (Comsa et al., 1975; Carrier et al., 1987) and an increase in T cell engraftment (Taub et al., 1994). In natural killer cells, PRL has been reported to augment cytotoxic effects (Cesano et al., 1994) as well as increasing susceptibility of primary leukemic cells (Oberholtzer et al., 1996). PRL reduces direct and spontaneous migration of polymorphonuclear cells (Cecilia et al., 1994) and regulates lymphocyte-epithelial cell adhesive interactions in the thymic nurse cell complex (Villa-Verde et al., 1995).

PRL and other pituitary hormones are suggested to act as stress-adaptation molecules important in maintaining immune system homeostasis (Dorshkind and Horseman, 2001). Under stressful conditions, PRL is needed to balance the negative effects of glucocorticoids and other immune or inflammatory mediators to maintain steady-state homeostasis. This interpretation is supported by *in vitro* studies showing PRL's protective effect in preventing GC-induced lymphocyte cell death (LaVoie and Witorsch, 1995; Buckley, 2001) and by *in vivo* studies showing that PRL improves macrophage and splenocyte functions following trauma-hemorrhage and infections (Zellweger et al., 1996a). A rapidly growing evidence of literature on PRL and its effects on the immune system has suggested several important immunomodulatory roles for this hormone; however, some of them appear to be contradictory, which indicate either an immunostimulatory (Spangelo et al., 1987) or an immunosuppressive (McMurray et al., 1991; Vidaller et al., 1992) role for PRL. The immunomodulatory role of Prolactin is mainly based on *in vitro* studies. Studies are also there which exclude any essential role for the PRL receptor in lymphocyte differentiation (Bouchard et al., 1999). It is reported that PRL receptor-deficient mice develop mature functional B, T, and NK cells and demonstrate the capacity to generate diverse types of immune responses *in vitro* as well as *in vivo*. Report on PRL-deficient animals (Horseman et al., 1997) has also indicated that PRL is not required for normal hemopoiesis.

II. CONCLUSION

In conclusion, this systematic review underscores the indispensable roles of the pineal and pituitary glands as central orchestrators of the neuroendocrine-immune axis, a complex crosstalk that has been extensively elucidated through murine models. The synthesised literature clearly demonstrates that these endocrine structures are engaged in a highly coordinated, bidirectional communication network essential for maintaining immunological homeostasis in mice.

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Studies utilizing mouse models consistently confirm that pineal melatonin acts as a potent, pleiotropic immunomodulator. By counteracting stress-induced immunosuppression, melatonin has been shown to prevent the cellular depletion and involution of critical lymphoid organs, specifically the thymus and spleen, in mice. This highlights its role as a vital buffer against immunosenescence and neuroendocrine-related immune dysfunction, driven primarily by its immunoenhancing, antioxidant, and anti-apoptotic effects on murine lymphocytes.

Concurrently, murine research delineates the complex, multifaceted regulatory influence of the pituitary gland. Pituitary hormones such as prolactin function as critical survival factors and stimulants for cellular immunity and lymphocyte proliferation in mice. However, this immunoenhancement is carefully balanced by the immunoregulatory and often immunosuppressive effects mediated through the hypothalamic-pituitary-adrenal (HPA) axis—pathways frequently mapped in murine studies using glucocorticoid models—ensuring that immune responses are tightly controlled to prevent auto-reactivity.

While the preclinical foundation linking these neuroendocrine pathways to immune regulation in mice is robust, future research must priorities elucidating the precise intracellular signaling mechanisms at the receptor level within specific murine immune cell populations. Ultimately, deciphering the exact pharmacological modulation of melatonin and prolactin in the mouse model provides a critical, translational stepping stone for developing integrative neuroimmunomodulatory therapies aimed at managing stress-induced immune suppression and autoimmune disorders.

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