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Invited Review Article

Control of immunity and allergy by steroid hormones

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ABSTRACT

Steroid hormones, especially glucocorticoids, androgens, and estrogens, have profound influence on immunity. Recent studies using cell-type specific steroid hormone receptor-deficient mice have revealed the precise roles of some of these hormones in the immune system. Glucocorticoids are known to have strong anti-inflammatory and immunosuppressive effects and pleiotropic effects on innate and adaptive immune responses. They suppress the production of inflammatory cytokines by macrophages and DCs and the production of IFN-γ by NK cells, thus inhibiting innate immunity. By contrast, glucocorticoids enhance the immune response by inducing the expression of IL-7R and CXCR4 in T cells and the accumulation of T cells in lymphoid organs in accordance with the diurnal change of the glucocorticoid concentration. Thus, glucocorticoids suppress innate immunity but enhance adaptive immunity. Androgens suppress the homeostasis and activation of ILC2s and the differentiation of Th2 and Th17 cells and enhance the suppressive function of Tregs, thereby alleviating allergic airway inflammation. Thus, these steroid hormones have pleiotropic functions in the immune system. Further investigations are awaited on the regulation of immunity and allergy by estrogens using cell-specific steroid hormone receptor-deficient mice.

Introduction

Steroid hormones play pleiotropic roles in metabolism, physiology, and sexual development. Steroid hormones are classified into three classes: glucocorticoids, mineralocorticoids, and sex hormones. Among them, glucocorticoids, androgens, and estrogens have been reported to influence the immune system. Glucocorticoids have strong anti-inflammatory and immunosuppressive effects and are used to treat allergies and autoimmune diseases and prevent graft rejection in transplantations.[1] On the other hand, androgens and estrogens are known for their immunomodulatory effects.[2] For example, thymic involution is reversed by castration or ovariectomy. Furthermore, sex bias is well recognized in the prevalence of allergic and autoimmune diseases.[3] Additionally, since the biological clock controls the plasma levels of steroid hormones, these hormones have a role in the circadian control of the immune system.[4,5] In this review, we discuss recent research using receptor-deficient model mice on the control of immunity and allergy by steroid hormones.

Steroid hormones

Steroid hormones include glucocorticoids, mineralocorticoids, androgens, estrogens, and progesterone. In terms of immune regulation, glucocorticoids, androgens, and estrogens are the major steroid hormones that impact the immune system. They bind to nuclear receptors in the cytoplasm and transmit their signals by the activation or repression of target gene transcription or by the modulation of other transcription factors by direct interactions. The receptors include glucocorticoid receptor (GR), androgen receptor (AR), and estrogen receptor-α and -β (ERα and ERβ).[1,2] Steroid hormones are mainly produced in the adrenal cortex for glucocorticoids, testis for androgens, and ovary and placenta for estrogens, though small amounts of the hormones are ectopically produced.[1] Overall, their production is controlled by complex mechanisms. The production of glucocorticoids, for example, is induced by the circadian rhythm and stress via the hypothalamic-pituitary-adrenal (HPA) axis,[1] while the production of androgens and estrogens is controlled by the hypothalamic-pituitary-gonadal (HPG) axis, which also triggers the menstrual cycle (Fig. 1).

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Roles of glucocorticoids in immunity

Glucocorticoids are a self-defense hormone with complex effects on multiple organs.[1] The major function of glucocorticoids is the upregulation of blood glucose levels and the arousal of the brain, which together prepare the body for activities of the day and the fight or flight response when encountering enemies. In addition, glucocorticoids have strong anti-inflammatory and immunosuppressive effects and are used to treat inflammatory, allergic, and autoimmune diseases and prevent graft rejections in transplantations. These suppressive effects seem to contradict the self-defense role of glucocorticoids, complicating understanding of their function.

There are two signals that induce the production of glucocorticoids in the adrenal cortex (Fig. 1). One is the circadian rhythm, and the other is stress. The biological clock in the suprachiasmatic nucleus, also known as the central clock, transmits signals to the hypothalamus, the pituitary gland, and the adrenal cortex by the HPA axis, which stimulates glucocorticoid production in the adrenal cortex. By this mechanism, the blood glucocorticoid concentration peaks just before dawn in humans, remains high during the daytime, and drops during the nighttime. In addition, glucocorticoids synchronize the central and peripheral clocks by directly resetting the transcription of clock genes in peripheral cells. On the other hand, the stress signal excites the limbic system of the brain, which stimulates glucocorticoid production via the HPA axis.

Cell type-specific GR-deficient mouse models have suggested glucocorticoids suppress innate immunity via macrophages, DCs, and natural killer (NK) cells. Macrophages and DCs play crucial roles in the initiation and augmentation of inflammation. Two studies reported that the production of the inflammatory cytokines IL-1β, TNF-α, and IL-6 is reduced in macrophages and DCs in macrophage-specific LysM-Cre and DC-specific CD11c-Cre GR-deficient mice upon LPS-induced inflammation.[6,7] These studies indicated that glucocorticoids exert their anti-inflammatory effects in part via macrophages and DCs. NK cells eliminate virus-infected cells and tumor cells by the direct cytotoxicity of perforin and granzymes and secrete IFN-γ to enhance the type I immune response by macrophages and cytotoxic T cells. The Ugolini laboratory analyzed the effect of glucocorticoids in host resistance to endotoxic shock and viral infection via group 1 innate lymphoid cells (ILCs).[8,9] After the repetitive administration of LPS, group 1 ILC-specific Ncr1-Cre GR-deficient mice exhibited elevated IFN-γ production by NK cells and higher mortality. Additionally, upon mouse cytomegalovirus infection, the mice showed reduced PD-1 expression and increased IFN-γ production by NK cells, which exacerbated tissue inflammation. Taken together, these studies indicate the suppressive function of glucocorticoids in innate immune cells.

In contrast to the suppression of innate immunity, there is limited evidence on the effects of glucocorticoids on adaptive immunity. One pioneering study showed the induction of IL-7 receptor (IL-7R) expression in human T cells by glucocorticoid stimulation, suggesting an immunoenhancing effect.[10] We identified GR-binding motifs in the proximal enhancer of the IL-7Rα locus as responsible for the transactivation of the IL-7Rα promoter by glucocorticoids.[11] In another of our studies, the glucocorticoid-mediated IL-7R induction in T cells was lost in mice that had a targeted deletion of the enhancer.[12] In line with these studies, we later demonstrated that endogenous glucocorticoids trigger the diurnal change of IL-7R and CXCR4 expression in T cells and the accumulation of T cells in lymph nodes and spleen in the nighttime, which enhanced the immune response against infection, in mice with mutated GR-binding motifs and mice that were T cell-specific CD4-Cre GR-deficient (Fig. 2).[13] These studies demonstrated the immunoenhancing effects of glucocorticoids at physiological oscillating concentrations.

These studies also revealed the circadian control of immunity by glucocorticoids. In addition to glucocorticoids, two other factors, the biological clock and adrenergic nervous activity, have been reported to be involved in the circadian control of immunity (Fig. 2). Suzuki *et al.* revealed using β_2-adrenergic receptor-deficient mice that β_2-adrenergic receptor signaling in T and B cells reduces the lymphocyte egress from lymph nodes at nighttime.[14] The resulting accumulation of lymphocytes in the lymph nodes augmented the immune response after antigen immunization. Druzd *et al.* also tested the circadian control of immunity by the peripheral clock by deleting *Bmal1*, a clock gene, specifically in T cells.[15] The mutant mice failed to show the diurnal accumulation of T cells in the lymph nodes at nighttime. They also showed a downregulation of the homing receptor CCR7 and upregulation of the egress receptor S1PR1. These T cell-specific BMAL1-deficient mice showed less clinical symptoms and demyelination of the spinal cord when present with experimental allergic

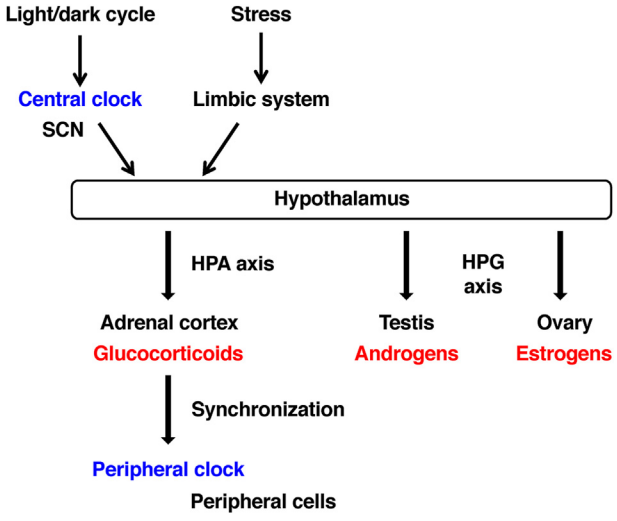

Fig. 1. The production of glucocorticoids and sex steroid hormones. The circadian rhythm and stress induce the production of glucocorticoids by the hypothalamic-pituitary-adrenal (HPA) axis. Androgens and estrogens are produced by the hypothalamic-pituitary-gonadal (HPG) axis. Glucocorticoids synchronize the central and peripheral clocks. SCN, suprachiasmatic nucleus.

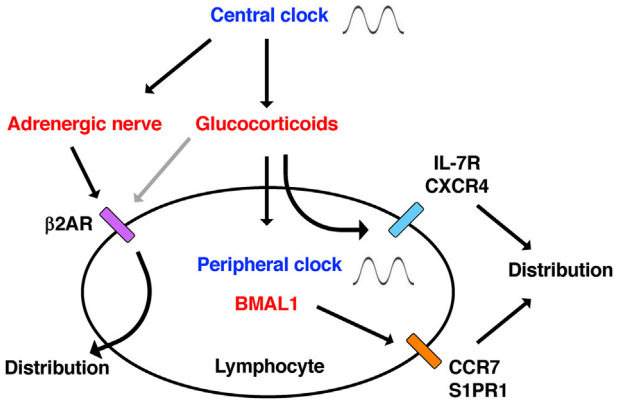

Fig. 2. The circadian control of immunity. The circadian control of immunity is mediated by the peripheral clock, glucocorticoids, and adrenergic nerve activity. These signals induce the accumulation of lymphocytes in peripheral lymphoid organs at nighttime in mice, in part by regulating the expression of chemokine and cytokine receptors. β2AR, β_2-adrenergic receptor.

encephalomyelitis, the mouse model of multiple sclerosis. Thus, adrenergic nervous activity and the peripheral clock as well as glucocorticoids appear to control the circadian rhythm of immunity. Since glucocorticoids synchronize the central and peripheral clocks and facilitate β_2-adrenergic receptor signaling, glucocorticoids likely play essential roles in controlling the circadian rhythm of immunity directly and indirectly by regulating the peripheral clock and β_2-adrenergic receptor.

Roles of sex hormones in immunity and allergy

It is reported that male and female gonads impact the involution of the thymus. The size of the thymus peaks at puberty and gradually diminishes after adolescence, a phenomenon called thymic involution. The administration of androgens or estrogens into mice rapidly reduces the size of the thymus.[16,17] The most affected population in the thymus is immature $CD4^+CD8^+$ double positive thymocytes. Conversely, the castration or ovariectomy of adult mice causes re-enlargement of the involuted thymus. Olsen *et al.* examined AR in thymic atrophy after androgen administration.[18] Testicular feminization AR-mutant (AR^{tfm}) mice showed thymus enlargement and androgen insensitivity. The transplantation of control bone marrow cells into these mice had no effect on these phenotypes. On the other hand, the transplantation of AR^{tfm} bone marrow cells into control mice with androgen administration resulted in normal thymus atrophy. Thus, this study indicated that AR in thymic stromal cells contributes to thymic atrophy. Additionally, thymic epithelial cell-specific, but not T cell-specific, AR-deficient mice show thymus enlargement.[19] Taken together, these results suggest that androgen/AR signaling promotes thymic involution via thymic epithelial cells.

Asthma is allergic airway inflammation characterized by elevated and sustained type 2 immune responses.[20] It is accompanied with eosinophil infiltration, mucus production, and IgE elevation at early phases and with AHR and airway remodeling at later phases. There is a sex bias in the prevalence of asthma in adults.[21,22] In childhood, more boys suffer from asthma than girls, but after puberty, the frequency of male patients drops, while that of female patients increases. The major cellular components responsible for the development of airway inflammation include adaptive immune cells, such as T and B cells, and innate immune cells, such as DCs, macrophages, eosinophils, neutrophils, and ILCs, as well as stromal cells such as bronchoalveolar epithelial cells and blood vascular and lymphatic endothelial cells. Therefore, sex hormones may impact the sex bias of asthma through any of these cell types.

Keselman *et al.* reported that in a mouse model of allergic airway inflammation with intraperitoneal sensitization and intranasal challenge of OVA allergen, female mice exhibited severe inflammation compared with male mice, as evidenced by elevated eosinophil infiltration and mucus production and increased numbers of alveolar macrophages expressing the M2 macrophage markers YM1 and iNOS.[23] The enhanced M2 differentiation of alveolar macrophages was in part due to increased IL-4 receptor (IL-4R) expression after the OVA challenge, and IL-4 stimulation induced a higher expression of YM1 and another M2 marker, ARG1, in the bone marrow-derived macrophages of female mice compared with male mice. Furthermore, macrophage-specific LysM-Cre ERα-deficient female mice exhibited a reduced expression of YM1 in alveolar macrophages after the OVA challenge. Thus, estrogen/ER signaling enhances the M2 polarization of alveolar macrophages in allergic airway inflammation.

The same group tested the role of AR in male mice using the same mouse model for allergic airway inflammation.[24] Eosinophil infiltration and mucus production were alleviated in male mice. In addition, the levels of two eosinophil-recruiting chemokines, CCL24 and CCL5, and an eosinophil-activating cytokine, IL-5, were reduced in the BAL fluid of the male mice, along with a reduced mRNA expression of *Ccl2*, *Ccl24*, and *Ccl5* in alveolar macrophages. Furthermore, the M2 polarization of alveolar macrophages was inhibited in the AR-deficient male mice, as evidenced by the reduced expression of the M2 genes *Retnla* and *Arg1*. Thus, androgen/AR signaling promotes the M2 polarization of alveolar macrophages, which may lead to exacerbated airway inflammation.

Taken together, both estrogens and androgens appear to promote the M2 differentiation of alveolar macrophages in allergic airway inflammation. However, this scenario is not necessarily consistent with the sex bias of asthma. In the first study,[23] eosinophil infiltration and mucus production, both evidence of lung inflammation, were not examined. However, mutant male mice showed fewer symptoms of lung inflammation in the second study,[24] indicating that androgen/AR signaling enhances allergic airway inflammation via macrophages. Future studies should evaluate the role of the M2 polarization of alveolar macrophages in allergic airway inflammation.

ILCs, especially type 2 ILCs (ILC2s), are key regulators of inflammatory and allergic diseases, especially at early phases. Laffont *et al.* tested whether sex hormones influence ILC2s.[25] At steady state, ILC2s in lung and adipose tissue and ILC2 progenitors in bone marrow were reduced in male mice compared to female mice. However, the number of ILC2s in lung was recovered in castrated male mice. Thus, androgens disturb the differentiation and homeostasis of ILC2s in males. In acute airway inflammation induced by the repetitive intraperitoneal injection of IL-33, which mainly activates and increases ILC2s, male mice had fewer ILC2s and less infiltration of inflammatory cells in the lung compared to female mice; a phenotype that again vanished in castrated male mice. In addition, the transplantation of male AR-deficient bone marrow cells into normal mice diminished the sex difference in lung inflammation. Taken together, androgen/AR signaling negatively regulates the homeostasis and activation of ILC2s in a cell-intrinsic manner. Thus, there exist differences in ILC2 homeostasis between males and females, reaffirming sex differences in immunity. Because lung inflammation in that study was examined mainly in the IL-33 administration model, a similar study using a lymphoid lineage-specific IL-7R-Cre AR-deficient mice is desired.

Th2 and Th17 cells are involved in chronic airway inflammation characterized by the infiltration of eosinophils and neutrophils. Fuseini *et al.* tested the effects of sex hormones on Th2 and Th17 cells in chronic airway inflammation by the repetitive intranasal administration of HDM allergen.[26] The infiltration of eosinophils, neutrophils, macrophages, and lymphocytes in BAL fluid was reduced in male mice compared to female mice, and a concomitant decrease of IL-13 and IL-17A in the lungs was observed. The infiltration of inflammatory cells in the lungs, the serum IgE level, the AHR, and the number of Th2 and Th17 cells in lung were all elevated in castrated or AR-mutant (AR^{tfm}) male mice to the level of normal female mice but reduced in ovariectomized female mice to the level of normal male mice. Furthermore, the differentiation of naive CD4 T cells into Th17 cells, but not Th2 cells, in culture was less in male mice compared to female mice unless the cells came from AR^{tfm} male mice. Thus, sex hormones have a number of effects on the differentiation of Th2 and Th17 cells and lung inflammation.

Recently, our lab demonstrated that T cell-specific CD4-Cre AR-deficient mice show exacerbated allergic airway inflammation.[27] After intraperitoneal sensitization and intranasal challenge with HDM allergen, the infiltration of eosinophils, neutrophils, and CD4 T cells and the AHR were increased in T cell-specific AR-deficient male mice, suggesting elevated Th2 and Th17 responses.

Importantly, T cell-specific CD4-Cre ERα/β-deficient female mice showed no change in lung inflammation. Thus, androgen/AR signaling, but not estrogen/ER signaling, impacts allergic airway inflammation via T cells. Furthermore, the addition of dihydrotestosterone reduced the expression of IL-4 and IL-13 in Th2 cells differentiated from the naïve T cells of control mice but not of the AR-deficient mice. AR bound to an AR motif in the 5' untranslated region of the *Dusp2* gene in Th2 cells and transactivated the *Dusp2* promoter. Thus, androgens suppress cytokine production by Th2 cells and mitigate allergic airway inflammation, which partially explains why male mice exhibit less severe asthma than female mice.

The pleiotropic effects of sex hormones on the differentiation of Th2 and Th17 cells in culture appear to be in contradiction with androgens suppressing but estrogens enhancing the differentiation in gonadectomized mice.[26] Since, in the culture observations, the differentiation was carried out without the addition of androgens, the androgen concentration may have been too low to stimulate differentiation. In addition, because the infiltration of neutrophils and the production of IL-17A in T cells were elevated, Th17 differentiation may have been enhanced in T cell-specific AR-deficient mice.[27] Future in vitro studies should test the effects of androgens on Th17 differentiation in culture.

Tregs suppress the functions of other Th cells and thereby can control inflammatory and allergic diseases. Gandhi *et al.* tested the effects of androgens on Tregs in airway inflammation.[28] The infiltration of eosinophils and neutrophils and the number of Th2 cells were elevated in female mice compared to male mice by the repetitive intranasal administration of *Alternaria* extract, but no sex difference was observed in AR-deficient mice. However, although the number of lung Tregs was unchanged between males and females, the suppressive function of male Tregs was stronger than that of female Tregs. Furthermore, Treg-specific Foxp3-Cre AR-deficient male mice exhibited severe airway inflammation compared with control male mice. Thus, androgen/AR signaling enhances the suppressive function of Tregs and thereby alleviates the allergic airway inflammation caused by Th2 cells.

Taken together, these studies indicate that androgen/AR signaling has pleiotropic effects on macrophages, DCs, ILC2s, Th2 cells, and Tregs (Fig. 3). Androgen/AR signaling promotes the M2 polarization of macrophages and the suppressive function of Tregs, but also suppresses the homeostasis and activation of ILC2s and the differentiation of Th2 and Th17 cells in airway inflammation. Therefore, by any of these mechanisms, androgens mitigate allergic airway inflammation via immune cells. On the other hand, there is less evidence that estrogen/ER signaling is involved in the pathogenesis of the allergic airway inflammation via immune cells, though estrogens are suggested to have some enhancing function on allergic airway inflammation. Many studies on sex hormones have incorporated immune cells but not stromal cells, such as bronchoalveolar epithelial cells, which should also be considered in future studies.

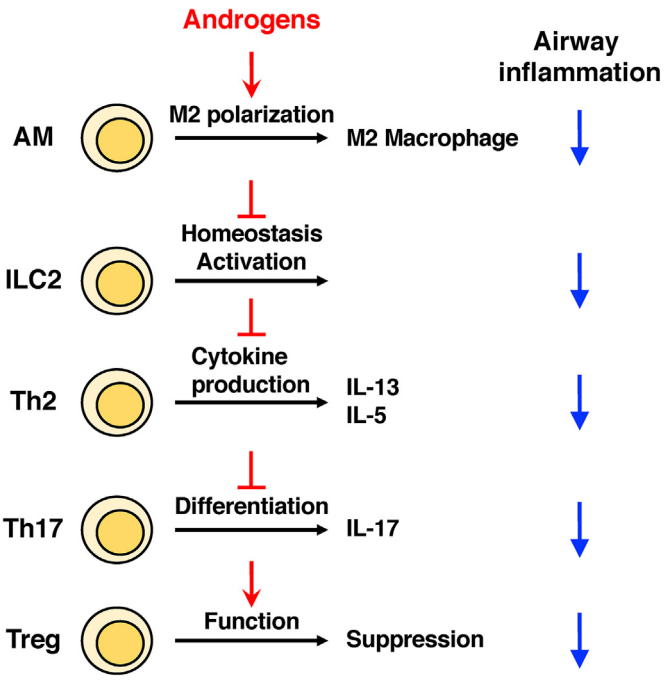

Fig. 3. Roles of androgens in airway inflammation. Androgens have pleiotropic effects on macrophages, ILC2s, Th2 cells, Th17 cells, and Tregs. Outcomes of androgen action on each cell type in airway inflammation are shown. AM, alveolar macrophage.

Conclusions

Studies using cell type-specific steroid hormone receptor-deficient mice have clarified the pleiotropic functions of steroid hormones on the immune system. Glucocorticoids are known for their strong anti-inflammatory and immunosuppressive effects in innate immunity but immunoenhancing effects on adaptive immunity. These contradictory effects are not easy to explain. As for sex hormones, androgens especially have multiple suppressive effects on innate and adaptive immune responses, but the effects of estrogens are less understood. In contrast to immune cells, there are few studies on the roles of steroid hormones in stromal cells. Future studies on sex hormones in immunity and allergy using stromal cell-specific steroid hormone receptor-deficient mice should be considered.

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Conflict of interest

The authors have no conflict of interest to declare.

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