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Review Article

Immune Modulation in Goats by Melatonin and Other Hormones: A Novel Horizon of Research

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Abstract

Goats are the primary producers of meat, milk and leather in the tropical and temperate countries from time unknown. In global as well as Indian economic scenario goats are regarded as "Poor man's Cow". But, the management of immune system of this animal was neglected by the researchers for prolonged time. Immune system of the body of an individual is an open circuit and is being regulated by a number of hormones (gonadal steroids/ neurohormones/ metabolic hormones) and factors (cytokines, chemokines and lymphokines). Some of the hormones are having immune suppressive functions (particularly the gonadal steroids and cortisol/ corticosterone) or some of them are having neutral effect on immune modulation. Goats are ruminant short day breeders and their seasonality in terms of reproduction and immunity is under influence of melatonin. Melatonin is regarded as immunostimulator in most of the species having a direct correlation with interleukins (particularly with IL-2) in a paracrine manner it regulates immunity. Administration of exogenous hormones *in vitro* is an approach that can directly measure the effects of said hormone on immune cell proliferation. It also helps in understanding the cross-talk between the metabolic (thyroxin, cortisol), gonadal steroid (testosterone, estrogens) and circulatory cytokines (IL-2, IL-6, TNF-α, IFN-γ) with potent immunostimulator melatonin on isolated goat splenocytes and thymocytes. In the present review we elaborated the effects of different hormones in vivo and in vitro along with melatonin in a seasonal short day breeder i.e. goat.

Keywords: Goat; Gonadal steroids; Glucocorticoids; Immunity; Hormones; Melatonin

Abbreviations

%SR: % Stimulation Ratio; ACTH: Adrenocorticotropic Hormone; AR: Androgen Receptor; BMR: Basal Metabolic Rate; CD4: Cluster of Differentiation 4, CD5: Cluster of Differentiation 5; CD8: Cluster of Differentiation 8; CRH: Corticotrophin Releasing Hormone; DNA: Deoxyribo Nucleic Acid; ERα: Estrogen Receptor Alpha (α); GH: Growth Hormone; GM-CFU: Granulocyte Macrophage- Colony Forming Unit; HPA-Axis: Hypothalamu-Pituitary-Gonadal-Axis; IL-2: Interleukin-2, IL-6: Interleukin-6; IL-7: Interleukin-7; IL-10: Interleukin-10; IFN-γ: Interferon- Gamma (γ); MT1: Melatonin Receptor Type 1; MT2: Melatonin Receptor Type 2; NK Cells: Natural Killer cells; NO: Nitric Oxide; Prl: Prolactin; ROS: Reactive Oxygen Species; Th-1: T-helper cell type-1; Th-2: T-helper cell type-2

Introduction

Goats are cosmopolitan and found across all agro-ecological environments and nearly in all livestock production systems [1]. Goats are suitable for very extensive to highly mechanized production system [2,3]. India is bestowed with 17% of total world's goat population comprised of 21 recognized and many non-descript local breeds [4]. In the tropics and sub-tropics, the interest in goat production has grown only in recent years. In the bio-industry, goats are underutilized and poorly understood resource even more under estimated in terms of veterinary research. A fair understanding of goat physiology and its industrial capabilities and economic outputs will be helpful in increasing the overall productivity of tropical goat farming systems. Despite of the large goat population, diversity and their economic significance, the caprine research in India particularly to the indigenous goats has been neglected by ruminant researchers. Although small ruminants are a major component of the livestock sector in most parts of the world including India, yet the information about goats and its physiology is very limited and fragmented. The importance of small ruminants for meat production in the tropics was well recognized by Payne [5]. However, small-ruminant production has some constraints and disease, which are associated with high mortality, decline in productivity and reproductive performance and even public health concerns [6,7].

Why to study goats?

The goat is known as a poor man's cow all over the world. In Switzerland, the milk goat is said to be the "Swiss baby's foster mother". The goat is an animal that adapts itself readily to almost any climate. The goat is the principal meat producing animal in India and its flesh is preferred over other animals' meat. Goats' flesh also provides better price than mutton and beef in most of the urban markets. Mohair from Angora goats and Pashmina from Kashmiri goats are greatly valued for the manufacture of superior dress fabrics and shawls. The intestines of goats are used to make cat-gut. The average milk production of a (Indigenous/local) doe in India is 55 kilograms per lactation term. Goats along with sheep have an important role in income generation, capital storage, employment

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generation and improving household nutrition. The manures of goats are used as herbal fertilizers by the rural Indians.

Goats as an experimental model

Goats are large mammals which have many similarities to humans in terms of physiology. They are easy to handle and suffer from many diseases which affect humans. They also have short gestation periods yet give birth to young of a similar weight to human babies, making them excellent for studying development and genetics. They are also used extensively in veterinary research, studies of digestion in ruminants, and research on the impact of farming on the environment. Goats are frequently used as a model for cattle and other large mammals, as they are smaller, less expensive to keep and easier to breed. Moreover, goats are ruminant short day breeders and seasonality in terms of reproduction and immunity has not been explored in this animal model even after domestication. Thus, this animal has been made an interesting model for endocrine research particularly for melatonin hormone.

Role of different hormones in sex dependent immune response

There is evidence that differential environmental and social interactions can account for some of the sex differences in mortality, it is clear that males and females differ in immune function [8] for several immune indices [9]. In general, sexually mature females seem to have higher immune activity than male co-specifics. For example, females of many species, including humans, have higher circulating immunoglobulin levels than male co-specifics [10]. Females also mount higher antibody responses after an immunological challenge than males [9]. However, virtually all studies indicate that females exhibit higher resistance to tumour and parasites than males [11,12]. Many sex differences in immune function appear to be organized early in development and are activated at the time of puberty [11], although some appear only to be activated by peri-pubertal increases in sex steroid levels. Females are also more resistant than males for/against many diseases [9]. The disadvantages for such superior immunological function and resistance to disease among females include enhanced proclivity for developing autoimmune disease [9]. Animal models for many human autoimmune diseases exist, and hormonal manipulations in these animal models have indicated the involvement of sex steroid hormones in their expression [13]. Furthermore, natural hormonal changes in humans (e.g., pregnancy, menopause) have an effect on immune function and some diseases. Generally, estrogens are immune stimulatory, glucocorticoid and androgens are immune compromising, and thyroxin can be either stimulatory or suppressive of immune function in species specific manner. In our study on goats the sexual dimorphism in terms of immune modulation has prevalence and will be discussed in the subsequent sections. But, reports regarding immunomodulatory roles of different hormones in goats are not well documented so we will be confining our review on the data obtained from our results with reference from the rodents on roles of hormones in immunity and roles of hormones in modulation of various physiological functions in goats.

Role of gonadal steroids in immune modulation

Steroid genesis is the biological process by which steroids are generated from cholesterol and transformed into other steroids. Both clinical and experimental evidence support the hypothesis that gonadal steroids regulate immune function. This conclusion is based on the following observations: (i) a sexual dimorphism exists in the immune response; (ii) the immune response is altered by gonadectomy and sex steroid hormone replacement; (iii) the immune response is altered during pregnancy when the amount of sex steroid hormone is increased; and (iv) the organs responsible for the immune response contain specific receptors for gonadal steroids. However the effects/ involvement of gonadal steroids in regulation of immunity of goats have never been discussed in season and gender dependent manner.

Role of testosterone

It is apparent that the immune and reproductive systems are intimately interconnected and that androgens are important components of these interactions. Indeed, the immune system can be modulated by androgens in some cases; conversely, activation of the immune system, particularly the innate arm, is associated with suppression of the reproductive neuro endocrine axis [14]. As evidenced trade-offs between reproduction and immune function may be mediated directly via communication between the reproductive and immune systems in certain contexts [15], although these interactions tend to be complex. Several studies in both animals and humans have been performed to understand the influence of sex steroids on the immune system. Testosterone generally suppresses immune function as castration of adult male rodent's results in increased immunoglobulin levels, increased hum oral and cell-mediated immunity, and increased lymphatic organ size, including thymic, splenic, and lymph nodal masses [9]. Androgen receptors have been identified in thymic tissues, particularly in the epithelial, lymphatic portion of the thymus [16]. Androgenic effects on lymphocytes may be in direct or through aromatization of androgens to estrogens, because no androgen receptors have been found on circulating lymphocytes [8].

The apparent immunosuppressive effects of androgens may sometimes be due to glucocorticoids [17,18] at least in certain experimental contexts. Androgens exert considerable effects on the size and composition of the thymus. In one study, testosterone replacement in castrated male mice caused thymic regression, with a shift towards expression of mature thymocytes and predominance of the suppressor/cytotoxic CD4- CD8+ phenotype over the helper CD4+ CD8- phenotype [19]. Mechanisms of testosterone-induced thymus involution are incompletely understood, but decreased cell proliferation; changes in cell trafficking and increased apoptosis are some of the possible mechanisms involved. On the other hand, documentation of classical AR expression in peripheral T cells has not been reported but the net effect of androgen action (direct or indirect) seems to be an enhanced suppressor effect [20]. The number of pre-B cells in bone marrow and mature peripheral B cells increases in male mice after castration [21]. It has been reported that treatment of mice with dihydrotestosterone (a non-aromatized androgen) suppressed the expansion of lineage precursors (IL-7 responsive precursors) when added to short-term co-cultures of lymphocytes and stromal cells [22]. There are conflicting data concerning the effects of castration and androgens on peripheral B cells. CD5+ cell subsets have been implicated as an important source of auto-antibodies. In a recent study, castration in male mice was shown to

selectively increase splenic cellularity and the number of peripheral blood lymphocytes due to newly emigrated immature B cells.

However, in goats the effect of testosterone in modulation of reproduction is well documented [23-25] but role of this gonadal steroid in immune modulation has never been studied in goats or sheep except for a single study of [26] demonstrating the circulatory level of testosterone and seasonality in immune functions in Indian goats *C. hircus*. In most of studies with goats in relation with hormone testosterone generally focus on their reproductive seasonality in arid [27] or semi-arid [28] conditions in rams and goats respectively. But, role of testosterone on goat/sheep immune modulation is totally lacking. In the present studies on goats in our lab, we found interesting results on splenocyte and thymocyte cultures to note cell mediated immunity upon testosterone supplementation *in vitro* in a season and sex dependent manner. An immune suppressive role of testosterone was noted in vitro which not only reduced cell proliferation in terms of % Stimulation Ratio (%SR) in a season dependent manner but also reduced the release of cytokines (IL-2, IL-6, TNF-α) [29].

Role of oestrogens

Sex steroids act as negative regulators in both the thymus and bone marrow, but androgens and oestrogen tend to affect different subsets of immune cells. In general, androgens seem to inhibit immune activity, while oestrogen seems to have a more powerful effect on immune cells and to stimulate immune activity. Oestrogen receptors have been localized in the cytosol of circulating lymphocytes [11], CD8+ cells [30] and thymic cells [31]. Physiological treatment of estrogens, or the estrogens receptor antagonists, tamoxifen and FC1157a, enhances pokeweed mitogen induced immunoglobulin synthesis of B-lymphocytes [32]. Cyclic exposures to pharmacological doses of estrogens are more effective in boosting antibody formation than chronic oestrogen exposure [9]. Pharmacological doses of estrogens also suppress cell-mediated immunity [33]. Tamoxifen inhibits the effects of estrogens on antibody formation and cell-mediated immunity [34]. Taken together, the effects of physiological doses of oestrogen appear to enhance immune function. Oestrogen stimulates CD4+CD8- cells and can activate an extra-thymic pathway of auto-reactive T cell differentiation in the liver [35]. Several studies have established that oestrogen is a potent inhibitor of stromal cell-dependent B cell lymphopoiesis *in vitro*. Oestrogen also affects peripheral B cells and hum oral immunity. Manipulation of female reproduction by exogenous oestrogen treatment is a very common and ancient practice in milk cattle breeds. In the study of sheep particularly the effect of oestrogen is very much prevalent in female reproduction [36] but not in immunity. Studies were performed in goats with circulatory levels of oestrogen [37] but the immunomodulatory role or oestrogen has never been tested in sheep or goats. The study of [38] in mice suggests that oestrogen is immunestimularatory in nature. On the contrary, our present study on female goats suggests that oestrogen supplementation *in vitro* has suppressed immunity in different seasons being in equivocal with similar results as reported by others and cited previously [33].

Role of stress hormone – Glucocorticoid

Glucocorticoids are the principal negative regulators of an important neuroendocrine axis (Hypothalamus–Pituitary–Adrenal (HPA) axis. Glucocorticoids are now recognized as powerful mediators of many physiological processes including reproduction and immune activity. Unlike other hormones, glucocorticoids tend to suppress both reproduction and immune function [39]. High circulating corticosterone concentrations suppress innate (i.e. natural killer cell activity), cell-mediated (i.e. cytokine production) and hum oral (i.e. antibody production) immune responses in laboratory rats and mice [40]. Males and females often differ in the types of stressors they encounter, especially during the breeding season [41]. Thus, exposure to stressors may influence sex differences in immune function and subsequent resistance to infection [42]. Interaction between glucocorticoids and the immune system is complex and bidirectional. Stressor- induced elevated glucocorticoid concentrations can modulate immune activity; however, activation of the immune system can also drive the production of glucocorticoids [43]. Because glucocorticoids tend to suppress inflammation but be induced by pro-inflammatory stimuli, they have been conceptualized as 'brakes' on the immune system, having evolved to prevent runaway inflammation and promote fine-tuning of the immune response [44]. A wealth of information demonstrates how glucocorticoids suppress immune function [43], which led to the conjecture that glucocorticoids are largely responsible for decrements in immune activity in free-living animals in winter [45]. Now there is compelling evidence that in certain contexts glucocorticoids can enhance aspects of immune function which may be immune redistribution in disguise [46]. Particularly, in goats the circulatory level of corticosterone has been reported under normal as well as under thermal stress has been reported by correlating it with plasma melatonin level [47]. But, literature on the immunomodulatory role of glucocorticoids in goats are completely lacking. Our data on the *in vitro* supplementation of dexamet has one (a synthetic glucocorticoid) to delineate its role goat immune modulation in a season and sex dependent manner suggest that in both males and females it is immune suppressive in terms of %SR. However, effect of dexamethas one supplementation in females is more prominent during winter under *in vitro* proliferation assay as during winter females are under gestational as well as cold stress (Somenath Ghosh, Ph. D thesis; unpublished data).

Role of metabolic hormone – Thyroxin in immunomodulation

Thyroid hormones are basically known to regulate Basal Metabolic Rate (BMR) of the body. But the immunomodulatory role of this hormone is least known and in need to be elucidated. However, reports suggest that it is helpful in differentiation, growth, metamorphosis, metabolism [48] and play a prominent role in regulation of reproduction [49]. Some previous reports suggest that thyroxin (T4) caused thymus enlargement and increase in number of peripheral lymphocyte [50]. However, thyroidectomise resulted in hypoplasia of lymphoid organs [51] as thyroid hormones are reported to increase the nucleated cells in spleen and thus improving the immune status of an immune compromised animal to the threshold level [52]. Some of the reports are contradictory to the previous citations some scientist [53] reported that under *in vivo* and *in vitro* conditions thyroxin has no role in immune modulation. Some other report [54] suggests that thyroxin in immune inhibitor in nature. Most of these reports are mainly from birds but not from mammals. Some partial report [55] suggests that thyroid hormone functions may be modulated by melatonin and it can also affect the

lymphoid organ function by modulating Pineal-Thyroid Axis [51]. But, the exact role of thyroid hormone function in modulation of immunity is till date controversial or partial and needs to be explored in details. In goats particularly, the role of thyroxin even including the circulatory level was not studied. However, from energetic and metabolic point of view this is an excellent animal model and its adaptability to different environmental conditions may suggest the speciality in its metabolism under the influence of thyroxin. Our *in vitro* results of goat thymocyte and splenocyte culture in sex and season dependent manner is first of its kind suggesting that there is lack of immune enhancing or immune suppressive role of thyroxin alone in goat immune modulation, however, in combination with melatonin it acts as immune stimulatory (Somenath Ghosh, Ph. D thesis; unpublished data).

Role of prolactin (Prl) in immunomodulation

In most of the studies prolactin is regarded as the hormone of lactation and it is being used as enhancement of milk production from very long time [56]. Its role in immunity has never been studied in sheep or goats. Some partial reports [57] suggested that the circulatory level of prolactin and its role in reproduction and post-gestation in goats but, immunological aspect of this hormone is totally lacking in both sheep and goats. In our present study of spelnocytes and of thymocytes culture it was well evident that individually Prl was immunostimulatory in nature particularly in females during winter (Kaushalendra, Ph. D thesis; unpublished data). The results were significant in the sense that goats are short day breeders and during winter particularly for females it is exerting its immunostimulatory role in ameliorating cold as well as gestational stress.

Role of Growth Hormone (GH) in immunomodulation

Growth Hormone (GH) in most the cases is regarded as immune neutral under different clinical [58] or pathological [59] conditions. But, role of this hormone in general physiological or immunological condition has never been studied in any well established laboratory animal model (rat, hamster) or any other model (like human, sheep). For goats even the circulatory level of growth hormone in different age groups and in sex dependent manner is not known till date. Our present study in immunological model in terms of supplementation with GH with splenocyte and thymocyte culture under *in vitro* condition has focussed some role on of this particular hormone on immune- modulation is significant. The reason is that this hormone is least explored in immune – modulation and our study on goats is the first one is to study the role of this hormone in immunomodulation in a positive manner and further to explore out the same for our future studies (Kaushalendra, Ph. D thesis; unpublished data).

Melatonin and immune function

In recent years much attention has been devoted to the possible interaction between melatonin and the immune system [60]. Melatonin has significant immunomodulatory roles in immune compromised states. In 1986, Maestroni et al. [61] first showed that inhibition of melatonin synthesis causes inhibition of cellular and hum oral responses in mice. Late afternoon injection of melatonin increases both the primary and secondary antibody responses to SRBC [62].

Melatonin and innate immunity

A number of studies support the immune regulatory action of melatonin on the body's innate immunity [60]. Melatonin stimulates the production of progenitor cells for Granulocytes and Macrophages (GM-CFU) and has a general stimulatory action on hemopoiesis in rodents [63]. Melatonin receptors are detectable in monocyte/macrophage lineage [64] and melatonin binding to these receptors stimulates the production of GM-CFU cells [65]. Exogenous melatonin augments NK cells and monocytes in both the bone marrow and the spleen with a latency of 7 to 14 days in mice [66]. As both these cells are components of the non-specific immune system, the findings suggest that melatonin could be an effective way for arresting neoplastic growth and for destroying virus-infected cells. Stromal cells contain receptors for kappa opioid cytokine peptides, melatonin-induced release of opioid peptides from these stromal cells in bone marrow could be involved in the regulation of hemopoietic cell proliferation [63]. Macrophages have been shown to form large amounts of Nitric Oxide (NO) upon activation by ROS that mediate their microbicidal properties. This excessive production of NO can be harmful to the body as it can result in the development of degenerative diseases [67]. In a recent study melatonin was found to decrease NO concentration in macrophages by suppressing inducible NO syntheses expression [39].

Studies demonstrated that the thymus is a primary target of melatonin's action. Thymus is an organ of youth in mammals, yet any influences on the thymus in youth will have profound effects on the immune system of elderly mammals. The severe loss of thymocytes with age is the main cause of structural thymic atrophy and thymic weight loss. Melatonin administration increased the total number of thymocytes in old mice by inhibiting glucocorticoid- or hydroxyl radical-induced thymic apoptosis [68]. The reversal of age-associated thymic involution by melatonin added further support to the concept that melatonin can be a potential therapeutic agent for correcting immunodeficiency state associated with aging and possibly other immune compromised states like severe stress [69]. Finally, Yu et al (2000) [70], demonstrated that orally administered melatonin can substantially promote the survival (anti-apoptosis) of precursor B lymphocytes which is responsible for hum oral immunity.

Melatonins enhance both cell-mediated and hum oral immunity. The immune enhancing effect of melatonin involves opioid peptides; melatonin stimulates cells to secrete opioid peptides that have up-regulatory effects on a variety of immune cells [71]. According to [72], melatonin is a part of a complex physiological system that coordinates reproductive, immunological and other physiological processes to cope up with energetic stressors during winter. There is a possibility that melatonin could act as an autocue in bone marrow as shown by the demonstration of melatonin synthesis in bone marrow cells of mice and humans [73]. The existence of specific melatonin binding sites in lymphoid cells provides evidence for a direct effect of melatonin in the regulation of the immune system. Melatonin also counteracted the inhibitory effect of prostaglandin E2 on IL-2 production in human lymphocytes via its MT1 membrane receptor [74]. Collectively, these studies indicate that melatonin possesses important immune enhancing properties and suggest that melatonin may favour a Th-1 response. Besides the release of pro-inflammatory Th-1 cytokines, such as IFN-γ and IL-2 administration of melatonin to antigen-primed mice increased the production of IL-10, indicating that melatonin can also activate anti-inflammatory Th-2-like immune

responses in certain circumstances [75]. Therefore, it is not yet clear whether melatonin acts only on Th-1 cells or also affects Th-2 cells. This is an important subject as the Th-1/Th-2 balance is significant for the immune response [71]. In addition, an inhibitory influence of melatonin on parameters of the immune function has also been demonstrated, i.e., in human NK cell activity, DNA synthesis, IFN-γ and TNF-α synthesis, as well as the proliferation of T lymphocytes and lymphoblastic cell lines were depressed by melatonin [71].

The role of melatonin in modulation of goat reproduction and maintenance of seasonality is documented in goats [76] particularly focussing on its regulatory role in reproductive seasonality. Melatonin, in goats can also be possible to present its data in immune ameliorating actions (when treated with testosterone, oestrogen, glucocorticoid, thyroxin, growth hormone and prolactin). In our *in vitro* study of thymocyte and splenocyte culture melatonin supplementation not only improves immunity but also ameliorates gonadal steroid (testosterone/estrogen) [29] and dexamethasone induced immune compromised condition up to the control level (Somenath Ghosh, Ph. D thesis; unpublished data). Thus, melatonin act as a buffer-hormone to regulate immunity even under stressful conditions and under immune-suppressed condition caused due to gonadal steroid. The role of melatonin supplementation with thyroxin was quite interesting. In our study, thyroxin played non-significant role in improvement of immunity. But, co-supplementation with melatonin significantly improved immune status; particularly in females during winter (Somenath Ghosh, Ph. D thesis; unpublished data). This may be due to the fact that winter is stressful for both the sexes due to "cold stress" and particularly for the females due to gestational stress. At that time circulatory level of thyroxin was also high (Somenath Ghosh, Ph. D thesis; unpublished data) in females. The same scenario was repeated for the case of prolactin which during winter plays immunostimulatory action with melatonin. However, growth hormone presented neutral effect on immunity but co-supplementation with melatonin and growth hormone has been shown to immunostimulatory. Thus, it may be possible that melatonin behaved like an opportunistic hormone to use thyroxin in immune enhancement even though thyroxin alone is immunologically neutral.

Expression of hormone by Immune cells

Lymphocytes express receptors for a wide variety of hormones, including cortisol, prolactin, GH and melatonin. Immune cells are also capable themselves of expressing many hormones. Over 20 different neuroendocrine hormones and/or mRNA for hormones including ACTH, Thyroid Stimulating Hormone (TSH), GH, prolactin and CRH are expressed by lymphocytes and/or monocytes [76]. In our studies on goats we found significant variations in MT1, MT2, AR and ERα expressions in thymus in sex and season dependent manner. We have also found that particularly the thymus is having its own machinery for steroid genesis and both thymus and spleen are having own enzymatic system for melatonin synthesis [29]. Thus, it may be possible that melatonin is modulating immunity in goats not only by its higher circulatory level in season and sex dependent manner but also modulates immunity by making hormonal-microcircuit at lymphatic tissue levels [77].

Conclusion

It was previously believed that the immune system of the body is a "closed circuit" being regulated by cytokines. But, with the advancement of molecular science research, now it is well established that open circuit system of immunity is regulated by a number of factors and hormones. Hormones regulate different physiological functions like reproduction, metabolism and stress management. Gonadal steroids are of prime importance for reproduction but concerning about immunity testosterone and estradiol are immunosuppressive in nature. Thyroxin in general is responsible for regulation of body metabolism and hence was less examined for immune system but some reports suggest it as immune-enhancer or immunologically neutral. Glucocorticoid is principally responsible for stress management of the body and also a known immunesupressor. Melatonin, the prime regulator of seasonality in reproduction and immunity in seasonal breeders is immune-enhancer in almost all organisms including human. Though, endocrine regulation of immunity in maintenance of body homeostasis is well documented in different species but less effort was given to goats. Goats are ruminant short day breeder and free grazing animals. During summer they are under "heat stress" with low level of melatonin. During monsoon they are highly infected with different endo and ecto-parasites and thus are under "inflammatory stress" with high level of cortisol and moderately high level of melatonin. Besides this, monsoon is reproductive preparatory phase for goats with high levels of testosterone and oestradiol. Reproduction is executed during winter in terms of gestation in females. Thus, during winter male goats are only under "cold stress" but females are under both gestational and cold stress with high level of melatonin, thyroxin and prolactin. As our results suggest during summer, monsoon and winter melatonin along with other hormones either acting as a buffer to ameliorate the immunosuppressive effects of gonadal and/adrenal steroids or acts as an opportunistic hormone by making thyroxin as an immunoenhancer to enhance immunity. Thus, in this context the present attempt of ours may through some light on the complex regulation of immunity by different hormones. This may drag attention of different veterinarians and basic researchers to work on this economically important seasonal short day breeder to maintain them healthy and productive in a farm.

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