Review

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Maintenance of Thermal Homeostasis with Special Emphasis on Testicular Thermoregulation

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Abstract

The testicular thermoregulation is maintained by a complex anatomical structures and physiological phenomena including convection, conduction, radiation and evaporation. The testicular temperature variation has a deleterious outcome on the reproductive performance of male reproductive system, though, duration and intensity of the insult is the pivot point. By regulating the altered thermal offense, the reproductive performance can be improved, however, with a consistent increase in the global temperature, there is a need of extensive investigations to undermine the thermoregulatory mechanism, its performance, anatomical and physiological adaptations, in the upcoming hot and humid environment.

Keywords: Heat stress, scrotum, testes, testicular cone, thermal balance

Introduction

The maintenance of internal milieu is a basic phenomenon observed in human and other warm blooded mammals to cope with the temperature fluctuations in the external environment (Nakamura and Morrison, 2007). The central nervous system orchestrates a repertory neuronal machinery to constantly tackle the environmental thermal challenges. A variety of mechanisms are exercised including the blood circulation to the skin, metabolism of the brown adipocytes, thermogenesis by striated muscles, and some species-specific apparatuses like panting and sweating to shield the thermal offence (Morrison and Nakamura, 2011). Afferent and efferent neuronal pathways are converged in the brain thermal clock to collect and convey thermal information and to potentiate appropriate regulatory strategy in the response tissue (Morrison and Nakamura, 2011). For instance, the sympathetic branch of the autonomic nervous system (ANS) activates along with a tachycardia when the cutaneous temperature falls. The mechanism is fast enough to generate the required amount of heat that the core and brain temperature remains unaltered (Nakamura and Morrison, 2007). So, there is only a slight or no change in the core temperature of the body (Figure 1) (Guyton et al., 2006) as well as the brain tissues with the exposure of an individual to the cold environmental conditions (Bratincsák and Palkovits, 2005). This is because of rapid elicit response mechanism. On the skin, a family of transient receptor potential (cation channels) is supposed to sense the temperature over a wide range of temperature, however, none of these channels are convincingly proven to be the thermoreceptor that may be involved in initiating a molecular thermoregulatory response (McKemy et al., 2002).

The cutaneous temperature data is transmitted to the spinal dorsal horn via somatosensory nerve strands, which have some of the best known ascending thermosensory pathways that synapse with the thalamic neurons, for the judgment of the skin temperature (Craig, 2002). However, there are at least three classes of such afferent neurons involved in the sensation of heat, cold and mechanical changes to the skin.

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Apart from the skin, many other core body temperature information centers exist including the abdomen, spinal cord and the brain. Among them, the abdominal thermal information is quite complex to study as its nerves fibers also contain the information of appetite, taste, thirst and other gastric influxes along with the thermal information. It is suggested that the thermal informations, before reaching the preoptic area, are amended in the lateral parabrachial nucleus (Geerling and Loewy, 2008; Gupta et al., 1979). The studies have shown that the spinal cord thermal activation affects the neurons in the preoptic region suggesting that the spinal cord might have some thermal receptors similar to the cutaneous thermal receptors that are, somehow, involved in evoking the thermogenic response. It is still not clear that how these fibers may be interacting with those of the preoptic region, however, it is supposed that they may be co-involved in the cutaneous thermal input as the deep body temperature is not directly affected by the change in the environmental temperature (Bratincsák and Palkovits, 2005; Guieu and Hardy, 1970; Lomax et al., 1964).

With the change in the environmental temperature, a number of neurons in the central nervous system (CNS) show altered activity indicating their thermal response but the most concentrated area for thermoregulatory neurons is the preoptic area. After their discovery, they became the area of interest for the thermoregulatory studies especially after the findings that the loss of the neurons in this area leads to disturbed regulatory responses. Their dischargeability is markedly increased with the increase in local and skin temperatures (Boulant and Hardy, 1974; Nakayama et al., 1961; Nakayama et al., 1963).

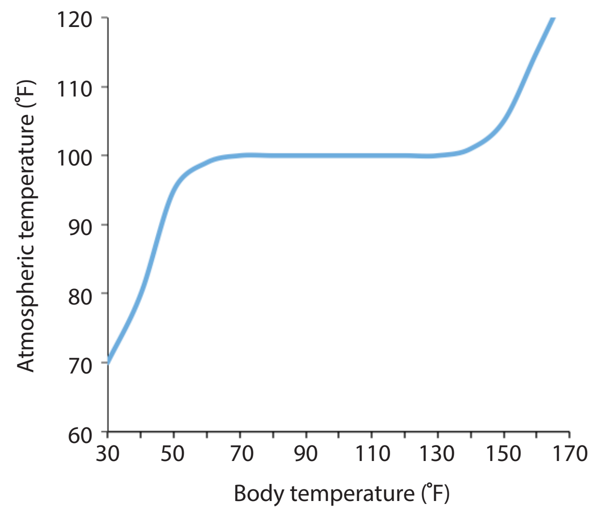

Figure 1. Effect of high and low atmospheric temperatures of several hours' duration on the internal body "core" temperature. Note that the internal body temperature remains stable despite wide changes in atmospheric temperature

There is a need to keep the core temperature of the body in a narrow range of temperature for which the hypothalamus has temperature sensitive neurons. A recent study reveals that there are the two types of nuclei in the hypothalamus; preoptic and dorsomedial, which have body temperature modulating activity and alterations in these areas lead to alterations in the core temperature (Zhang et al., 2017). Both the areas have an effective regulatory molecular connections for thermogenesis (Liedtke, 2017). Even now, there is a major study required to pin point the receptors for the thermosensitivity in the preoptic area on the neurons as well as specific markers for such neurons need further investigation.

Since skin is the first organ to sense the threats in the environmental temperature, it has the key role in triggering a thermoregulatory response although some animals, including human, have thermoregulatory responses even on the non-thermal signs like lightening, thunder or even news. It is a matter of great interest that some of the thermoregulatory responses are not processed by the preoptic area (Nakamura and Morrison, 2008). The cutaneous blood flow is routed to control the heat loss to the environment especially in the area of skin devoid of hair. During thermic intimidations, the decreased and increased blood flow is observed via sympathetic vasoconstriction and vasodilation (Wallin and Charkoudian, 2007). The contraction of the smooth muscle related to the vasomotor action of the cutaneous blood vessels is largely considered to be influenced by acetylcholine, a neurochemical mediator. Fewer studies support the role of nitric oxide via nor-epinephrine, another neurochemical mediator. These difference of findings may be due to the local and general thermal status of an individual (Hodges et al., 2008; Holowatz et al., 2005; Kellogg et al., 2007). However, during the process of cutaneous vasodilation, the visceral vasoconstriction of unknown mediation is observed.

The thermogenic response of heart through the activation of sympathetic mediation along with tachycardia is reported responses to the cold challenges to the body. The cardiac output is also maintained through the process of tachycardia. These processes are in accord with the shivering and production of heat from brown fat tissues (Nakamura and Morrison, 2007). The shivering of the skeletal muscle has long been recognized essential response to cope up with the cold environment, however, the mechanism and the neuromediators are hardly explored except the rhythmic gust of the alpha neurons are involved in the activation of the associated skeletal muscles and the intensity of shivering response (Schäfer and Schäfer, 1973).

Another predominant response to hyperthermia is sweating that helps to keep the core body temperature with in an ambient temperature range. The evaporative cooling is efficiently mediated by the skin, especially bare one. It provides a huge surface area in all the mammals with the exception of a few species which rely on the respiratory system through panting and salivation. The mechanism that evokes the release of sweat from

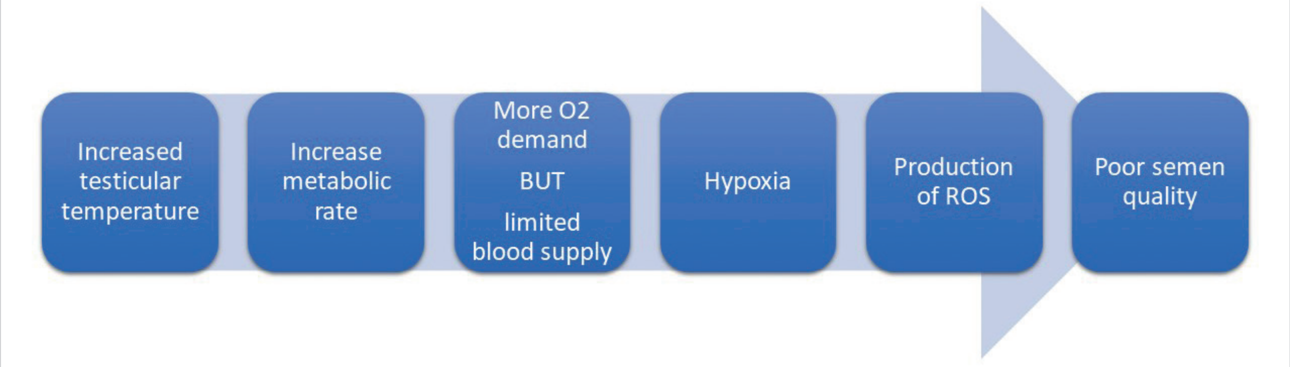

Figure 2. Schematic diagram to show the mechanism of thermal offense on the semen quality. ROS: Reactive Oxygen Species

the glands is still not known but it is supposed that the heat sensitive receptors of the skin are possible pathway to the spinal neurons (Morrison and Nakamura, 2011). The saliva, on the other hand, has inconstant nature as it is devoid of the proteins and is secreted and dispersed on the body. A similar mechanism may be present for the salivation as that of the sweat glands as very little is published in this connection. As a large volume of blood is diluted through evaporative cooling, there must exist a very efficient and quick mechanism between the cutaneous and circulatory systems (Whyte and Johnson, 2005).

Testicular thermoregulation

Although all the body organs are susceptible to heat damage but the testicles are unique in a sense that they are damaged even at a temperature optimal for the other organs. The reason, why the testicular temperature is kept lower than the body temperature is a mystery. The idea of scrotal thermoregulation was first floated by Moore and Quick (1924). There are few theories like; lower temperature may have role in lower mutation rate of the spermatozoa (Eheenberg et al., 1957), minimize physical damage to the testicles (Chance, 1996), decorative purpose (Portmann, 1952), to limit the blood supply to growing sperm cells and to enhance the mitochondrial oxidative enzymatic activity (Freeman, 1990) and optimum sperm production with minimum damage to DNA, mutation and better storage (Bedford, 2004; Werdelin and Nilsonne, 1999). Externalization of the testes does not seem necessary but the lower testicular temperature, however, is required as some species have internal testes with lower testicular temperature than core temperature (Hansen, 2009) and some others show seasonal externalization behaviour (Atkinson, 1997). The theories of the evolution of the scrotum revolve around the requirement of an ideal temperature, lower than the body temperature, for optimum spermatogenesis (Stanfield and Germann, 2008; Wallage et al., 2017).

The scrotum is a key organ in thermoregulation that has been extensively studied for its attachment with the ventral body wall, the amount of subcutaneous fat, number of hair follicles, extent of blood and lymph vasculature, the composition of the tunics, structural and functional details of the sweat glands (Artyukhin, 2007b; Cividini, 2017; Kastelic, 2014a; Setchell, 1978; Setchel, 2006; Souto et al., 2017). Thermoregulation of the scrotum is maintained by a complex combination of anatomical, physiological and behavioural adaptations and mechanisms. The scrotum is a skin extension that is attached to ventral body wall through the pendulous neck. The skin is thin in most of the mammals, devoid of sebaceous glands and richly supplied with blood vessels (Kastelic et al., 1997a).

A study has shown that the anatomical structure of the scrotum, testicular vascular cone and testicular morphology has a significant influence on the testicular thermoregulatory capabilities and hence affects the sperm quality. In their comprehensive study, they established that semen quality is positively correlated with the testicular volume and subcutaneous temperature of the scrotum and negatively correlated with the scrotal surface and testicular temperature. The temperature gradient, volume of the testes and testicular artery are positively associated with the increased sperm production, scrotal surface and testicular circumference and negatively associated with wall thickness of the vessels (Brito et al., 2004).

Thermal stress: Mechanism and effects

Failure to maintain the optimum testicular temperature increases the metabolic rate of the organ, which in consequence demand more oxygen. But as far as testes are concerned, their blood supply is limited and unaltered, therefore, an increase in the metabolic rate leads to hypoxia and production of reactive oxygen species, which reduce the quality of semen (Setchell, 1998) as shown in Figure 2. The amount of blood supply increases only when the testicular temperature is well above the body temperature (Setchell et al., 1995), but does not increase anymore on further increase on body temperature (Mieusset et al., 1992). At the same time as the testicular weight decreases with the heat exposure, so the overall blood supply to the organ stays the same (Setchell et al., 1991).

The major cause of the thermal damage is oxidative stress (Paul et al., 2008; Paul et al., 2009; Pérez-Crespo et al., 2008). The thermal stress alone has adverse effects only on the semen volume and mass motility of the sperms and the thermal stress in combination with nutritional stress decreases the volume along with scrotal width and length as well as testosterone level (Maurya et al., 2016).

It has been shown that local heating of the scrotum has general effects on the body like panting and sweating behaviour without altering the core body temperature (Robertshaw and Vercoe, 1980a). An interesting phenomenon is a rise in rectal temperature on cooling the scrotum to a certain extent (Vash et al., 2002). The scrotum has heat and cold detecting receptors that activate the ventromedial hypothalamic nucleus (Li and Thornhill, 1996; Li and Thornhill, 1998). The cold receptors are not activated until the local temperature is between 10-20ºC, however, cooling the scrotum does not cause shivering or thermogenesis by the metabolism of brown fat which suggests that there is a different mechanism of activating the center which causes shivering and fat metabolism (Li and Thornhill, 1993; Li and Thornhill, 1998). The physiological basis of this singularity still needs further clarifications but the scrotal heating cause panting and rise in respiratory frequency and lower the body temperature that indicates some activation of preoptic neuron (Maloney et al., 2003).

The blood flow pattern in the testicles does not depend on the heart and respiration rate but their frequency increases and the amplitude decreases with the increase in the testicular temperature and returns to normal after removing the stress (Setchell et al., 1995). There is no effect on the fluid flow in the rete testes or on the blood-testes barrier with the temperature (Setchell et al., 1996) except slight disintegration after seven days of stress (Turner et al., 1982). There is an increase in flow of anions and lysine following the stress (Main and Waites, 1977).

The testicular insulation has been studied in detail with a wide variety of experimentation on both, the testes and epididymis, collectively as well as independently. The experimental models are of quite diverse in nature but the results concluded that there are fewer pathological changes in the sperm count, however, pronounced morphological deformities and mobility incapacities of varying nature depending upon the time and nature of insulation are observed when there is improper heat dissipation and the raised testicular temperature. Most common of them are the testicular weight loss on heating and recovery on removing the heat stress (Bartlett and Sharpe, 1987; Galil and Setchell, 1988; Jannes et al., 1998; McLaren et al., 1994; Sailer et al., 1997; Van Zelst et al., 1995), increased apoptosis in spermatocytes (Lue et al., 1999), the pyriform heads (Barth and Bowman, 1994; Lagerlof, 1938), decreased motility (Austin et al., 1961; Vogler et al., 1993), longer meiotic phases, elongated spermatids which are easily injured (Austin et al., 1961), abnormal acrosomes, abnormal tails and presence of protoplasmic droplets (Wildeus and Entwistle, 1983), decapitated sperm, droplets and sperm tail abnormalities (Wildeus and Entwistle, 1986), absence of tail, knobbed acrosome, Dag defect and nuclear vacuolation (Barth and Bowman, 1994; Vogler et al., 1993), distal mid-piece reflex, detached head, mitochondrial sheet defect, microcephalic head, teratoid, coiled principal piece and abnormal DNA (Barth and Bowman, 1994), mid piece and head defects (Kastelic et al., 1996a), poor development of the embryo obtained from heat stress sperm (Paul et al., 2008) and underweight fetus and placenta (Jannes et al., 1998; Paul et al., 2009).

The heat stressed individuals, on recovery, show better semen motility characteristics, however, the sperm abnormalities of acrosome and the mid piece persist even after removing the stress for some time (Saab et al., 2011). Some infertile individuals are reported to improve the sperm quality on long term cooling of the testes, even, (Jung et al., 2001) and on ligation of the dilated veins (Pasqualotto et al., 2003).

Factors affecting scrotal thermoregulation

The testicular temperature always remains lower than the core body temperature by a difference of 2-7ºC irrespective of the ambient temperature, still, the temperature gradient depends upon the regions of the scrotum; proximal, middle or distal. So the testicular surface vary in the temperature dynamics, the bottom is the coolest and top, being close to the body is the hottest area while the middle area stands between the two extremes (Kastelic et al., 1995). The more the distance from the body, the higher is the temperature gradient (Gábor et al., 1998; Kastelic, 2014b; Lunstra and Coulter, 1997; Silva et al., 2017; Skinner and Louw, 1966). A varying degree of temperature suggests that every part of the testicles require a unique temperature to operate. The temperature is particularly low in the region of the epididymis signifying a cool storage temperature in the tail because an increased storage temperature of the spermatozoa causes a significant rise in the embryonic mortality (Blazquez et al., 1988). The tail is cooler than the rest of the epididymis may be owing to its closer association with the vascular cone (will be discussed later in this article) as well as its physiological role in sperm storage (Kastelic et al., 1995).

Testicular vascular cone

Traditionally, the testicular vascular cone containing the pampiniform plexus is the site for effective exchange of heat across the vessels during the process of counter-current flow of blood resulting in lowering the testicular arterial blood temperature and raised venous blood temperature. The average efficacy of the cone is 91% for the transfer of heat under *in vivo* and 100% *in vitro* (Figure 3) (Glad Sørensen et al., 1991) indicating no loss of heat during transfer via passive transfer termed as counter-current transfer process (Figure 4). The cone is also the area of highest temperature close to the scrotum with a network of blood capillaries and the heat is lost through convection and radiation (Coulter and Kastelic, 1994). The morphological study of the angioarchitecture of the testicular artery especially its length, convolution and association with the vein have a significant role in the elucidation of thermoregulation (Khalifa and Noor, 2017). The testicular artery occurs singly in most of the cases with a few exceptions in man (Asala et al., 2001; Mostafa et al., 2008; Raman and Goldstein, 2004), bull (Amselgruber and Sinowatz, 1987) and buffalo (El-Gaafary et al., 1980). The artery may be as long as 240 cm convoluted in 20 cm (Osman et al., 1979). Its wall thickness also depletes (Hees et al., 1984) along the length, starting from the abdominal aorta to the testes. It is highly coiled around the testicular vein in the entire testicular vascular cone (Figure 5) (Einer-Jensen and Hunter, 2005) in most of the species, however, the degree of convolutions varies; highly coiled in camel (Osman et al., 1979), with moderate convolutions in goat and buffalo (Abu-zaid and Gad, 1999; Borthakur and Dhingra, 1979; Dhingra, 1979) and least in donkey (Fehlings and Pohlmeyer, 1978). The testicular vessels arrangement is classified into four types of pattern; pattern I in ram and buffalo, pattern II in camelids, pattern III in donkey and pattern IV in rabbit (Elayat et al., 2014; Khalil, 2013). Briefly, in addition to other differences, tunica vasculosa and arteriosa of marginal artery in addition to the fashion of its termination determines the type of pattern. The density of the tunica vasculosa in type I pattern is prominent in the distal one-third of the testis while, proximally, it appears flimsy, while in type II pattern, the tunica arteriosa testis is poorly dense. In type III pattern the density of the tunica arteriosa testis is quite opposite to that of type I as it more pronounced in the distal two third of the testis. The density is poor and less distinct in type IV pattern.

The diameter of the testicular artery shows some drastic changes over the phase from prepubertal to post-puberty. As the individual reaches towards it puberty, the association of the testicular artery with that of vein becomes stronger, their walls become thinner and the diameter increase dramatically to facilitate an effective exchange of material and heat with fewer defects in sperms (Brito et al., 2012; Cook et al., 1994).

The testicular vascular cone is not only responsible for heat exchange but also for transportation of other macro and micro-molecules including testosterone. Testosterone recirculates from testicular vein back into the testicular artery resulting in ten times higher concentration of the hormone in the gland, responsible for the maturation of the spermatocytes (Einer-Jensen and Hunter, 2005).

A unique feature of the intratesticular thermoregulation is the opposing temperature gradients of the scrotal surface and the testicular parenchyma. The testes are vascularized from bottom to top and scrotum from top to bottom. As a consequence, the testicles are cooler at the top while scrotum at the bottom and vice versa for converse situation (Gunn and Gould, 1975; Kastelic et al., 1997b). However, the temperature of the blood in the testicular artery post-testicular cone is similar at the bottom of the testis but significantly cools down just before entering the parenchyma (Kastelic et al., 1996b).

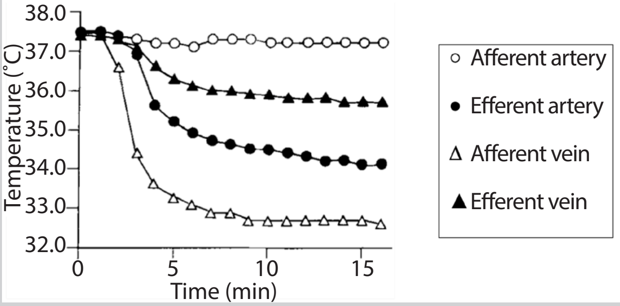

Figure 3.Temperature changes (ΔT ˚C) in the blood vessels of the spermatic cord in an in-vitro experiment with a bull testis. The pampiniform plexus was perfused with citrate plasma at 32˚C, and the testicular artery with citrate plasma at 37˚C (Glad Sørensen et al., 1991- Figure courtesy of Glad Sørensen – used with permission)

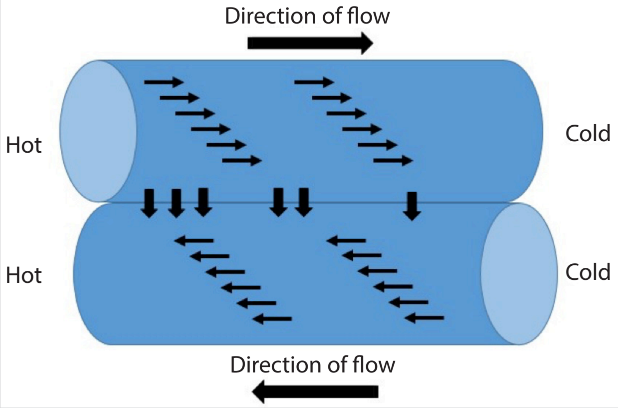

Figure 4. Model of counter-current transfer of heat or a substance between two tubes

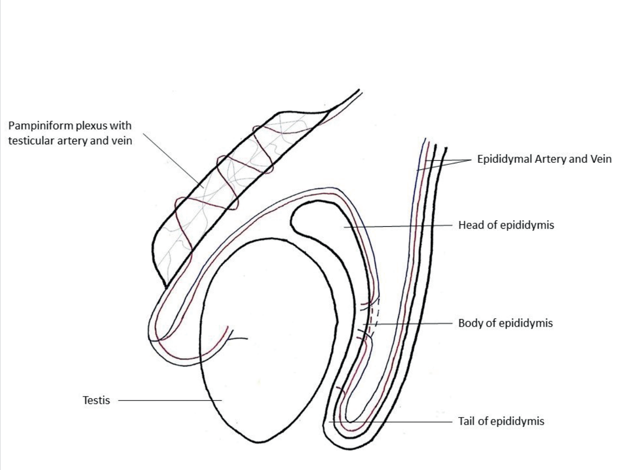

Figure 5. Model of counter-current transfer of heat or a substance from the venous blood in the pampiniform plexus to the blood in the testicular artery. The testicular artery also supplies the caput and part of the corpus of the epididymis

Environmental temperature

The increased ambient temperature has an indirect effect on the scrotal temperature as individuals having covered scrotum, with dense hair or fleece, show a significant rise in the scrotal surface temperature as well as the scrotal subcutaneous temperature, however, a non-significant rise in the intratesticular temperature (Kastelic et al., 1999). A morphometric study of the testis concluded that variations in seasonal temperature markedly influences morphology of the testicular tissue and activity of Leydig cells (Pasha et al., 2011). In another comprehensive study, a total 29 parameters of male reproductive system were studied out of which 16 were markedly influenced by natural environment (Qureshi et al., 2015). Nevertheless, there is a positive linear relationship between the scrotal surface temperature and the internal testicular temperature (Kastelic et al., 2001). As the ambient temperature rises, the temperature difference between the scrotum and the environment decreases which leads to decreased ability of the scrotum to dissipate heat into the environment which, in return, raises the temperature of blood in the testicular vein. It results in poor exchange of heat between the testicular artery and vein and finally there is the supply of warmer blood to the scrotum and raised testicular temperature (Garcia, 2013; Marai et al., 2008; Sealfon and Zorgniotti, 1991). So, it seems quite appropriate to monitor the ambient temperature of the animal's environment otherwise it is a thermal stress on the testes.

Scrotal circumference

The individuals with larger scrotal circumference tend to have lower scrotal temperature on account of having a larger surface area but there may also be involvement of amount of blood supply variations. Moreover, the scrotal temperature is like wisely influenced by the behavioral and postural variations that depend on the housing practices (Wallage et al., 2017). The bipartite scrotum has a better reproductive performance on account of the greater surface area and thinner medial epidermis compared to partially bipartited or without bipartition at all; in spite of the fact that they have more number of apocrine sweat glands (Nunes et al., 2010).

Sweat glands and hair follicles

A neural reflex is responsible for sweating with at least two components; scrotal skin heat receptors and sympathetic nerves of adrenergic nature (Setchell, 1978). The sweat glands of the body and the scrotum are under the collective adrenergic neural control, however, the amount of sweat produced is as much as five times the thorax because of larger sized glands that lead to huge amount of moisture loss and cooling of the scrotum (Robertshaw and Vercoe, 1980a).

The sweat gland size, number and density on the cutaneous surface of the skin serve as a good determinant for the estimation amount of heat loss through evaporative cooling that was first measured by the amount of sweat evaporated per unit area during summer and other seasons (Robertshaw and Vercoe, 1980b). The number of secretory units of the scrotum is higher than that of the neck or abdomen of the same individual. The concentration of the glands gradually increases distally on the scrotum that supports the fact to cooler distal area of the scrotum (Blazquez et al., 1988). Irrespective of the size and number of the sweat glands, the evaporation rate is also higher in the scrotal region compared to the lumbosacral region (Blazquez et al., 1994). A significantly huge volume of vapours is evaporated compared to the rest of the body for which the considerably larger size of the scrotal sweat glands is responsible (Amakiri, 1974; Lyne and Hollis, 1968; Waites and Voglmayr, 1962; Weiner and Hellmann, 1960). The amount of the sweat is not only affected by the size and the number of the glandular units (Blazquez et al., 1988) but also by the capacity which may be as high as ten discharges per hour from them (Waites and Voglmayr, 1963).

Ultra-structural and immunohistochemical studies on the secretory cells of the sweat glands display the presence of abundant rough endoplasmic reticulum, network of golgi apparatus along with secretory vesicles involved in the secretion of beta-defensin. Thus, these glands not only regulate the temperature of the testicles with a narrow range but also provide non-specific immunity against the microbes (Yasui et al., 2007). The physical appearance of the scrotum also changes with breeding behavior i.e. smooth and fine at high breeding interims and rugose and thick at the low (Abdullahi et al., 2012).

The hair traps the air and creates a local mechanism to entrapping the convected heat and keeping the body warm, however, their absence on the scrotum facilitates an easy heat loss (Blazquez et al., 1988). The number of hair follicles also decreases from the young to an adult individual.

Vascularization, innervation and musculature

The male reproductive system is commonly attributed to be highly influenced by anatomical features, physiological conditions and nutritional status of an individual as well as temperature and humidity changes in the environment. A number of individual studies have emphasized the importance of each parameter. The themoregulatory center is supplied with sympathetic fibers of postganglionic part of lumber region, stimulation of which has vasoconstrictive response in the smooth muscles of cutaneous arterioles in the scrotum (Langley and Anderson, 1895). The vasoconstriction tone is lost during the direct local heating of the scrotal skin via sensing of the cutaneous scrotal receptors mediated by sympathetic pathway causing the dilatation of the arterioles. Contrarily, the total loss of tone is observed with the raise of core body temperature accompanied with the heat loss by radiation and sweat (Setchell, 1978).

However, recent findings suggest that it is the blood microvasculature of the scrotal integument which is involved in the testicular thermoregulation, and not the secretions of apocrine glands. The epidermis shows a dense network of vessels that is comparable to the skin vascular system. The underlying tunica dartos has a specific vascular system. It is attached to the blood vessels (arterioles and venlues) from one end and to the rete dermis on the other end, so, it ensures a uniform nutrient supply to the whole layer (Artyukhin, 2007a; Godynicki et al., 2013).

Two types of muscles, smooth and skeletal muscles namely tunica dartos and cremaster, respectively, are responsible for contraction under the sympathetic innervations of lumber origin in response to the alterations in the optimum temperature so that an optimum distance from the body may be maintained. The former being a smooth muscle is capable for sustained contraction and keeping the testicles closer to body for longer periods of time but the later exhausts sooner on account of its skeletal nature (Gibson et al., 2002; Schwarz and Hirtler, 2017).

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