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The descent of testis and reason for failed descent

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Although an enormous number of theories have been proposed to explain the descent of testis, none has provided a satisfactory explanation that covers the whole spectrum. Recent evidence suggests a hitherto unrecognized mechanism. This novel explanation precisely defihes all of the factors proven to be involved in the process, and links the features associated with normal or failed descent.

The gubernaculum gives rise to both smooth and striated muscles. The testis is descended through the processus vaginalis via the propulsive force generated by the muscles. Propulsion describes the risk of torsion. Failure in descent in associated with a diminution in smooth muscle content, and a decrease in sympathetic tonus that depends on androgens.

Alterations in G-protein linked signaling due to differences in primary messengers resulting from changes in sympathetic and parasympathetic tonuses provide the basis for blunting of testosterone response to human chorionic gonadotropin (hCG) and the decrease in fertility, but also for the increase in the risk of malignancy.

Key words: gubernaculum, descent, testis, autonomic nervous system, crytorchidism, G-proteins.

The testis develops in the abdomen and descends into the scrotum at around the 28th week of gestation. Despite proposition of a large number of theories, the mechanism of descent still remains unexplained[1,2].

The necessity of an intact hypothalamic- pituitary-gonadal- axis, and the roles of the gubernaculum, processus vaginalis and genitofemoral nerve have long been appreciated. However, none of the theories proposed to date satisfactorily explains the roles of factors that have been unanimously shown to take part in the process of descent. Furthermore, none of the theories provide explanation for the features associated with an either fulfilled or failed descent such as inguinal hernia, hydrocele, epididymo-vasal anomalies, decrease in spermatogenesis, increase in the risk of malignancy, and blunting in responses of luteinizing hormone (LH) to luteinizing hormone-releasing hormone (LHRH) and of testosterone to to human chorionic gonadotropin (hCG).

Evaluation of the process through a hitherto unrecognized perspective provides not only a satisfactory explanation, but defines the roles of factors that take part in the process precisely, and links all of the features associated with fulfilled or failed descent.

Myogenesis within the gubernaculum

The process of descent is a work. Work is defined as force times distance. It is apparent that a force is required for descending the testis. The tissue that generates a physical force is the muscle. However, the development of muscles in the gubernaculum, in which the processus vaginalis develops, remains controversial[1].

Initial descriptions of the gubernaculum have suggested the presence of smooth[3-7], or striated[8-10] muscles. Furthermore, disappearance of preceding abundant smooth muscle has been shown to succeed the descent of testis[7].

Besides the above-mentioned direct evidence, many reports in the literature provide indirect evidence for myogenesis within the gubernaculum. Fentener Van Vlissingen et al. have shown that the amount of hyaluronic acid decreases in gubernaculum during the inguinoscrotal descent[11]. On the other hand, Heyns et al. have shown a decrease in chondroitin and increase in dermatan sulfates without confirming the decrease in hyaluronic acid content[12]. Changing patterns of glycosaminoglycan synthesis are essential for

muscle formation[13]. Although their effects and functions on muscle development largely remain unknown[14], each glycosaminoglycan exerts different effects[15]. Hyaluronic acid actively inhibits the process of myogenesis[16]. Regulated removal of hyaluronic acid is an important process that helps the mesenchymal cells to condense and interact[17]. Chondroitin sulfate is required during early myogenesis. At subsequent stages of development, dermatan sulfate is found[13]. Therefore the reported alterations and accumulation of protein during the time of testicular descent[18] may actually reflect the development and differentiation of muscles in the gubernaculum.

The gubernaculum is usually described as resembling the Wharton's jelly[10]. The expression patterns of glycosaminoglycans and stromal cells according to the duration of pregnancy are relatively well evaluated in Wharton's jelly compared to those in the gubernaculum. Proliferating mesenchymal precursor cells initially express only vimentin. By the time they acquire degrees of differentiation, they begin to additionally co-express desmin, and α smooth muscle actin, and finally they acquire a smooth muscle cell phenotype[19]. While those cells are accepted to represent various stages of differentiation towards myofibroblasts by some authors[20], others accept those cells to actually represent the steps towards smooth muscle differentiation[21]. Extra-cellular matrix of Wharton's jelly also contains glycos-aminoglycans, which are produced in context with development of muscles[19]. If the gubernaculum resembles Wharton's jelly, similar alterations should be expected within the gubernaculum during various time points of development.

Contrary to the existence of those direct and indirect evidences, the gubernaculum is usually accepted as a primitive mesenchymatous tissue, which gives rise to the striated cremaster muscle (CM) at the periphery[9,22].

Sacs associated with male inguinal hernia contains smooth muscle and myofibroblasts. While sacs associated with hydrocele contain less, sacs associated with undescended testis contain the least smooth muscle and myo-fibroblasts. On the other hand, sacs associated with female hernia additionally contain striated muscle[23-25]. The smooth muscle content of sacs has been suggested to determine the clinical outcome[26,27]. Structures distal to an undescended testis and distal to the sac in girls with inguinal hernia are accepted to represent the postnatal gubernaculum. Apart from the mesothelial lining, those structures contain identical tissue components as the sacs to which they are attached[28]. However, the obliterated processus vaginalis and peritoneum do not contain any smooth or striated muscle[23]. The smooth muscle presented in sacs reveals contractile properties as other smooth muscles[29].

The striated CM has some distinguishing properties. Although it receives somatic innervation from the genitofemoral nerve, it is not under voluntary control. Striated muscles with motor end plates, but controlled by autonomic nervous system are encountered in the esophagus and urethral sphincter[30,31]. The CM reveals a type 1 fiber predominance[32,33]. Striated muscles of esophagus and urethral sphincter also share the same property[34,35]. Despite the opposing views which exist[36], striated muscles of esophagus and urethral sphincter are reported to transdifferentiate from the preceding smooth muscles[37,38].

The presence of muscle in sacs and structures accepted to represent the post-natal gubernaculum, and the similar properties of CM to the transdifferentiated muscles have necessitated a re-evaluation of myogenesis within the gubernaculum. The gubernaculum of a 12 week-old male fetus contains striated muscle. However, it does not express MyoD. Since down regulation of MyoD inhibits the differentiation towards striated muscle[39], those striated muscles represent the muscles that are not going to proceed to subsequent steps of development, but the going to disappear. Samples from 22-week-old fetus reveal myofibroblasts. During the 22-nd and 23-rd weeks, vascular smooth muscle expresses MyoD and striated muscle that expresses MyoD, appears. Although vascular smooth muscle ceases to express MyoD after 23rd week, the striated muscle expresses MyoD even in the gubernaculum of the evaluated oldest fetus, who was 28 weeks old. The striated muscle has been positive for α-smooth muscle actin during the 25-28 week period. Recent experiments have shown that a phenotypic switch from vascular smooth to skeletal muscle can occur.

Both MyoD and insulin-like growth ractor (IGF) signaling system play roles in switch[40]. The appearance of striated muscle with Myo-D expression following the expression of Myo-D by the vascular smooth muscle, and expression of α-smooth muscle actin by the striated muscle may reflect the development of the CM muscle from the vascular smooth muscle. Differentiation of myofibroblasts towards the smooth muscle progresses, and smooth muscle appears in the gubernaculum at 27 weeks of age[41]. These findings are in accord with those reported by Youssef and Raslan[7].

If the term gubernaculum refers to the primitive mesenchymal tissue, it ceases to exist after the development of muscles. On the other hand, the primitive tissue termed the gubernaculum does not represent a helm or a rudder as suggested[1]. Rather, it is the antecedent tissue that will eventually give rise to muscles to propel the testis.

The gubernaculum is suggested to give a supporting fascia to the epididymis[42]. On the other hand, it is known that the sacs may present vaso-epididymal structures. The incidence of encountering a vaso- epididymal tissue decreases with age, and it is rarely encountered among postpubertal males[43]. That evidence suggest that the gubernaculum may also supply the muscle layer of the vaso-epididymal structures. On the other hand, the disappearance of accessory structures during the time course suggests the possibility of postnatal alterations in vaso-epididymal structures.

Myogenesis within the gubernaculum appears to be a very special process. The timing of the appearance of smooth muscle varies in different parts of the developing fetus. While the smooth muscle develops at the 27th week in the gubernaculum, the human bladder is well developed by 9.5 weeks of age[44], and the smooth muscle is formed at the 31st week in the uterus[45].

Although many clinical series have revealed the absence of anomalies of Insl3 (relaxin-like) factor[46-48], and although anomalies of its receptor account for only a very limited number of patients[49,50], there has been a growing interest in the role of Insl3 in establishing the localization of a gonad[51]. Insl3 is involved in growth and differentiation, and it is constitutively expressed in testis, ovary, trophoblast, epididymis, uterus, heart, lung and hypothalamus[52]. The uterus and gubernaculum, which are both vulnerable to the effects of Insl3, reveal some similarities in the development of smooth muscle. Until 16 weeks of gestation, smooth muscle cells are not found in the human uterus. Spindle shaped cells, containing few myofilaments with well developed organelles, first appear at the 18th week. These cells which are described to form an intermediate between undifferentiated mesenchymal cells, and mature smooth muscle cells, most probably represent myofibroblasts. Smooth muscle differentiation is proposed to begin at the 18th week, and the myometrium is formed at 31st week[45]. Similar features for the development of smooth muscles are also described in the ureter and ductus deferens. The similar developmental patterns in tissues vulnerable at Insl3, and the defective myogenesis in the gubernaculum of Insl3 gene knockout mice[53] suggest that Insl3 has a role in the myogenesis[54].

The detrusor normally expresses smooth muscle markers. However, both smooth and striated muscle markers are expressed in the bladder of patients with myelomeningocele[44]. Those expressions suggest the pattern of innervations to play a role in the development of such striated muscles. Since the sacs associated with female hernia contain striated muscle in addition to the smooth muscle[24], the development of muscles in the gubernaculum appears to be a sexually dimorphic process governed by the sexually dimorphic autonomic nervous system.

Descent of testis

The testis descends through the processus vaginalis[55]. Smooth muscle develops around the processus vaginalis in the gubernaculum. However, obliterated processus vaginalis lacks smooth muscle[23]. Therefore the smooth muscle is presented transiently during a time interval in accord with the descent of testis. There is a unique explanation for the transient presence of a force-generating tissue during this time period. Smooth muscle is presented to descend the testis. The physical force that descends the testis is the propulsive force generated by the smooth and striated muscles derived from the gubernaculum. The process of testicular

descent through the processus vaginalis resembles the passage of a bolus through the esophagus.

Propulsion explains in-utero testicular torsion

Encountering a vanishing testis due to torsion during intra-uterine life or diagnosing an intra-vaginal testicular torsion during the perinatal period is not a rare occurrence for pediatric surgeons. The propulsion provides a satisfactory explanation for the risk of undergoing torsion for a testis during descent.

Reason for failed descent

If the descent it propulsion, failed descent should reflect a failure in propulsion. Sacs associated with undescended testis contain the least smooth muscle[23,24]. The least smooth muscle content would reflect a defective myogenesis. On the other hand, the absence of smooth muscle in obliterated processus vaginalis points out the necessity of disappearance of smooth muscle for the obliteration of the processus vaginalis[23]. Therefore the diminution in the amount of smooth muscle most probably reflects attempts at obliteration. Premature diminution in the amount of smooth muscle may have resulted in inadequacy of the force required to descend the testis. On the other, some other reasons that alter the contractile properties of muscles, or a common mechanism that both diminishes the smooth muscle content and alters the contractile properties, may have played roles in the inhibition of descent. The comparative evaluation of smooth and striated muscles associated with descended or undescended testis would reveal the alterations that may help to enlighten the reason for failed descent.

While revealing similar spontaneous activities, and responses at electrical field stimulation, phenylephrine and serotonin, smooth muscles associated with undescended testis differ from smooth muscles associated with inguinal hernia only through the lack of response against carbachol[29]. Neurotransmitters of the autonomic nervous system act through receptors coupled to G-proteins. In G-protein linked signaling, less response indicates desensitization of the receptor resulting from more agonist exposure[56]. Absence of response against the muscarinic cholinergic agonist carbachol indicates that the smooth muscles associated with undescended testis have been exposed to excessive parasympathetic tonus.

Although adrenergic innervation of striated muscle is well known, the physiologic role of adrenergic innervation has not been established clearly[57]. Sympathetic tonus is exerted through catecholamines via beta-2 adrenergic receptors on the skeletal muscle. Cremaster muscles also present those receptors[58]. Type 2 fibers appear to be more responsive to beta-adrenergic stimulation[59].

Histopathologic evaluation of CMs associated with undescended testis reveals more pathological findings[60]. Angular fibers and group atrophy indicate a damage of neurologic origin in CMs associated with undescended testis[61]. Although the CMs associated with both descended and undescended testes reveal similar fiber type distributions, the diameters of type 2 fibers reveal a decrease in CMs from boys with undescended testis[32,33]. While the diameters of type 1 fibers are as large as those encountered in boys with inguinal hernia, type 2 fibers are as small as those encountered in girls with inguinal hernia[33]. Preservation of distribution of fiber types suggests the lesion to involve not the motor neuron, but the autonomic nervous system. On the other hand, selective decrease in diameters of type 2 fibers suggests a decrease in beta-2 adrenergic effect[33]. The decrease in beta-2 adrenergic effect indicates a less exposure to sympathetic tonus.

Some androgen effects on the muscle are known to be fiber type specific[62], and androgens enlarge type 2 fibers[63], The decrease in the diameter of type 2 fibers additionally explains the pathway of androgenic effects upon striated muscles. Since the sympathetic system is also sexually dimorphic and depends on androgens[64], androgenic effects upon striated muscles appear to be exerted through the sympathetic tonus.

Cremaster muscles associated with un-descended testis reveal more response against the beta- adrenergic agonist, isoprenaline[65]. More response provides additional evidence that supports less exposure against sympathetic tonus in boys with undescended testis.

Electron microscopic evaluation has shown a decrease in the number of non-myelinated fibers in peripheral nerves associated with

undescended testis[66]. The evaluation of cremaster reflex through electromyography has excluded a defect in afferent neurotransmission, and suggested the decrease in non-myelinated nerve fibers to reflect a decrease in the number of sympathetic nerve fibers[67]. Therefore the persistent decrease in sympathetic tonus among boys with undescended testis appears to be associated with a decrease in the number of sympathetic fibers.

Sympathectomy is associated with significant increases in calcitonin gene-related peptide (CGRP) and substance P immunoreactive sensory fibers[68]. In deed, the afferent system has been considered among the mechanisms that establish sexual dimorphism in the autonomic nervous system. This consideration has been based on the presence of androgen receptors in afferent fibers, and the absence of androgen receptors in sympathetic fibers[64]. Evaluation of contractile responses against CGRP and substance P have revealed less responses among CMs associated with undescended testis. Less responsiveness has indicated more exposure to CGRP and substance P of CMs associated with undescended testis, and provided indirect support for the decrease in sympathetic tonus[65].

Cremaster muscles associated with undescended testis have revealed higher amplitudes of contraction compared to the CMs associated with inguinal hernia[69]. On the other hand, those muscles depend less on calcium entry through voltage gated calcium channels for generating a contraction[65]. Electron microscopic evaluation has additionally revealed contracted fibers, and round and electron dense mitochondria that suggest mitochondrial calcium overload in CMs associated with undescended testis[66]. Increased contractility that depends less on calcium entry together with the presence of contracted fibers, and mitochondria with calcium overload have suggested an increase in the levels of cytosolic calcium. On the other hand, evaluation of total calcium contents has revealed a significant decrease in CMs associated with undescended testis[70]. Problems related to the motor neuron increase the total calcium content. The decrease in total calcium content has supported the alteration to not involve the motor neuron[70]. Despite the evidence of increase in cytosolic calcium, the less lower calcium content can be explained by less calcium entry into the cells, but mobilization of calcium from internal stores. Stored calcium is released from sarcoplasmic reticulum of striated muscles via the ryanodine and/or inositol 1,4,5-trisphosphate (IP3) sensitive channels[71]. The evaluation has failed to reveal any difference among caffeine sensitivities of CMs according to the testicular localization, and has ruled out the participation of ryanodine sensitive channels for the increase in cytosolic calcium levels among boys with undescended testis[69]. Since calcium influx into the cell is enhanced by beta-2 adrenergic effect[72], and beta-2 adrenergic stimulation also activates sarco-endoplasmic reticulum calcium pump[73], the alterations in CMs associated with undescended testis can be explained partly by the decrease in beta-2 adrenergic effect. Inhibition of sarco-endoplasmic reticulum calcium pumps and release of calcium from IP3 sensitive stores require generation of IP3. IP3 is generated through activation of phospholipase C (PLC). During IP3 generation, diacylglycerol which activates protein kinase C (PKC), is also generated as a co-product. PKC inhibits calcium entry into the cell[71]. In addition to a decrease in beta-adrenergic effect, the inhibition of calcium influx by PKC, and the inhibition of sarcoplasmic reticulum calcium pumps by IP3 explain the decrease in total calcium content, and the increase in cytosolic calcium.

The sympathetic and parasympathetic effects balance each other in tissues under the control of the autonomic nervous system[74]. Ligand binding to beta-2 adrenergic receptors that are coupled to G-proteins releases α_s, thus activating adenyl cyclase to generate cyclic cyclic adenosine monophosphate (AMP). On the other hand, the parasympathetic system acts through activating PLC[74]. The evidence gained from the smooth and striated muscles associated with undescended testis reveals less exposure against sympathetic, but more exposure against parasympathetic tonus.

Least smooth muscle content, together with a persistent decrease in sympathetic tonus that is associated with a decrease in the number of sympathetic nerve fibers, appears to be the reason for the failure of descent.

Experimental support for the failed propulsion and less sympathetic tonus association

The testis freely moves up and down through the patent inguinal canal throughout life in rats. Although the role of primitive mesenchymal tissue, termed the gubernaculum, has been overemphasized through considering a determinative role for the initial descent, those concurrent descents that follow ascents take place in the absence of the primitive mesenchymal tissue. There is no reason to assume that the initial descent is different from those subsequent descents that follow ascents. The gubernaculum in rats is the progenitor of the mechanism that repeatedly ascends and descends the testis. The gubernaculum also gives rise to muscle in rats. However there is no smooth muscle development, and only striated muscles with circular and longitudinal oriented fibers that resemble the upper esophagus develop[75]. The descent and ascents in rats may have succeeded via those muscles through iso-peristaltic and reverse-peristaltic activities in a similar fashion encountered during swallowing and vomiting. Although the mechanism reveals differences in human and rat, propulsion appears to be common. Therefore the propulsion theory has been tested in rats.

While steroidal anti-androgens do not hamper the descent, descent of testis can be inhibited through administration of non-steroidal anti-androgen during 15-19 days of fetal life in rats. The CMs of those rats reveal evidence of less dependence on calcium entry through voltage gated calcium channels for generating a contraction. Furthermore, those muscles are exposed to less sympathetic tonus, which indicates the involvement of sympathetic tonus in anti-androgen induced inhibition of descent in rats. On the other hand, administration of steroidal anti-androgen does not affect the contractile properties of CMs[76]. However, it should be noted that both steroidal and non-steroidal anti-androgen inductions do not totally mimic the findings encountered in boys with undescended testis. While steroidal anti-androgen that does not inhibit the descent lowers the serum testosterone levels, the non-steroidal anti-androgen that inhibits the descent increases the serum testosterone levels[77]. On the other hand, boys with undescended testis are exposed to less bioavailable testosterone levels[78]. Therefore anti-androgen induced undescended testis in rats can not represent the undescended testis encountered in human.

Descent of testis can also be inhibited in rats through subjecting to chemical sympathectomy by 6-OH dopamine during the 15-19 day period of fetal life[79]. The CMs of those rats reveal evidence of less dependence on calcium entry through voltage gated calcium channels for generating a contraction, and evidence of subjection to less sympathetic tonus.

Those experimental evidences support the involvement of sympathetic tonus for propelling the testis, and the involvement of sympathetic tonus during anti- androgen induced inhibition of descent.

The retractile and the ascending testes

Although the definition of retractile testis differs among authors, it is unanimously accepted to represent the hyperactivity of cremasteric reflex. On the other hand, the normoactivity of the cremasteric reflex, and the possibility of suprascrotal localization for a testis through a superficial reflex have not been questioned. Since a superficial reflex can not be induced repeatedly, and because induction of an already induced reflex is not possible, suprascrotal localization for a testis can not be explained through a superficial reflex[80].

The electromyographic evaluation of the retractile testes has revealed a decrease in the latent period, but an increase in the duration of contraction[67]. Those findings closely resemble the findings encountered in boys with undescended testis. Therefore the suprascrotal positioning is determined by the degree of contraction in the CMs, which involves the dominance of parasympathetic tonus that increases the calcium in the cytosol. A CM associated with a testis, which has accomplished the descent initially, may subsequently be contracted through persistence of a subtle increase in cytosolic calcium levels. If the CM becomes so contracted, it my ascend an initially descended testis to permanently locate in a suprascrotal position. Thus, the suprascrotal localizations of testis represent a spectrum that varies from minimal retraction to ascent depending on the contracture of CMs via

increases in cytosolic calcium levels determined by the intensity of decrease in sympathetic, but increase in the parasympathetic, tonuses. The common histopathology shared by the ascending testis and the testis undescended since birth provides additional evidence for their vulnerability against similar stimuli[81].

In seasonal breeders such as the ferret, the testes are in the abdominal cavity during the quiescent period, but migrate into the scrotum during the reproductive season[82]. The decrease in androgen levels, which decreases the sympathetic tonus, also explains the retraction of testis during quiescence among seasonal breeders via parasympathetic tonus dependent increase in cytosolic calcium levels.

The effects of dominance of parasympathetic tonus upon testes

Increases in cAMP activate the transcription of specific target genes that contain cAMP response element. Regulation of gene expression by cAMP plays an important role in controlling the proliferation and differentiation of animal cells[71]. The decrease in sympathetic tonus, thus less of an increase in cAMP levels in boys with undescended testis, provides an explanation for the decrease in spermatogenesis.

Continuous stimulation of the PKC pathway by phorbol esters results in the development of tumors[71]. Dominance of parasympathetic tonus, thus more stimulation of the PLC pathway, explains the increased risk of malignancy through increase of PKC in males who have experienced undescended testis.

Testosterone secretion is accepted to be under the primary control of pituitary LH. On the other hand, retrograde tracing from the testis has revealed staining of spinal cord, brain stem, hypothalamus and the telencephalon[83]. A neural pathway between the central nervous system and the testis has been proposed to exist[84]. A direct neural mechanism has been suggested to take part in the regulation of peripheral endocrine gland functions[85]. It is known that turning on the enzyme adenyl cyclase to increase cAMP, initiates testosterone production in the Leydig cells of the testis[86].

Since chemical sympathectomy decreases testicular concentrations of testosterone[87], the decrease in sympathetic tonus in boys with undescended testis provides rational basis for the blunting of testosterone response to hCG through the decrease in tonus that stimulates adenyl cyclase. Furthermore, the autonomic nervous system appears to establish the neural pathway between the central nervous system and the testis.

Those pathyways suggest a developmental basis for blunting of testosterone response to hCG, and the decrease in fertility, and for the increase in the risk of malignancy among boys with undescended testis.

However, the pathway also raises the possibility of acquired factors. The $G\alpha_s$ activity that acts to stimulate adenyl cyclase is further decreased in testis at temperatures that exceed the scrotal temperature[86]. Additionally, function of the $G\alpha_i$ protein that acts to inhibit adenyl cyclase, is induced in testes subjected to higher temperatures[88].

The sensory fibers that contain CGRP and substance P are characteristically sensitive to capsaicin. Capsaicin sensitive fibers are involved in nociception and thermal sensation[89]. Capsaicin activates specific vanilloid receptors. Vanilloid receptors can also be activated by heat[90]. Activation of vanilloid receptors by noxious heat results in release of CGRP and substance P. Release of those afferent neurotransmitters from the testis exposed to temperatures above the scrotal temperature bears the potential to augment the already predominating harmful pathway of signaling.

The blunting in testosterone response to hCG, decrease in fertility and increase in the risk of malignancy in an undescended testis appear to reflect the sum of both developmental and acquired factors.

The pathway explains the effects of hormones in the treatment of undescended testis

Human chorionic gonadotropin or LHRH is used in the hormonal treatment of undescended testis[91,92]. Their use for differentiating the retractile or true undescended testis has also been proposed[93].

For the LH and hCG to act, they should bind to the lutropin/choriogonadotropin receptor. This receptor is a member of the G- protein coupled receptors. Ligand binding to the

receptor mainly activates adenyl cyclase[94]. At high temperatures, stimulation of adenyl cyclase via the lutropin/choriogonadotropin receptor is inhibited[95]. Furthermore, an inhibitory effect upon adenyl cyclase is exerted at higher temperatures[88]. Since the stimulation of adenyl cyclase is already less in boys with undescended testis, the proposed pathway explains the variations in response to hormones according to the location of a testis.

On the other hand, the non-genomic effects of testosterone are exerted through the G-protein coupled receptors. Testosterone binding to those receptors activates PLC[96], thus augmenting the already predominating pathway of signaling that causes problems in boys with undescended testis.

Gonadotropin-releasing hormone (GnRH) or hCG administration before surgery in boys with undescended testis has been reported to decrease the number of spermatogonia per tubule[97]. Since those hormones may actually inhibit adenyl cyclase activity at higher temperatures, the described pathway helps in understanding the effects of the hormones on an undescended testis.

Concluding remarks

The gubernaculum gives rise to both smooth and striated muscles. The testis descends through the processus vaginalis via the physical force generated by the propulsive activity of those muscles under the control of the sexually dimorphic autonomic nervous system. The diminution of smooth muscle content, and alteration of contractile properties through a decrease in sympathetic tonus that involves a decrease in the number o sympathetic fibers, causing a relative increase in para-sympathetic tonus, impair the intra-scrotal localization of a testis. The alterations in signal transduction provide a basis for blunting of testosterone response to hCG and decrease in fertility, and for increase in the risk of malignancy.

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