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The possible role of AMH in shortening the gubernacular cord in testicular descent: A reappraisal of the evidence

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ABSTRACT

Background/Aim: Anti-Müllerian hormone (AMH), also called Müllerian inhibiting substance (MIS), is glycoprotein hormone secreted by the fetal Sertoli cells to regulate regression of the Müllerian ducts, the anlagen of the uterus, fallopian tubes, and upper vagina. After its existence was predicted in 1946 and its isolation and purification in the 1970's, a huge amount of information has been gathered on its molecular biology and function in the last 30–40 years. Once thought to be a locally acting factor in the male fetus during sexual differentiation, it is now recognized as an endocrine hormone present in both sexes and with functions throughout life. One of the remaining controversies is the possible role of AMH during fetal testicular descent. In the human with aberrant AMH function, the boy has cryptorchidism with persistent Müllerian duct syndrome (PMDS), where the testes are often intraabdominal and on an abnormally long gubernacular cord. By contrast, in rodent models knockout of the AMH gene does not cause cryptorchidism.
Methods/Results: In this review we examined the evidence in the literature for and against a role for AMH in testicular descent and considered the implications of the different anatomy of the gubernacular cord in rodents versus children.
Conclusion: We conclude that AMH may have a role in shortening the gubernacular cord in humans which is concealed in rodent models by differences in anatomy of the gubernacular cord in rodents. The controversy could be resolved by re-examination of the gubernacular cord in boys with PMDS and mice with AMHKO.
Type of study: Review.
Level of evidence: V

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Anti-Müllerian hormone (AMH, also known as Müllerian inhibiting substance, MIS) was first proposed to exist in 1946 by Alfred Jost in a series of experiments in which he grafted fetal testis into rabbit fetuses [1–3]. AMH was found to cause regression of the Müllerian duct, the anlage of the fallopian tube, uterus and upper vagina. After a bioassay was developed in 1969 [4], there was rapid progression in purification and ultimate biochemical identification of AMH as well as advances in its biological functions [5], such as its possible role in testicular descent [6], which remains controversial.

In this study we have reviewed the literature about AMH, testicular descent in humans and rodents, the human with persistent Müllerian duct syndrome (PMDS) and the mouse with AMH knockout (AMHKO) to investigate the possible reasons for differences in anatomy of PMDS and AMHKO in rodents.

1. Materials and methods

A literature review was undertaken of the English and Spanish literature from the 1940's to the present, searching for articles about AMH, MIS, testicular descent, cryptorchidism, PMDS and AMHKO. Databases searched included PubMed, Medline, Web of Science and Google Scholar. Many of the initial references on AMH are in French, and were available to the authors already, so formal review of the French literature was considered unnecessary. The initial search revealed 3182 articles

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about AMH, 371 on MIS, 268 on PMDS and 54 on AMHKO. Recent publications on the role of AMH in the adult ovary were excluded.

2. Results

Initially AMH was thought to be just a locally acting factor in the male fetus, causing regression of the adjacent Müllerian duct [7], but found to be in both testis and ovary in the chick embryo and mature birds [8]. However, it was recognized in the chicken that not only was AMH present in the embryonic ovary as well as the embryonic testis, but also that it was measurable in both gonads after hatching [8]. Once the possibility of postnatal production was appreciated, it was quickly found to be present in the mammalian postnatal testis as well as the ovary. Also, recent research has shown that it has an important role in the ovulatory cycle in women, and can be used as a marker for ovarian function [9,10].

The role of hormones in testicular descent has been studied extensively, and current research has demonstrated that different hormones control the two morphological stages (see below). Animal models of androgen blockade with cyproterone acetate (CPA) demonstrated that testicular descent in rodents from the initial embryonic position down to the bladder neck was inhibited only a slight degree, consistent with another hormone being involved [11]. AMH was initially suggested as the possible hormone causing the first phase of testicular descent when the biphasic model of testicular descent was proposed [6,12,13]. This was based on the fact that in humans with persistent Müllerian duct syndrome (PMDS) [14–16], the Müllerian ducts were preserved and the testes were in the same position as the ovaries.

With the proposal of a biphasic model of testicular descent and the genito-inguinal ligament, or gubernaculum, as the primary structure controlling the process, AMH was considered a likely candidate to stimulate the swelling reaction in the gubernaculum until the discovery that insulin-like hormone 3 (INSL3) was the hormone controlling enlargement of the rodent gubernaculum [17,18]. Further evidence against a role for AMH in the first phase of descent was the development of the AMH knockout mouse, which had descended testes [19]. In addition, a female rabbit immunized against purified bovine AMH had 9 out of 12 male offspring with persistent Müllerian ducts, but all had normally descended testes [20].

INSL3 has been shown to control growth of the gubernaculum in the swelling reaction, which requires deposition of glycosaminoglycans [18,21]. In addition INSL3 has been suggested to enhance mesenchymal cell differentiation towards myogenesis of the cremaster muscle within the gubernaculum as part of inguinoscrotal descent [22]. In vitro studies of the rat gubernaculum, however, have suggested that both testosterone and AMH might augment the role of INSL3 in gubernacular growth [23]. This suggests that AMH may have subtle effects on the gubernaculum in the rodent [19], and leaves open the question of what controls shortening of the gubernacular cord in rodent models and humans.

A key issue in the controversy about whether AMH has any role in shortening the gubernacular cord and the first phase of descent remains the difference in anatomy between AMH knockout in the mouse and PMDS in human [24]. Despite the fact that in both species there is a single genetic defect (albeit one natural versus the other man-made) leading to loss of AMH function, the resulting anatomy is profoundly different (see below). To understand the reason for these anatomical differences when AMH function is disrupted, we need to look at the species differences between rodents and humans [25].

3. Normal anatomy

The anatomy of the genital tracts and gonad varies across mammalian species [26]. Gonadal position depends on the relative traction of the cranial suspensory ligament (CSL) versus the gubernaculum as well as the development of the genital ducts, particularly the Müllerian ducts, which form the fallopian tubes, uterus and upper vagina in females. The mesenchyme of the urogenital ridge persists after regression of the mesonephros in the female to form the broad ligament. Also, species differences in Müllerian duct fusion to form the uterus and in the broad ligament lead to significant differences in the final position of the ovary [27]. The different anatomy of the female genital tract between humans and rodents is associated with major differences in the gonadal ligaments, the CSL and gubernaculum (Fig. 1). In the rodent, the ovary is behind the lower pole of the kidneys, with the substantial CSL anchoring it on a short mesentery to the posterior abdominal wall. The female gubernaculum forms the ligament of the ovary and the round ligament, which take an almost straight pathway from the lower pole of the kidney to the uterus and on to the internal inguinal ring, to terminate just beyond the external ring [28]. By contrast, the human T-shaped genital tract is very different in shape from the V-shaped rodent uterus, which is associated with the ovary behind and very close to the internal inguinal ring, rather than adjacent to the kidney [29]. The female gubernaculum in the human takes a zigzag pathway to the inguinal canal, first passing medially as the ligament of the ovary to the uterus, and then laterally again as the round ligament to the internal ring [29], although whether the ligament of the ovary is part of the gubernaculum is disputed by some authors [30]. The CSL is vestigial in the human, while in the rodent it is a definite structure.

Not only is the female gubernaculum in the rodent different from the human but so is the male gubernaculum (Fig. 2). In both species transabdominal descent occurs by a swelling reaction in the gubernaculum to create the gubernacular bulb, under INSL3 control. However, the proximal attachment of the bulb to the gonad and epididymis forms an elongated gubernacular cord in the rodent. This is important because, during the inguinoscrotal phase when the gubernacular bulb migrates to the scrotum, the long cord enables the testis to remain in the lower abdomen or inside the inguinal canal until it finally descends at puberty. By contrast, in the human the gubernacular cord is absorbed into the bulb in mid gestation, so that the testis and epididymis become intimately attached to the inside of the bulb (within the PV), and the gubernaculum and testis can descend in concert to the scrotum (Fig. 2). At 19 weeks' gestation in the fetus the gubernacular cord is still long, similar to that of the rodent [31]. At the completion of the inguinoscrotal phase, but before the proximal PV closes, the main difference between humans and rodents is in the gubernacular cord, which is incredibly short in the human compared to the rodent.

4. Abnormal anatomy when AMH function is deficient

In the AMHKO mouse the testes descend normally, consistent with a normal (or near-normal) swelling reaction in the gubernaculum [32] controlled by Insl3 [17,18], and normal inguinoscrotal migration of the gubernaculum. The gubernacular cord remains long, but there are no reported measurements of its length to see whether it is the same or longer than normal. The Müllerian ducts are preserved to produce an infantile uterus in the absence of gonadal estrogens. In addition, the presence of normal testicular androgens has produced regression of the cranial suspensory ligament, as well as normal inguinoscrotal descent.

The anatomy of the genital tract in humans with PMDS [33–39] is quite different from the mouse model, as all affected males present with cryptorchidism, either bilateral intraabdominal testes (~70%) or unilateral cryptorchidism (~30%) (Fig. 3) [24]. In the latter case there is either an undescended testis with an adjacent fallopian tube (known as 'hernia uteri inguinalis') or transverse testicular ectopia (TTE), where the testis (with its adjacent fallopian tube) has descended into the contralateral inguinal canal. The contralateral testis may be inguinal or scrotal, but if the ectopic cryptorchid testis is pulled, the descended testis can be pulled back into the abdominal cavity as the gubernacular cord is often 5–10 cm in length rather than the normal length of <1/2 cm.

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