General and Comparative Endocrinology 223 (2015) 87–107

Contents lists available at ScienceDirect

General and Comparative Endocrinology

journal homepage: www.elsevier.com/locate/ygcen

Review

The role of Amh signaling in teleost fish – Multiple functions not restricted to the gonads

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ARTICLE INFO

Article history:
Received 17 June 2015
Revised 24 September 2015
Accepted 25 September 2015
Available online 30 September 2015

Keywords:
Amh
AmhrII
Fish
Brain–pituitary–gonadal axis (BPG-axis)
Fsh
Spermatogenesis

ABSTRACT

This review summarizes the important role of Anti-Müllerian hormone (Amh) during gonad development in fishes. This Tgfβ-domain bearing hormone was named after one of its known functions, the induction of the regression of Müllerian ducts in male mammalian embryos. Later in development it is involved in male and female gonad differentiation and extragonadal expression has been reported in mammals as well. Teleosts lack Müllerian ducts, but they have *amh* orthologous genes. *amh* expression is reported from 21 fish species and possible regulatory interactions with further factors like sex steroids and gonadotropic hormones are discussed. The gonadotropin Fsh inhibits *amh* expression in all fish species studied. Sex steroids show no consistent influence on *amh* expression. Amh is produced in male Sertoli cells and female granulosa cells and inhibits germ cell proliferation and differentiation as well as steroidogenesis in both sexes. Therefore, Amh might be a central player in gonad development and a target of gonadotropic Fsh. Furthermore, there is evidence that an Amh-type II receptor is involved in germ cell regulation. Amh and its corresponding type II receptor are also present in brain and pituitary, at least in some teleosts, indicating additional roles of Amh effects in the brain–pituitary–gonadal axis. Unraveling Amh signaling is important in stem cell research and for reproduction as well as for aquaculture and in environmental science.

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1. Introduction

The presence of Müllerian ducts is a characteristic feature of the female urogenital system in tetrapod vertebrates. The German physiologist Johannes Peter Müller described the development of the gonads in several vertebrates and he concluded that different tissues give rise to the different ducts of the genital systems in male and female (Müller, 1830). An inhibitor that promotes the regression of the Müllerian duct in male embryos was postulated and later discovered by the French endocrinologist Alfred Jost in 1953. This factor was named Anti-Müllerian hormone (Amh) or Müllerian inhibiting substance (Mis) (Jost, 1953; Josso, 2008).

Amh is mainly known for its function during the regression of Müllerian ducts in tetrapod male embryos but during the last three decades it became apparent that Amh has multiple effects in gonad development and gametogenesis. Already Alfred Jost postulated the involvement of Amh in the control of germ cell maturation (Jost, 1972). Recent evidence showed that Amh prevents the continuation of the first meiotic phase in germ cells of both sexes and that meiotic germline cells give a negative feedback on somatic Amh expression in mammals (Lee and Donahoe, 1993; Rey et al., 2003). Furthermore, Amh over-exposition leads to a loss of germ cells and inhibits steroidogenesis and postnatal Leydig cell development (Behringer et al., 1990; Racine et al., 1998; Teixeira et al., 2001; Josso and di Clemente, 2003; Rey et al., 2003).

Amh belongs to the Bmp group of the Tgfβ superfamily of growth factors (Massague et al., 2005). Tgfβ ligands are key regulators of cell proliferation, differentiation, apoptosis and migration. The active ligand is generated by processing of the conserved C-terminal part of the protein and binds as a dimer to dimers of type I- and type II receptors. Several phosphorylations lead to an activated receptor complex which provokes Smad activation and dimerization in the cytoplasm. The Smad transcription factor complex becomes trans-located to the nucleus and activates or represses the expression of target genes (Schmierer and Hill, 2007; di Clemente et al., 2010). Non-Smad mediated signal transductions and ligand-independent effects were also reported. This indicates that several downstream mechanisms exist (Moustakas and Heldin, 2009; Kang et al., 2009).

The sources of Amh in mammals are Sertoli cells until puberty in males and granulosa cells of early follicles in females. The specific Amh-type II receptor is located on Sertoli cells and Leydig cells in testes or theca cells and granulosa cells in ovaries (di Clemente

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http://dx.doi.org/10.1016/j.ygcen.2015.09.025
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and Belville, 2006). This indicates that Amh acts in an autocrine and/or paracrine manner. Amh level in postnatal life is controlled by follicle-stimulating hormone (Fsh) and androgens. In males Fsh has a stimulating effect on Amh secretion whereas androgens repress Amh expression (Rey et al., 2003; Grinspon and Rey, 2010). In ovaries current models suggest inhibition of Amh expression by estrogens, whereas Fsh switches from an Amh inducer in early follicles to an inhibitor in later stages of folliculogenesis (La Marca et al., 2009; Monniaux et al., 2013). The serum Amh level became a well-established marker for Fsh and androgen activity in the testis and a diagnostic endocrine marker for ovarian function in mammals (Grinspon and Rey, 2010; La Marca et al., 2010). Many aspects about the physiological role of Amh in ovary and testis remain speculative and need further investigation.

Teleost fish have no Müllerian ducts but they have *amh* orthologs. The first *amh* ortholog in teleosts was identified in the Japanese eel in 2002. The authors showed that eSRS21 (Eel Spermatogenesis Related Substance; synonymous with Amh and Mis) is expressed in Sertoli cells and is involved in the control of germ cell development (Miura et al., 2002). Thirteen years later several *amh* genes and a few of *amh*-type II receptor genes (*amhrII*) are known and their expression patterns analyzed. In this review we outline the different *amh* expression patterns and functions in fish – the largest and most divergent vertebrate group with formidable plasticity in sex differentiation and sex determination mechanisms (Devlin and Nagahama, 2002; Schartl, 2004; Volff, 2005; Baroiller et al., 2009a; Schulz et al., 2010; Heule et al., 2014).

2. Expression patterns of *amh* and *amhrII* in teleost fish

2.1. amh gene structure and alternatively spliced transcripts

amh appears as a single copy gene in vertebrates from the data analyzed so far, although one may expect additional copies in teleosts as a result of the fish-specific genome duplication (Meyer and Schartl, 1999; Volff, 2005). Duplicated *amh* genes were discovered for the Patagonian pejerrey, the pejerrey and the Nile tilapia only (Hattori et al., 2012; Yamamoto et al., 2014; Eshel et al., 2014; respectively). In the first two species the second copy (*amhY*) has acquired a role in sex determination (see Section 3.5.). The *amh* gene in teleosts consists of 7 exons except rainbow trout *amh* with 6 exons. It encodes for proteins from about 500 amino acids up to 571 amino acids. Human and mouse proteins are in the same range with 554 amino acids and 560 amino acids, whereas Amh from chicken is a bit larger with 644 amino acids. Mammalian and bird Amh proteins are encoded by 5 exons. The additional exons in most fishes are caused by insertion of intronic sequences into 2 exons corresponding to exons 1 and 5 of mammalian and bird *amh*. As a result, two more exons (exons 2 and 7) are generated in fish but the intron positions in general are conserved (Rodriguez-Mari et al., 2005; Halm et al., 2007; Kluver et al., 2007; Jamin et al., 2008; Poonlaphdecha et al., 2011; Hattori et al., 2012). In line with the conserved gene structure, the vertebrate *amh* genes are part of a conserved syntenic cluster. Interestingly, the neighboring genes are involved in reproduction and cell cycling (Rodriguez-Mari et al., 2005; Paibomesai et al., 2010). The deduced protein sequences of fish *amh* show the characteristic Tgfβ-domain at the C-terminus (encoded by the last exon) and an N-terminal Amh-domain, which is typical for the Amh protein family (Fig. 1). The Tgfβ-domain of fish Amh shows sequence homologies from 50% in phylogenetically distant groups to 98% in closely related species (Poonlaphdecha et al., 2011). The identity between the Tgfβ-domains in fish and mammalian Amh sequences is about 40%. The N-terminal Amh-domain is less conserved and shows only 20% identity between fish and mammals. Phylogenetic analysis reveals that fish Amh proteins are grouped together in a distinct clade (e.g. Poonlaphdecha et al., 2011). Common features include an N-terminal leader sequence and a plasmin protease cleavage site (R-X-X-R) immediate upstream to the Tgfβ-domain which is necessary for processing of the Amh ligand. Such typical protease recognition sites are predicted in all fish sequences as a double motif (R-X-X-R-X-X-R) except the Japanese flounder with only one protease cleavage motif (Yoshinaga et al., 2004). The protease cleavage sites indicate processing of fish Amh to be similar to mammalian Amh. Furthermore, all of the cysteine residues of the Tgfβ-domain and two further cysteine residues in the remaining protein are conserved (e.g. Poonlaphdecha et al., 2011). Since Amh is a glycoprotein in mammals (Rey et al., 2003), glycosylation sites are expected in fish Amh sequences as well. But information about glycosylation of fish Amh is limited and the only relevant study reveals that Amh in zebrafish testis is not glycosylated (Skaar et al., 2011).

Gene expression analyses by reverse transcription (RT)-PCR often use primer pairs which amplify short gene fragments only. Especially in quantitative RT-PCR experiments commonly short amplicons are preferred. Therefore, expression analysis with selected primer pairs may fail to detect alternatively spliced transcripts. Alternative splicing, however, is a common mechanism, especially in the gonads, to regulate gene activity and function (Blencowe, 2006; Elliott and Grellscheid, 2006). Therefore, cloning and amplification of larger gene fragments is needed. In medaka *amh* we detected intron retention for all introns to different extent and in different variations but no other kind of alternative splicing (Pfennig et al., unpublished result). The presence of a potential antisense transcript was ruled out by specific, opposite-orientated PCR controls as established for the medaka *tert* gene (Pfennig et al., 2008). In all cases of intron retention premature stop codons cause the formation of a truncated Amh protein which lacks the conserved Tgfβ-domain encoded by exon 7. Mostly introns 1 and/or 5 remain in the partially spliced *amh* transcripts (see Fig. 1 for gene structure). The mis-splicing occurs during the whole course of development in both sexes. Correctly spliced transcripts were found mainly in adult testes. Interestingly, in females (around hatching) and males (29–39 days after hatching (dah)) the percentage of the *amh* variant with the retention of intron 5 was highly elevated (own unpublished results). This is remarkable because at these developmental time points also meiosis starts in females and males, respectively, as indicated by *scp3* (synaptonemal complex protein 3) expression (Kluver et al., 2007; Kanamori et al., 2008).

Alternatively spliced *amh* variants were also reported for two other fish species, the European sea bass and the Atlantic salmon (Halm et al., 2007; von Schalburg et al., 2011). Here, alternative splice sites lead to transcripts that encode truncated proteins lacking the Tgfβ-domain. Whereas in the European sea bass and medaka the correctly spliced variant is dominant or amounts to 50% of all transcripts (Halm et al., 2007; Pfennig et al., unpublished data), in the Atlantic salmon only very low levels of a Tgfβ-domain coding transcript variant can be found in adult testis and ovary (von Schalburg et al., 2011). Interestingly, Halm et al. (2007) showed a sex-specific elevation of one of the truncated variants in adult ovaries of the European sea bass.

For both the European sea bass and the Atlantic salmon, *amh* expression and alternative splicing of *amh* transcripts were also observed in the brain (Table 1, Section 2.2.8.) and other extragonadal tissues (Halm et al., 2007; von Schalburg et al., 2011). This indicates an extragonadal role of Amh. The detection of *amh* in the heart of European sea bass even suggests a function of Amh apart from reproduction, and this also holds true for a putative role of Amh as a regulator of the cardiovascular system of humans and mice (Dennis et al., 2013). Unlike fishes, alternatively spliced *amh*

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