INVITED COMMENTARY

Variations on a theme: testis-derived neuropeptide hormones

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The article by Untergasser et al. in this issue describes a novel growth hormone variant (GH-V) transcript in the testis (1). GH-V is a product of the growth hormone (GH) gene family, a 50 kb cluster of five highly conserved genes. These genes are 91–99% identical to each other and are located on human chromosome 17 (2). In 5′-3′ order these genes are: GH-normal (GH-N), placental lactogen-like (PL-L), placental lactogen A (PL-A), GH-V, and PL-B. This gene locus evolved from a common ancestral gene about ten million years ago, most likely by a series of three sequential gene duplications (2). Except for PL-L, each of the other genes in this family produces a 217 amino acid prohormone that is cleaved to a mature 191 amino acid hormone. In the human testis, the five genes of the GH cluster are all expressed at different levels (PL-A/PL-B > GH-V > GH-N) (3). The functional roles of their peptide products and the importance of the quantitative differences in peptide production remain to be determined.

The GH-N gene is the predominant family member expressed in the anterior pituitary and yields a major 22 kDa GH product, a minor 20 kDa product, and several post-translational variants. PL-A and PL-B are primarily expressed in the placenta. Both encode human placental lactogen (hPL). Produced in massive amounts by syncytiotrophoblastic cells, hPL is similar in structure to GH but has, on an equimolar basis, only 0.5% of the affinity for the GH receptor (4). Although the PL-L gene was initially considered to be a pseudogene, multiple mRNA transcripts have been identified (5). However, the PL-L protein products are believed to be nonfunctional.

Like PL-L, the GH-V gene was originally categorized as a pseudogene, but it is now known that the gene is transcribed and translated. The product, designated GH variant (GH-V), differs from GH by 13 amino acids and is continuously secreted during the second half of pregnancy by the placenta (6). In the placenta, GH-V isoforms arise from at least four alternatively spliced mRNAs (7). Placental GH-V accounts for the majority of immunoactive growth hormone detected in the maternal circulation in the latter part of human pregnancy. At the same time, maternal pituitary GH-N production is suppressed (8). In vitro, GH-V is a potent GH analog, which binds to both GH and prolactin receptors. GH-V has equivalent mitogenic bioactivity to GH-N, but significantly less lactogenic activity. It has been postulated that its role during pregnancy is to optimize maternal transfer of nutrients to the fetus.

The testis appears to have an exquisitely interwoven intratesticular network of hormonal regulators. It represents a specialized arena for these proteins to function in a paracrine manner since it provides an inner tubular compartment which is anatomically isolated from the rest of the body by the blood–testis barrier. The testis also undergoes dramatic changes during its lifetime – both the one-time maturation to puberty and the daily cycles of spermatogenesis. Paracrine factors probably undergo differential developmental expression as they regulate the processes of spermatogenesis and spermiogenesis.

The Leydig, peritubular, and Sertoli cells of the testis provide the milieu essential for germ cell development and steroidogenesis. Testosterone, which is synthesized and secreted by Leydig cells, serves as the primary paracrine stimulus of germ cell development. Its actions are aided by a variety of peptide hormones and growth factors. Many of these are eutopically produced by the testis and are involved in paracrine, autocrine, and/or juxtacrine processes.

The list of neuroendocrine hormones and growth factors that are produced by the testis continues to grow. In addition to the GH gene products, it includes growth hormone releasing hormone (GHRH), pituitary adenylate cyclase activating peptide, gonadotropin releasing hormone, corticotropin-releasing hormone, oxytocin, arginine vasopressin, thyrotropin releasing hormone, substance P, neuropeptide Y, insulin-like growth factors (IGFs), transforming growth factor-β (TGF-β), fibroblast growth factor, and platelet derived growth factor (PDGF) (9). In the testis, most compounds are transcribed and translated in a manner identical to that identified in other tissues, such as the hypothalamus and pituitary. Some, intriguingly, are produced from testis-specific mRNA transcripts which arise from alternative splicing, while others undergo testis-specific post-translational modifications. This unique processing may occur due to the presence of testis-specific processing enzymes. It has been shown that the three known forms of the pro-
protein convertase-4 have a unique testicular-restricted distribution (10).

The testicular GH-V variants, GH-V and GH-V2, were previously described by Untergasser et al. in 1997 (3). This same group has now demonstrated an additional testicular transcript, GH-VΔ4, whose function is unknown (1). Untergasser et al. speculate that its translated protein may be a chimera composed of the GH-V cytokine portion and a cystine-knot structural motif. Cystine-knots are found in a number of small proteins – including nerve growth factor, PDGF, TGF-β, and human chorionic gonadotropin – and are often associated with dimer formation (11).

The presence of multiple transcripts of the same gene resulting in proteins with slightly different structures implies that there may be divergent biological activities for each translated protein. Variant products often have different patterns and affinities for receptor binding, providing a means to lend physiological complexity to a single gene’s expression.

When considering the function of such novel GH gene transcripts, it is appealing to contemplate an intra-testicular GH axis, since all components of this axis (GHRH, GH, IGF-I and IGF binding proteins [IGFBP]) are produced locally. The presence of testis-specific forms of the components of the axis suggests unique testicular functions. These hormones may function by mechanisms which are independent of one another, or may function in different positions within a hierarchical cascade of action. To date, however, there is no concrete evidence for interaction between the individual factors and thus no proof that an intratesticular GHRH–GH–IGF-I–IGFBP axis exists.

Elucidation of this exciting field continues. Transgenic and knockout animals are being developed for several of these testis-associated factors. These animal models will help us determine the roles of testicular-produced products. Ultimately, these investigations will improve our scientific understanding of spermatogenesis and may eventually guide us towards targeted approaches for the treatment of male infertility.

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References