INVITED COMMENTARY

Mutations of the G protein-coupled receptors of the hypothalamic–pituitary–gonadal axis. Where do we stand?

Manuela Simoni

Institute of Reproductive Medicine of the University, Domagkstr. 11, 48129 Münster, Germany

Gonadal function is controlled by the two gonadotropins luteinizing hormone (LH) and follicle-stimulating hormone (FSH), produced by the pituitary gland under regulation of the hypothalamic hormone gonadotropin-releasing hormone (GnRH). LH, FSH and GnRH act through binding to specific receptors, which are members of the G protein-coupled receptor family. In recent years, it has become evident that germline mutations of the gonadotropin and GnRH receptors are involved in some forms of hypogonadism and pathologic pubertal maturation. Moreover, as these hormones have tropic and growth-promoting roles in their target organ, it has been hypothesized that somatic activating mutation of their receptors might be involved in the generation of gonadal and pituitary tumors. This hypothesis is further supported by the relatively frequent finding of activating mutations of the closely related thyroid-stimulating hormone (TSH) receptor in hyperfunctioning thyroid adenomas.

The clinical manifestations of genomic mutations of the gonadotropin receptors have been reviewed recently and special emphasis has been given to the possibility that such mutations could be much more frequent than suspected and discovered so far (1–3). However, the search for mutations of G protein-coupled receptors of the gonadotropic axis has been much less rewarding than the analogous exercise in the thyroid field. At this stage, one wonders whether the phenotypes associated with such mutations, especially gain-of-function mutations, have been correctly postulated.

The clinical picture associated with inactivating mutations of the gonadotropin receptors is obvious and consists essentially of hypergonadotropic hypogonadism, resulting in primary amenorrhea (in cases of both LH and FSH receptor mutations) in females and Leydig cell hypoplasia with pseudohermaphroditism (LH receptor) and variable suppression of fertility (FSH receptor) in males. Recently, inactivating mutations of the GnRH receptor gene have been described in cases of hypogonadotropic hypogonadism (4, 5).

Activating mutations are more subtle. Whereas constitutive LH receptor activation is found in familial and sporadic cases of male-limited pseudoprecocious puberty (testotoxicosis), the only known activating mutation of the FSH receptor was found in a hypophysectomized patient with normal spermatogenesis in spite of undetectable serum gonadotropin concentrations (6). It is noteworthy that activating mutations of the LH receptor do not produce a phenotype in females. This lack of phenotype is puzzling, because transgenic mice overexpressing a highly bioactive LH analog have cycle irregularities and develop polycystic ovaries and ovarian tumors, and the males have subfertility and reduced testicular volume (7), whereas symptoms of LH receptor hyperactivation cease after puberty in boys with testotoxicosis. The effect of constitutive activation is even more veiled in the case of the FSH receptor, and the still unique case of a naturally occurring mutation of this type was discovered only because of the fortuitous coincidence of hypophysectomy. Ever since that discovery, many efforts have been devoted to the search for other cases of activating FSH receptor mutations, but the possible phenotype remains obscure. We and others have screened several potential candidates for a chronic FSH-like hyperactivity, such as boys and men with megalotestis, women with familial tendency to produce twins and triplets, and women with premature ovarian exhaustion. In no case could activating mutations of the FSH receptor be demonstrated. Thus, considering that activating mutations of the LH receptor have no phenotype in women and in men after puberty, it seems that gain-of-function mutations of both gonadotropin receptors are basically clinically irrelevant and escape diagnosis. Why?

Continuous exposure to hormone stimulation leads to a decreased response, a process known as desensitization. In vitro, Leydig cells, granulosas cells and Sertoli cells progressively lose the capacity to respond to sustained gonadotropin stimulation. This process of receptor loss (down-regulation) is the consequence of both phosphorylation and sequestration of the hormone receptor complexes within the cell and reduced receptor protein synthesis as a result of decreased transcription, reduced mRNA half-life, or both (8). In this way, the cell defends itself from potentially dangerous hyperstimulation and responsivity to the hormone is tightly regulated. There are no in vivo data on the down-regulation of constitutively active gonadotropin receptors, but transgenic mice, in which a constitutively active
stimulatory G-protein, αs, was targeted to the pancreas β cells, did not show any peculiar phenotype unless the animals were treated with a phosphodiesterase inhibitor (9). This in vivo model suggests that the organism might protect itself against chronic cAMP hypersecretion by accelerating the degradation of cAMP and, possibly, decreasing the expression of the receptors at the cell surface. If that is true, one would expect that, possibly decreasing the expression of the receptors at the cell surface. If that is true, one would expect that, in vivo, a constitutively active receptor is down-regulated with little clinical consequence. The exception of testotoxicosis might indicate that LH receptor down-regulation is not fully mature in prepubertal children, or that it requires the presence of LH, or both. Moreover, the maturation of the feedback control mechanism at puberty prevents hypersecretion of testosterone beyond the normal range in adults. The production of transgenic mice with constitutively active gonadotropin receptors will help to clarify this possibility.

The situation differs in the case of somatic mutations. After the demonstration that gain-of-function mutations of the α1a adrenergic receptor induce transformation in NIH 3T3 cells, suggesting the oncogenic potential of G protein-coupled receptors, somatic activating mutations of the TSH receptor were found in hyperfunctioning thyroid adenomas (10), although their oncogenic properties have not been tested in a fibroblast transformation assay. Indeed, a closer look into the adenyl cyclase activity of thyroid adenoma tissues with and without TSH receptor mutations suggests that tumor formation might require other factors besides TSH receptor mutations (11). Nevertheless, several receptors coupled to various G proteins have transforming capacity in NIH 3T3 cells, although in most cases receptors are oncogenic in vitro only in the presence of the agonist and functional activation of Ras (12, 13).

Are activating mutations of the G protein-coupled receptors of the pituitary gonadal axis involved in tumorigenesis? We and others (14) have found no evidence of FSH receptor mutations in specimens of granulosa cell tumors. Children with testotoxicosis have not yet been known to develop testicular tumors, although they should be kept under observation after puberty, as the further evolution of this condition remains essentially unknown. Similarly, the paper by Chanson et al. in this issue of European Journal of Endocrinology (15) suggests that activating mutations of the GnRH receptor gene are also not common in pituitary gonadotrope adenomas, although their existence would reasonably have been predicted. The GnRH receptor is coupled to Gq. The constitutive activation of the pathway dependent on Gq has been shown to be oncogenic in some transformation assays and the oncogenic role of Gαs in GH secreting tumors has been well demonstrated (12). In contrast, the lack of mutations of the GnRH receptor in gonadotrope adenomas corresponds to similar data showing lack of mutations of the TRH receptor and of the GHRH receptor in pituitary tumors deriving from thyrotropin- and GH-secreting cells respectively. This might indicate that chronic hyperactivation of the G protein signaling pathway is tumorigenic only when the defect originates beyond the receptor, possibly because, as suggested before, the cell has the potential to turn off the activated receptor. The current state of knowledge suggests that the G protein-coupled receptors do not have a pathogenetic role in the development of tumors, with the possible exception of a subset of thyroid adenomas.

After the first enthusiastic phase of discovery of gonadotropin receptor mutations, a certain state of frustration has set in. Instead of trying to guess the phenotypes, it would probably be better to go back to the laboratory and look inside the cell. We need stable and appropriate cell lines bearing the receptor mutations, and we need to study their long-term effects both in vitro and in vivo. The future might hold surprises.

References


Received 4 May 1998
Accepted 5 May 1998