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Growth hormone (GH) and reproduction: a review

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Résumé

Les interactions entre les fonctions de croissance et de reproduction mises en évidence chez de nombreux vertébrés, sont particulièrement aigües à certaines étapes du cycle vital des poissons. Nous décrivons les interactions endocrines existant entre les axes somatope et gonadotrope en insistant sur le rôle joué par l'hormone de croissance (GH). L'analyse comparée de ces phénomènes chez les mammifères, les poissons et les amphibiens permet de suggérer que la GH joue un rôle spécifique dans la physiologie de la puberté, la gamétogénèse et la fertilité. Nous mettons en évidence l'apport original des études effectuées sur le modèle poisson dans ce champ d'investigation.

Abstract

Interaction between growth and reproduction occurs in many vertebrates and is particularly obvious at certain stages of the life cycle in fish. Endocrine interactions between the gonadotropic axis and the somatotropic axis are described, the potential role of GH being emphasised. A comparative analysis of these phenomena in mammals, amphibians and fish, suggests a specific role of GH in the physiology of puberty, gametogenesis and fertility. It also shows the original contribution made by studies on the fish model in this field of investigations.

Introduction

Interaction between growth and reproduction occurs in many vertebrates and may be particularly evident at given stages of the life cycle in fish. In salmonids and many other teleostean species, body growth rate during the first months of life is an important parameter influencing the age of first sexual maturity (reviewed by Le Bail 1988). Depending on the species, growth-reproduction relationships can be contradictory or be more or less dependent

on environmental constraints (Stearns and Crandall 1984). Growth rate (and/or nutrition) is also believed to modulate female fecundity (Ivankov 1983; Bagenal 1969) and egg size (Gjerde 1986). In turn, growth is clearly modulated during the reproductive cycle. It is accelerated at the beginning of gametogenesis, then slowed down in maturing and spawning fish as compared to immature animals (Hunt *et al.* 1982; Le Bail 1988). Other aspects of growth-reproduction interaction could concern sex-related growth dimorphism (as de-

scribed in turbot, sea bass, tilapia or catfish for example) or cases of hermaphroditism in which sex inversion seems related to growth parameters.

While the manifestations of these tendencies have been described and often analyzed in terms of energetic costs or of reproductive strategy, the endocrine mechanisms underlying these phenomena have not been investigated to any great extent. Yet manipulation of growth and fertility through genetic engineering of hormones (*e.g.*, GH, GnRH antagonist) or through hormonal treatments are becoming effective, and may have side effects on non-targetted functions. For example, transgenic pigs and mice expressing the human growth hormone (hGH) gene are found to be hypofertile or sterile (Bartke *et al.* 1988; Pursel *et al.* 1989).

For these different basic and applied reasons it is of particular interest and even a matter of urgency, to better understand the interactions between the somatotropic and the gonadotropic endocrine axes.

Numerous endocrine factors linked to growth and metabolism could influence the various events leading to puberty or gamete production – and vice versa –. However, only the potential interactions involving the regulation of GH secretion or GH actions on the gonads will be emphasised in this paper.

Most available data on this subject derives from work on mammals and will be summarized here; nevertheless, in the last years fish provided quite original and complementary information in this field.

Gonadotropic axis interference with GH secretion

1) Steroids

In mammals, data support both a direct effect of sex-steroid hormones on organ growth as well as indirect effects through the modulation of endocrine factors known to be involved in growth. In particular, steroids modulate GH production and contribute to the sex related patterns of pulsatile GH secretion by acting at the pituitary and hypothalamus levels (reviews by Eden *et al.* 1987; Devesa *et al.* 1991).

Exposure to, or deprivation of, specific sex-steroids during the neonatal period cause permanent alteration of GH secretion profiles (Jansson *et al.* 1984, 1985, 1987). The steroid impact is not limited to the early period of imprinting. During establishment of puberty GH pulse amplitude and frequency increase rapidly, coinciding with an increase of nocturnal testosterone levels (Wennink *et al.* 1990). In the adult, steroids have been reported to act on the spontaneous (Carlsson *et al.*; Ho *et al.* 1987) and possibly the GRF-stimulated GH secretion: estradiol (E₂) would tend to reduce and testosterone (T) to enhance GH secretion (Evans 1985; Shulman *et al.* 1987). Moreover, exposure to E₂ can rapidly feminise the male pattern of GH secretion (Painson 1992).

Sex-steroids would act *via* the hypothalamus: T in male and E₂ in female can reverse the decrease of somatostatin (SRIF)-mRNA observed after gonadectomy (Werner *et al.* 1988) and T can stimulate SRIF gene transcription in neurons of the periventricular nucleus in rat (Chowen-Breed 1989). Recent experimental data show that E₂ may control the mode of hypothalamic SRIF signalling to pituitary somatotrophs by inhibiting SRIF release (while T stimulates it) (Painson *et al.* 1991, 1992). E₂ effects could be exerted at the level of catecholamine pathways involved in SRIF control (Devesa *et al.* 1991).

In fish, while the connection between endogenous steroid plasma levels and growth rate remains unclear, a few studies (Hunt *et al.* 1982; Le Bail 1988; Berglund *et al.* 1992) have suggested such a relationship during the reproductive cycle. For example, in salmonids slowly increasing circulating androgen levels were related to accelerated growth, while the rapidly increasing or high androgen levels coincided with low growth rate, even in stages where fish are believed to feed normally. This is in agreement with results obtained during treatment with exogenous steroids: Androgens have the most potent growth promoting effect (reviews by Donaldson *et al.* 1979; Jalabert *et al.* 1982; Higgs *et al.* 1982), even at very low dosage (1 to 10 ng testosterone/g feed, Lewis and Sower 1992). However, these effects are reduced or even reversed when high doses or longer treatments are applied

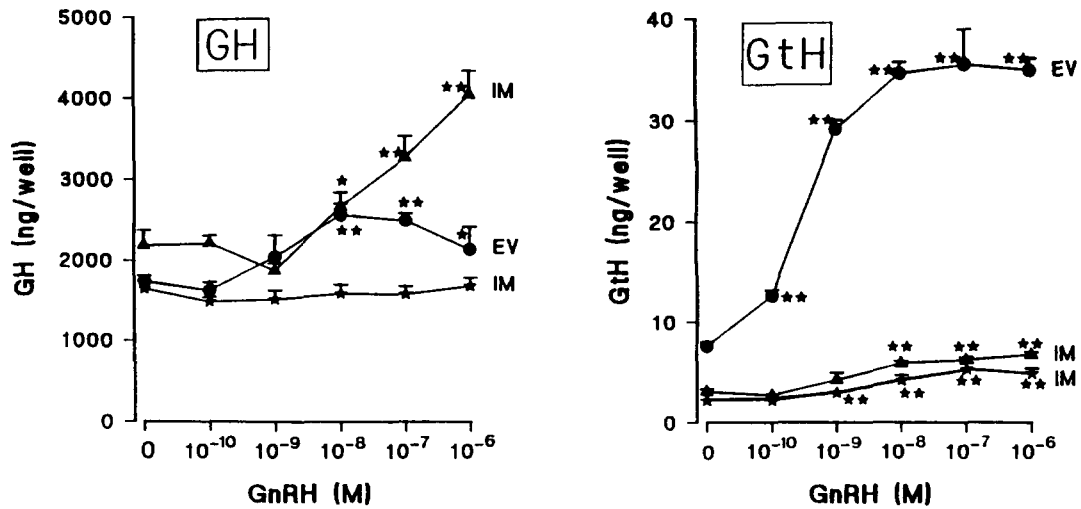


Fig. 1. Gonadotropin releasing hormone (GnRH) stimulation of GH and GtH secretions (ng/well/24hrs) by cultured pituitary cells from immature (IM) and early vitellogenic (EV) female rainbow trout. Cells (62000 cells/well) were precultured for 3 days before a 24h incubation with salmon GnRH. ($X \pm SEM$, $n = 5$ wells, * $p < 0.05\%$; ** $p < 0.01\%$). (Blaise, Weil *et al.* unpublished data).

(Shreck and Fowler 1982; Borghetti *et al.* 1989; Lewis and Sower 1992; Cotten and Le Bail, unpublished data), and they also vary according to the gonadal stage of treated animals (Berglund *et al.* 1992).

To our knowledge, few data suggested that, in fish, these observations could be linked to a modulation of GH secretory profiles by sex-steroids. Using histological methods, ovariectomy was found deleterious to GH cells, estrogen stimulation of the somatotrophs activity was reported (Young and Ball 1979; Olivereau and Olivereau 1979) and activity of plaice pituitary GH cells was shown to be correlated with testis maturity (Power 1992).

Trudeau *et al.* (1992) found that in gonad-intact female goldfish implantation of E_2 -containing silastic capsules (25 to 100 mg/kg; 5 days) stimulated GH serum levels throughout the reproductive cycle (2–4 times control levels) while T (100 mg/kg) had no effect. This *in vivo* E_2 treatment enhanced *in vitro* sGnRH and TRH stimulated GH release. On the other hand, in trout, a single injection of E_2 (10 mg/kg) suppressed GH levels (Björnsson *et al.*, 1992). Treatment of young salmon (smolts) with T implants (1 and 10 mg/kg) was without effect on GH plasma levels during the following 21 days (Le Bail *et al.* unpublished data). However, in these last

two cases the doses used may have been inadequate considering the biphasic response of growth described above. Also, subtle effects on GH pulsatility may be difficult to detect when measuring mean plasma levels.

2. Gonadotropin Releasing Hormone (GnRH)

A different and unexpected regulation of GH by the gonadotropic axis could also be located at the hypothalamo-pituitary level in fish:

GtH and GH releases are known to be controlled by a number of common neuroendocrine factors (*e.g.*, DA, NPY). Furthermore, recent studies in goldfish have shown that GnRH, until now considered to be strictly a gonadotropin releasing hormone, may also function as a GH releasing factor. Treatments with GnRH peptides are capable of increasing GH plasma levels and, *in vitro*, to stimulate GH release from pituitary fragments or dispersed pituitary cells (Marchant *et al.* 1989; Marchant and Peter 1989; Chang *et al.* 1990; Flett *et al.* 1992). Weil and collaborators found that, in trout, GnRH is also able to stimulate GH secretion by cultured pituitary cells obtained from males and females at different sexual stages (Blaise 1991). As illustrated in Fig. 1, the GH response to GnRH is

sometimes lower in amplitude, more variable and less reproducible between experiments than the GtH response. These differences could be due to the high basal GH secretion observed in culture (Fig. 1) in the absence of GH specific hypothalamic negative control by SRIF. A more appropriate culture condition to study GH response to GnRH is under investigation. Furthermore, using trypsin/DNAse dispersed goldfish pituitary cells, Cook *et al.* (1991) found that sGnRH analogues could bind to somatotrophs, thus supporting a direct action of GnRH on GH cells. Jobin and Chang (1992) and Chang *et al.* (1992, this issue) have provided evidence that the signal transduction system is essentially Ca^{++} dependent and differs from that involved in the action of GnRH on GtH secretion. However, one cannot exclude the possibility that GnRH action is also mediated through paracrine regulations in the pituitary. In fact, in the rat, Tilemans *et al.* (1991) reported GnRH modulation of DNA replication in the GH cells that was mediated by growth factors released from the gonadotrophs.

In an elegant study on goldfish, reduced brain GnRH levels have been temporally related to increased GH and GtH serum levels in ovulatory females and in males exposed to ovulating females (Yu *et al.* 1991). These data (together with the following information about GH influences on gonads) support the idea that this dual action of GnRH may be an important feature in the regulation of reproduction.

In mammals, a similar interaction between GnRH and GH secretion has only been shown in pathological cases linked to anorexia (Maeda *et al.* 1976) and acromegalia (Smals *et al.* 1987).

Somatotropic axis interferences with reproduction

Growth hormone influences puberty and gonad development

The prepubertal rise in GH and insulin-like growth factor 1 (IGF-I) could take part in sexual maturation that occurs at that stage in mammals:

In prepubertal female rats, experimental GH deficiency associated with normal growth rate con-

ditions resulted in delayed puberty (Ramaley and Phares 1980). Similarly, GH deficiency, obtained by introducing GH implants in the hypothalamus, induced delayed ovarian maturation linked to decreased LH receptors and a reduced progesterone response to gonadotropin (Advis 1981). Early studies had shown that, *in vivo* in males, restoration of spermatogenesis by androgens after hypophysectomy was enhanced by GH administration (Bocabella 1963) and that GH synergized with LH to increase testosterone secretion (Swerdlow and Odell 1977). Also in hypophysectomized male rats, GH administration is necessary to restore normal LH receptivity (Zipf *et al.* 1978). In contrast, treatment of normal heifers with bovine GH during the prepubertal period delayed the onset of puberty (Murphy *et al.* 1991). GH treatment during several oestrous cycles was without effect on ovulation, but increased the number of developing oocytes per ovary in heifers (Gong *et al.* 1991); GH also increased the concentration of progesterone in the plasma and altered the pattern of LH secretion in lactating cows (Schemm *et al.* 1990).

In dwarf, GH-deficient mice exhibiting delayed testicular maturation, hGH or hIGF-I supplementation induced the maturation of Leydig cell function (Chatelain *et al.* 1991). However, in GH-deficient mutant rats with reduced testicular size, GH treatment had either no effect or even a deleterious effect on testis growth and germ cell development when administered respectively after, or prior to, initiation of spermatogenesis (Skottner *et al.* 1989; Spiteri-Grech *et al.* 1991b, 1992).

In humans, diminished GH secretory capacity has been related to anovulatory dysfunction and to delayed puberty that can be readvanced by GH therapy (Sheikholislan and Stenpfe 1972; Ovesen *et al.* 1992). During the last 3 years, GH therapy has been studied and used with success as an adjuvant to gonadotropin treatment for ovulation induction in assisted human reproduction programs (Homburg *et al.* 1990; Burger *et al.* 1991; Jacobs *et al.* 1991) and one report mentions the induction of complete spermatogenesis in azoospermic patients with a similar therapy (Shoham *et al.* 1992).

Earlier studies in fish implicated GH in gonadal regulation: long term treatment with bovine GH

could enhance restoration of spermatogenesis in synergy with bovine LH in hypophysectomised killifish (Pickford *et al.* 1972) and could slightly accelerate oocyte development in coho salmon (Higgs *et al.* 1976). Ovine GH had a very modest and concentration-independent effect on E₂ and 17 α -hydroxy,20 β -dihydroprogesterone (17 α 20 β OHP) production by salmon vitellogenic ovary *in vitro* (Young *et al.* 1983). However, these observations were done with hormone preparations probably contaminated with LH and FSH.

Later on, high levels of circulating GH were reported in the final stages of the reproductive cycle: During gonadal recrudescence and spawning in goldfish (Marchant and Peter 1986) at the time of ovulation in white sucker (Stacey *et al.* 1984), and during spermiation in trout and Atlantic salmon, but not so clearly in the females (trout: Sumpter *et al.* 1991; Le Gac *et al.* 1991 and salmon: Le Gac, unpublished data). Yu *et al.* (1991) showed synchronised sharp GH surges in ovulatory females and spawning male goldfish. In contrast, Björnsson *et al.* (1992) concluded that GH plasma levels increased in sexually maturing Atlantic salmon 2 months prior to ovulation.

All these findings prompted investigations into the potential role of pure GH preparations on gametogenesis or steroidogenesis as well as the mechanism of GH action.

Evidence for direct gonadal site of action for GH

In mammals, GH strongly accelerates *in vitro* induced differentiation of cultured granulosa cells, as measured by progesterone production and/or aromatase activity. This effect was mainly exerted by an amplification of gonadotropin actions (Jia *et al.* 1986; Hsu and Hammond 1987; Hutchinson *et al.* 1988). In some of these studies the GH effects were mimicked by IGF-I, involved enhanced LH receptor induction, or had a possible influence on cAMP synthesis. Interestingly, stimulation of 20 α -hydroxyprogesterone has also been described (Jia *et al.* 1986).

A small stimulation of progesterone by GH alone was first noted by Hsu and Hammond (1987). More

recently Mason *et al.* (1990) reported a potent stimulatory effect of hGH (10 ng/ml for 48h) on the production of E₂ by human granulosa cells, which was not dependant on FSH action. Similarly, bGH (10 to 1000 ng/ml) significantly increased granulosa cell multiplication and progesterone production after 48h of culture in the presence of insulin stimulation (Spicer and Langhout 1991). Also, GH was found to directly increase progesterone production by human luteal cells *in vitro* (Lanzone 1992).

Finally, GH takes part in the control of ovarian IGF-I production (see below), and may control IGF-II secretion in human granulosa cells (Ramasharma and Li 1987).

Fewer studies have concerned direct effects of GH on mammalian testicular functions. Lawrence and Davies (1977) found that GH stimulated testicular protein synthesis. Tres *et al.* (1986) and Closset *et al.* (1990) found effects of GH on IGF-I production and mRNA expression in testis cells (see below). A stimulatory effect of hGH and IGF-I treatments on testosterone levels and testicular hCG receptors in Snell dwarf mice has been found (Chatelain *et al.* 1991). However, Closset *et al.* (1991) demonstrated that bovine and rat GH (injections of 50 μ g/day for 7 days) had marked effects only on pregnenolone production, testicular IGF-I content and rat Leydig cell multiplication; other effects obtained with human GH (on T, aromatase and LH receptors) probably resulted from the lactogenic properties of this molecule.

While GH receptors have never been characterized in mammalian gonads, low levels of GH receptor/binding protein mRNA have been detected in rat testis (Mathews *et al.* 1989), and GH receptor/binding protein-like immunological activity has been found in a large variety of somatic and germinal cells in testis and ovary (Lobie *et al.* 1990).

With regard to studies in fish, in 1988, Singh *et al.* found that, in hypophysectomised *Fundulus heteroclitus* (killifish), repeated injections of recombinant salmon GH (rsGH) (but also salmon gonadotropin (GTH) and salmon prolactin) prevented gonadal regression and increased plasma E₂ concentrations in females and of T in males. In the same study, *in vitro*, sGTH and rsGH could independently increase steroid secretion by isolated

gonadal tissues from trout or killifish. Van Der Kraak *et al.* (1990) found that purified carp GH, but not prolactin, could strongly potentiate the action of gonadotropin on E_2 and T production in short term incubations of goldfish ovarian tissue. In the same experiments, GH alone was ineffective. Finally, in vitellogenic ovaries of spotted sea trout, bGH and hCG were claimed to have additive effects (Singh *et al.* 1991). Apparent contradictions in these findings could result from different responses of gonads at various stages of maturation, from the use of different hormone doses, or from contaminations in GH preparations from different origin.

In female trout, recombinant trout GH (rtGH, 10 ng/ml) showed a synergistic effect with GTH2 to stimulate E_2 secretion by immature ovarian explants, while in vitellogenic ovaries rtGH tested at a higher dose (100 ng/ml) was effective alone (Fostier *et al.*, unpublished data). In cultured granulosa cells obtained before meiotic maturation, GH was able to increase the GTH stimulated conversion of 17α -hydroxyprogesterone into 17α -hydroxy, 20β -dihydroprogesterone ($17\alpha20\beta$ OHP), even at low concentrations (5 ng/ml) (Fostier *et al.*, unpublished data). The effects of purified sGH on two major steroids in cultured trout testicular cells were investigated: $17\alpha20\beta$ OHP secretion was stimulated by sGH and this effect increased with duration of culture and/or stimulation (2 to 8 days). In contrast, the 11-ketotestosterone production tended to be inhibited by sGH. These effects were observed in the absence or presence of GTH (Le Gac *et al.* 1992). Differences between these results and those reported above probably reflect the different acute and chronic effects of GH. *In vivo*, it was found that both GH and $17\alpha20\beta$ OHP increased sharply in salmonid blood during spermiation (the period of sperm production); this evolution was related to the *in vitro* $17\alpha20\beta$ OHP response to sGH that varied with the physiological stage of the gonad and appeared maximum during active spermiation (Le Gac *et al.* 1991). These data suggest a physiological role of GH, during the last stages of male fish reproductive cycle, in a phenomenon that could not be explained by the action of gonadotropins alone (Le Gac and Loir 1988).

A few data have already been obtained concerning the mechanisms of GH action. It was shown that ^{125}I -GH can bind to specific GH receptors in membrane preparations from mature trout testes (Le Gac *et al.* 1991, 1992) and from trout ovaries (Mourot *et al.* 1992) ($K_a = 1$ to $3 \times 10^9 \text{ M}^{-1}$). While the binding was fully characterized only in immature ovaries, binding was also detected in vitellogenic, preovulatory and post-ovulatory ovaries. These binding sites were similar to the GH receptors characterized in trout liver (Yao *et al.* 1991), however in both sexes the concentration of binding sites, reported per gram of fresh gonadal tissue, appeared to be in a range 100 times smaller than in the trout liver. Van Der Kraak *et al.*'s (1990) findings suggested that GH acted on preovulatory follicles by interfering with the cAMP transduction pathway. Singh and Thomas (1991) showed that the effects of GH on steroid production was abolished by actinomycin D or cycloheximide and that bovine GH (100 to 1000 ng/ml) and hCG (2.5 to 15 IU/ml) had similar stimulatory effects on cAMP accumulation in ovarian fragments. This would represent an unusual mechanism of GH action on a target tissue.

Gonadal IGF-I system

It is known that GH action may directly affect the cells being regulated or may be mediated through the modification of IGF-I production and/or IGF-I binding in target tissues.

An increasing amount of information is compatible with the existence of a complete intragonadal IGF system in mammals (reviewed by Adashi *et al.* 1992), amphibians (IGF mRNA expression, IGF-I and II production, IGF-I receptors and binding proteins) and to some extent birds (Huybrechts *et al.* 1991). Furthermore, IGF-I influences the gonadal somatic cell functions in all the mammalian species studied. In the testis, IGF-I exerts a stimulatory effect on basal and HCG induced T production by Leydig/interstitial cells and maybe also on 3β -hydroxysteroid-dehydrogenase and aromatase activities in these cells (Bernier *et al.* 1986; Benhamed *et al.* 1987; Lin *et al.* 1986; De Mellow *et al.* 1987).

IGF-I promotes Sertoli cell proliferation and energetic substrate metabolism (Mita *et al.* 1985) (see also reviews by Skinner *et al.* 1991; Bellvé and Zheng 1989; Jégou *et al.* 1992).

In the ovary, IGF-I acts as a paracrine/autocrine regulator of the granulosa (and luteal) cells by supporting cell proliferation, E₂ synthesis and aromatase mRNA, and progesterone production (reviewed by Adashi *et al.* 1985, 1992), though these growth promoting and cytodifferentiative effects could be exerted through two distinct granulosa cell populations (Monniaux and Pisselet 1992). IGFs and IGF-I-receptor gene expression and regulation vary during ovarian development and ovarian cycle (Einspanier *et al.* 1990; Zhou *et al.* 1992). Finally, IGF-I is involved in events that trigger mammalian and amphibian oocyte maturation (Maller 1990; Jalabert *et al.* 1991) and some data suggest that it is implicated in the meiotic process in the mammalian testis (Tres *et al.* 1986; Vanelli *et al.* 1988; Hansson *et al.* 1989).

sGH does not specifically stimulate *in vitro* ³H-thymidine incorporation by trout spermatogonia cultured alone for 3d. However, recombinant hIGF-I and hIGF2 stimulate DNA synthesis in these cells with as little as 5 or 10 ng/ml and in a dose-dependant way; for both IGFs at 100 or 250 ng/ml, the stimulation rate varies between 150 and 300%; this stimulation decreases to between 50 and 80% when spermatogonia are cocultured with Sertoli cells (Loir *et al.* 1991). However, it is not known whether trout Sertoli cells produce IGF and IGF binding proteins. IGF-I also increases the incorporation of ³H-thymidine in premeiotic cysts from the dogfish testis (Piferrer *et al.* 1992). In cultures of trout granulosa cells, the conversion of 17 α -hydroxyprogesterone into 17 α 20 β OHP appears to be stimulated by hIGF-I at 25 to 50 ng/ml (but not at lower doses) either alone or in combination with GTH (200 ng/ml). (Fostier *et al.*, unpublished data). Specific IGF binding sites have been demonstrated in carp ovary (Maestro *et al.* 1991; Gutierrez *et al.* 1992) and there is at least one report of IGF-I mRNA expression in salmonid testis and ovary (Duguay *et al.* 1992) that suggests local production and potential action of IGF in these tissues.

GH stimulation of IGF-I

Many of the described IGF-I actions are synergistic with FSH or LH. Furthermore, IGF-I, IGF-I-receptors and IGFBP appear to be strongly regulated by FSH (but also by LH and E₂) in granulosa cells (Hsu and Hammond 1987; Hernandez *et al.* 1991), by FSH in Sertoli cells and by LH in Leydig cells (Avallet *et al.* 1991), or by locally (intragonadal) produced factors. For these reasons, this growth factor is generally considered to amplify gonadotropin hormone action and/or to mediate the influence of FSH and LH on the gonads while potential GH effects are often minimized (Adashi 1992; Hammond *et al.* 1991). Interestingly, a recent report shows that IGF-I mRNA is primarily expressed in testicular interstitial cells other than Leydig cells and that this expression is not hCG/LH dependent (Moore *et al.* 1992).

In fact, IGF-I testicular concentrations in adult rats (Spiteri-Grech *et al.* 1991 a, b) and IGF-I secretions by isolated porcine Leydig cells or immature Sertoli cells (Chatelain *et al.* 1987; Avallet *et al.* 1991) were not found to respond to GH stimulation and Adashi (1992) reported that GH tended to reduce ovary IGF-I while strongly stimulating liver IGF-I.

However, *in vivo* GH treatment induced a 4 fold increase of testicular IGF mRNA content in immature hypophysectomised males (Closset *et al.* 1990). Human GH had a modest effect on IGF accumulation in Sertoli cell cultures (Tres *et al.* 1986), while a clear IGF-I mRNA positive response to GH was found in rat Leydig/interstitial cells (Lin *et al.* 1990). Also the type 1 IGF receptor of Leydig cells was up regulated by GH (Lin *et al.* 1988). Furthermore, GH injections to immature, hypophysectomized female rat increase the ovarian content of IGF-I (Davoren and Hsueh 1986), and porcine granulosa cell IGF-I production is GH stimulated *in vitro* (Hsu and Hammond 1987).

These data strengthen the hypothesis that GH could modulate some gonad functions; they also support the idea that GH influence is mediated, in part, through gonadal IGF-I secretion or binding, although differential effects of IGF-I and GH were demonstrated (Hong and Herington 1991).

GRF and gonadal function

This paragraph reports on the recent descriptive and experimental data obtained in amphibians and mammals suggesting that locally produced GH releasing factor (GRF) acts as a paracrine regulatory element in the gonads. High levels of a GRF-like peptide and its mRNA have been found in rat testis (Berry and Hirsch Pescovitz 1988) and ovary (Bagnato *et al.* 1992) and GRF-like material has been demonstrated in human gonads by immunohistochemical localization (Moretti *et al.* 1990). Rat GRF binds to a common receptor for VIP and GRF in rat ovary; it stimulates cAMP production and amplifies FSH induced progesterone and E₂ production by cultured granulosa cells (Moretti *et al.* 1990). Application of rat GRF to intact *Xenopus* follicles elicits an oocyte membrane transient outward current. The response involves the follicle cell layers, appears dependent on activation of K⁺ channels and involves a cAMP pathway (Yoshida and Plant 1991).

From these data we can hypothesise that gonadal GRF takes a part in promoting follicular maturation and trans-epithelial ion transfer in gonads, two important fields of investigation in teleost reproduction. Yet, this possibility remains to be explored in fish. We recently found that trout testicular protein extracts are able to increase GH secretion by trout pituitary cells in culture (Weil and Le Gac, unpublished data).

Other interactions

We want to mention the possible involvement of Somatotropin Releasing Inhibiting Factor (SRIF) in the regulation of FSH (Takano *et al.* 1992). Conversely, activin, a newly characterized protein that was originally considered to be produced by gonads and to act as a feed-back stimulatory factor of FSH secretion, was recently found to have a crucial inhibitory action on basal and GRF stimulated GH secretion as well as on GH biosynthesis (see Bilezikjian *et al.* 1990).

GH can also interfere with sex-steroids actions at least at two levels; Von Schoultz and Carlström

(1989) outlined a number of arguments suggesting that human sex-steroid binding protein (SBP or SHBG) was regulated primarily by GH, IGF-I and possibly other growth factors. In fact, we demonstrated that in trout, *in vivo*, variations of plasma SBP levels coincided with perturbations of the GH/IGF system (Foucher *et al.* 1992) and that *in vitro*, recombinant tGH (1–1000 ng/ml) maintained and stimulated SBP production by trout hepatocytes in culture (Foucher *et al.* 1991). Also, GH may exert a selective stimulation of rat liver cytosolic E₂ receptor (Lucier *et al.* 1981; Von Schoultz and Carlström 1989). However, in preliminary experiments in trout, no effect of sGH (100 ng/ml, 48h) was found on E₂ receptor mRNA expression in cultured hepatocytes (Valotaire *et al.* 1992).

In our hands, GH either alone or in cotreatment with E₂ (10⁻⁷–10⁻⁶ M) was found to have a slight inhibitory effect on vitellogenin (Vg) accumulation in trout hepatocyte culture medium (Foucher *et al.* 1991) and no effect on Vg mRNA concentration in cultured hepatocytes (Flouriot and Valotaire, unpublished data). However, *in vivo*, GH was shown to enhance the stimulatory effect of low E₂ doses (0.56 µg/3 times a week/24 days) on Vg plasma levels in female silver eels (Burzawa-Gerard and Delevallée-Fortier 1992).

Finally, the metabolic interfaces between growth and reproduction are complex mechanisms that cannot be neglected. One good example concerns the effect of nutritionally-induced growth restriction that specifically depresses gonadotropin secretion, may be through a failure of the GnRH secretory mechanism (Foster *et al.* 1989).

Conclusions

In many respects the results obtained with GH on fish reproduction resemble those found in mammals. GH may be modulated by steroids. GH interferes with testis and ovary development; it can strongly potentiate some effects of gonadotropin or act by itself on gonads; part of its influence could be mediated through gonadal IGF-I.

However, the use of the fish model has allowed

new findings that have not yet been obtained in mammals, like the demonstration of functional GH receptors in testis and ovary, the direct action of IGFs on male germ cell proliferation or the dual action of GnRH on GH and GTH.

Also to be considered in fish is the existence of somatolactin, a novel protein of the GH/PRL family which is suggested to play a role in reproductive physiology (Rand-Weaver *et al.* 1992; Planas *et al.* 1992).

Whether GH is essential for normal puberty, gametogenesis or fertility is still under debate. For example, in dwarf GH deficient mice, gonadal IGF-I production under LH/FSH regulation seems sufficient for a nearly normal development of the testis. In any case, medical and zootechnical applications of these findings already proved to be useful and will be continued.

GH and IGF effects reported here are probably distinct from their general growth and metabolism promoting effect on the body, and – were they confirmed to be of physiological relevance – they should be considered as specific regulators of gonadal function.

Finally, the occurrence in gonads of GRF production and action, of GH specific effects and of IGF-I production, binding and activity is astonishing and it is striking that the results of their action tend towards similar, or complementary, modifications of gonad function. The expression of a growth hormone-like gene in this organ is the only missing link that could allow us to propose that the gonad has an autonomous “somatotropic axis” on its own.

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