Growth hormone (GH) and reproduction : a review

Florence Le Gac, Océane Blaise, Alexis Fostier, Pierre-Yves Le Bail, Maurice Loir, Brigitte Mourot, Claudine Weil

To cite this version:

Florence Le Gac, Océane Blaise, Alexis Fostier, Pierre-Yves Le Bail, Maurice Loir, et al.. Growth hormone (GH) and reproduction : a review. Fish Physiology and Biochemistry, 1993, 11, pp.219-232. 10.1007/BF00004569 . hal-02715015

HAL Id: hal-02715015
https://hal.inrae.fr/hal-02715015

Fish Physiology and Biochemistry vol. 11 no. 1–6 pp 219-232 (1993)
Kugler Publications, Amsterdam/New York

Growth hormone (GH) and reproduction: a review

Florence Le Gac, Odile Blaise, Alex Fostier, Pierre-Yves Le Bail, Maurice Loir, Brigitte Mourot and Claudine Weil
Laboratoire de physiologie des poissons I.N.R.A., Campus de Beaulieu, 35042-Rennes-Cedex France

Keywords: GH, GRF, GnRH, IGF-I, testis, ovary, steroids, gametogenesis, amphibians, fish, mammals, human

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 somatrope 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 described 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 energic costs or of reproductive strategy, the endocrine mechanisms underlaying 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 (E_2) would tend to reduce and testosterone (T) to enhance GH secretion (Evans 1985; Shulman *et al.* 1987). Moreover, exposure to E_2 can rapidly feminise the male pattern of GH secretion (Painson 1992).

Sex-steroids would act *via* the hypothalamus: T in male and E_2 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 E_2 may control the mode of hypothalamic SRIF signalling to pituitary somatotrophs by inhibiting SRIF release (while T stimulates it) (Painson *et al.* 1991, 1992). E_2 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

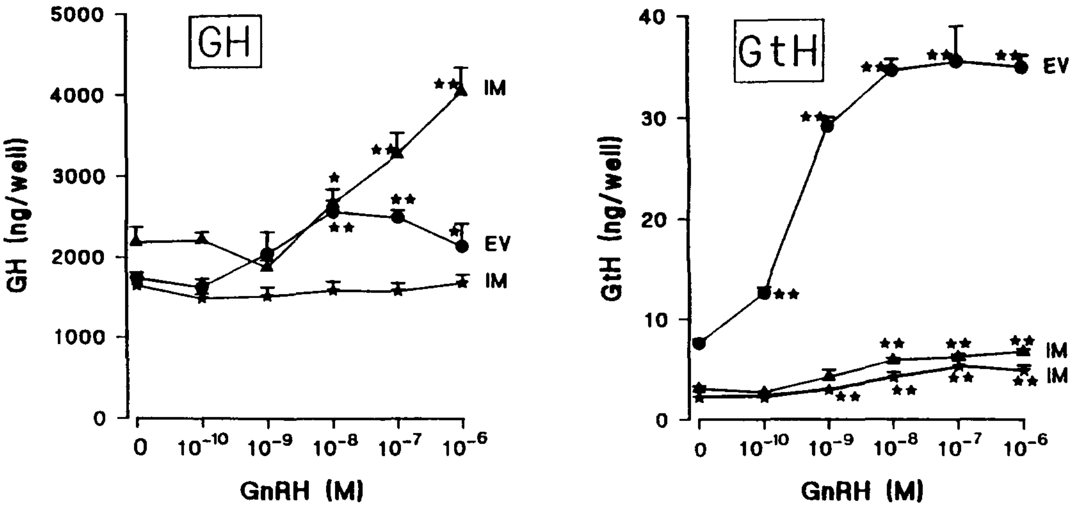

Fig. 1. Gonadotropin releasing hormone (GnRH) stimulation of GH and GTH secretions (ng/well/24hrs) by cultured pituitary cells from immature (IM) and early vitellogenic (EV) female rainbow trout. Cells (62000 cells/well) were precultured for 3 days before a 24h incubation with salmon GnRH. (X ± SEM, 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 reponse 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 pathophysiological 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 conditions resulted in delayed puberty (Ramaley and Phares 1980). Similarly, GH deficiency, obtained by introducing GH implants in the hypotahalmus, 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 (Swerdloff 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 E_2 and 17α-hydroxy,20β-dihydroprogesterone (17α20βOHP) 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 20α-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 E_2 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 μg/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 E_2 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 meïotic maturation, GH was able to increase the GTH stimulated conversion of 17α-hydroxyprogesterone into 17α-hydroxy,20β-dihydroprogesterone (17α20βOHP), 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: 17α20βOHP 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 17α20βOHP increased sharply in salmonid blood during spermiation (the period of sperm production); this evolution was related to the *in vitro* 17α20βOHP 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) ($Ka = 1$ to 3×10^9 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 follicules 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, E_2 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 meïotic process in the mammalian testis (Tres *et al.* 1986; Vanelli *et al.* 1988; Hansson *et al.* 1989).

sGH does not specifically stimulate *in vitro* ^{3}H-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 ^{3}H-thymidine in premeïotic cysts from the dogfish testis (Piferrer *et al.* 1992). In cultures of trout granulosa cells, the conversion of 17α-hydroxyprogesterone into 17α 20βOHP 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 E_2) 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 funcion

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 E_2 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 follicule 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 E_2 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 E_2 receptor mRNA expression in cultured hepatocytes (Valotaire *et al.* 1992).

In our hands, GH either alone or in cotreatment with E_2 (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 E_2 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.

References cited

Adashi, E.Y., Resnick, C.E., D'Ercole, J., Svoboda, M.E. and Van Wyk, J.J. 1985. Insulin-like growth factors as intraovarian regulators of granulosa cell growth and function. Endocr. Rev. 6: 400–420.

Adashi, E.Y., Resnick, C.E., Hurwitz, A., Ricciarelli, E., Hernandex, E.R., Roberts, C.T., Leroith, D. and Rosenfeld, R. 1992. The ovarian and testicular IGF-I system: a comparative analysis. *In* Spermatogenesis, Fertilization, Contraception. Molecular, Cellular and Endocrine Events in Male Reproduction. pp. 143–168. Edited by E. Niechlag and U. Habenicht. Sherring Fundation Workshop n°4, Springer-Verlag, London.

Advis, J.P., White, S.S. and Ojeda, S.R. 1981. Activation of growth hormone short loop negative feedback delays puberty in the female rat. Endocrinology 108: 1343–1352.

Avallet, O., Vigier, M., Chatelain, P.G. and Saez, J.M. 1991. Regulation by growth factors of Leydig cell differentiated functions. J. Ster. Biochem. Molec. Biol. 40: 453–464.

Bagenal, T.B. 1969. The relationship between food supply and fecundity in brown trout *Salmo trutta* L.J. Fish Biol. 1: 167–182.

Bagnato, A., Moretti, C., Ohnishi, J., Frajese, G. and Catt, K.J. 1992. Expression of the growth hormone-releasing hormone gene and its peptide product in the rat ovary. Endocrinology 130: 1097–1102.

Bartke, A., Steger, R.W., Hodges, S.L., Parkening, T.A., Collins, T.J., Yun, J.S. and Wagner, T.E. 1988. Infertility in transgenic female mice with human growth hormone expression: evidence for luteal failure. J. Exp. Zool. 248: 121–124.

Bellvé, A.R. and Zhengt, W. 1989. Growth factors as autocrine and paracrine modulators of male gonadal functions. J. Reprod. Fert. 85: 771–793.

Benhamed, M., Morera, A.M., Chauvin, M.C. and Peretti, E. 1987. Somatomedin C/insulin-like growth factor 1 as a possible intratesticular regulator of Leydig cell activity. Mol. Cell. Endocr. 50: 69–77.

Berglund, I., Mayer, I. and Borg, B. 1992. Effects of sexual maturation, castration, and androgen implants on growth in one and two year-old parr in a Baltic atlantic salmon (*Salmo salar* L.) stock. J. Fish Biol. 40: 281–292.

Bernier, M., Chatelain, P., Mather, J.P. and Saez, J.M. 1986. Regulation of gonadotropin receptors, gonadotropin responsiveness and cell multiplication by somatomedin C and insulin in cultured pig Leydig cells. J. Cell. Physiol. 129: 257–263.

Berry, S.A. and Pescovitz, O.H. 1988. Identification of a rat GNRH-like substance and its messenger RNA in rat testis. Endocrinology 123: 661–663.

Bilezikjian, L.M., Corrigan, A.Z. and Vale, W. 1990. Activin-A modulates growth hormone secretion from cultures of rat anterior pituitary cells. Endocrinology 126: 2369–2376.

Björnsson, B.T., Stefansson, S.O., Taranger, G.L., Hansen, T., Walther, B.Th. and Haux, C. 1992. Photoperiodic control of plasma growth hormone levels and sexual maturation of adult atlantic salmon. *In* Reproductive Physiology of Fish, p. 161. Edited by A.P. Scott, J.P. Sumpter, D.E. Kime and M.S. Rolfe. FishSymp 91, Sheffield.

Blaise, O. 1991. Action du GnRH sur les secretions *in vitro* de gonadotropine et d'hormone de croissance chez la truite arc-en-ciel (*Oncorhynchus mykiss*). D.E.A. thesis, Paris VI, France.

Blumenfeld, Z. and Lunenfeld, B. 1989. The potentiating effect of growth hormone on follicle stimulation with human menopausal gonadotropin in a panhypopituitary patient Fertil. Steril. 52: 328.

Boccabella, A.V. 1963. Reinitiation and restoration of spermatogenesis with testosterone propionate and other hormones after a long-term Posthypophysectomy regression period. Endocrinology 72: 787–789.

Borghetti, J.R., Iwamoto, R.N., Hardy, R.W. and Sower, S.

1989. The effects of naturally occurring androgens in practical diets fed to normal-sired progeny of coho salmon (*Oncorhynchus kisutch*). Aquaculture 77: 51–60.

Burger, H.G., Kovacs, G.T., Polson, D.M., McDonald, J., McCloud, P.I., Harrop, M., Colman, P. and Healy, D.L. 1991. Ovarian sensitization to gonadotrophins by human growth hormone. Persistence of the effect beyond the treated cycle. Clin. Endocrinol. 35: 119–122.

Burzawa-Gérard, E. and Delevallée-Fortier, B. 1992. Implication de l'hormone de croissance au cours de l'induction expérimentale de la vitellogenèse par l'oestradiol-17β chez l'anguille argentée femelle (*Anguilla anguilla* L). C.R. Acad. Sci., Paris 314: 411–416.

Carlsson, L., Eriksson, E., Seeman, H. and Jansson, J.O. 1987. Oestradiol increases baseline growth hormone levels in the male rat: possible direct action on the pituitary. Acta Physiol. Scand. 129: 393–399.

Chang, J.P., Cook, H., Freedman, G.L., Wiggs, A.J., Somoza, G.M., de Leeuw, R. and Peter, R.E. 1990. Use of a pituitary cell dispersion method and primary culture system for the studies of gonadotropin-releasing hormone action in the goldfish, *Carassius auratus*. Gen. Comp. Endocrinol. 77: 256–273.

Chang, J.P. Jobin, R.M. and Wong, O.L. 1992. Intracellular mechanisms mediating gonadotropin and growth hormone release in the goldfish, *Carassius auratus*. Fish Physiol. Biochem. 11: 25–33.

Chatelain, P.G., Naville, D. and Saez, J.M. 1987. Somatomedin C/insulin-like growth factor like material secreted by porcine Sertoli cells *in vitro*: characterization and regulation. Bioch. Biophys. Res. Comm. 146: 1009–1017.

Chatelain, P.G., Sanchez, P. and Saez, J.M. 1991. Growth hormone and insulin-like growth factor I treatment increase testicular luteinizing hormone receptors and steroidogenic responsiveness of growth hormone deficient dwarf mice. Endocrinology 128: 1284–1857.

Chowen-Breed, J.A., Steiner, R.A. and Clifton, D.K. 1989. Sexual dimorphism and testosterone-dependent regulation of somatotostatin gene expression in the periventricular nucleus of the rat brain. Endocrinology 125: 357–362.

Closset, J., Dombrowicz, D., Vandebroeck, M. and Hennen, G. 1991. Effects of bovine, human and rat growth hormones on immature hypophysectomized rat testis. Growth regulation 1: 29–37.

Closset, J., Gothot, A., Sente, B., Scippo, M.L., Igout, A. Vandenbroeck, M., Dombrowicz, D. and Hennen, G. 1989. Pituitary hormones dependent expression of insulin-like growth factors I and II in the immature hypophysectomized rat testis. Molec. Endocrinol. 3: 1125–1131.

Cook, H., Berkenbosch, J.W., Fernhout, M.J., Yu, K.L., Peter, R.E., Chang, J.P. and Rivier, J.E. 1991. Demonstration of gonadotropin releasing-hormone receptors on gonadotrophs and somatographs of the goldfish: an electron microscope study. Reg. Pept. 36: 369–378.

Davoren, J.B. and Hsueh, A.J.W. 1986. Growth hormone increases ovarian levels of immunoreactive somatomedin C/insulin-like growth factor I *in vivo*. Endocrinology 118: 888–890.

De Mellow, J.S.M., Handelsman, D.J. and Baxter, R.C. 1987. Short-term exposure to insulin-like growth factors stimulates testosterone production by testicular interstitial cells. Acta Endocr. 115: 483–489.

Devesa, J., Lois, N., Arce, V., Diaz, M.J., Lima, L. and Tresgueres, J.A.F. 1991. The role of sexual steroids in the modulation of growth hormone (GH) secretion in humans. J. Steroid Biochem. Molec. Biol. 40: 165–173.

Donaldson, E.M., Fagerlund, U.H.M., Higgs, D.A. and McBride, J.R. 1979. Hormonal enhancement of growth. *In* Fish Physiology Vol. VIII, pp. 456–598. Edited by W.S. Hoar, D.J. Randall and J.R. Brett. Academic Press, New York.

Duguay, S.J., Park, L.K., Samadpour, M. and Dickhoff, W.W. 1992. Nucleotide sequence and tissue distribution of three insulin-like growth factor I prohormones in salmon. Mol. Endocrinol. (In press).

Eden, S., Jansson, J.O. and Oscarsson, J. 1987. Sexual dimorphism of growth hormone secretion. *In*: Growth hormone – Basic and Clinical Aspects. pp. 129–151. Edited by O. Isaksson, C. Binder, K. Hall and B. Hökfelt. Elsevier, Amsterdam.

Einspanier, R., Miyamoto, A., Schams, D., Müller, M. and Brem, G. 1990. Tissue concentration, mRNA expression and stimulation of IGF-I in luteal tissue during the oestrous cycle and pregnancy of cows. J. Reprod. Fert. 90: 439–445.

Evans, W.S., Krieg, R.J., Limber, E.R., Kaiser, D.L. and Thorner, M.O. 1985. Effects of *in vivo* gonadal hormone environment on *in vitro* hGRF-40-stimulated GH release. Am. J. Physiol. 249: E276–E280.

Flett, P.A., Van Der Kraak, G. and Leatherland, J.F. 1992. N-methyl-DL-aspartate stimulates gonadotropin and growth hormone secretion in steroid-primed, immature rainbow trout. Abst. 2nd Int. Symp. Fish. Endocrinology, St. Malo, France.

Foster, D.L., Ebling, F.J.P., Micka, A.F., Vannerson, L.A., Bucholtz, D.C., Wood, R.I., Suttie, J.M. and Fenner, D.E. 1989. Metabolic interfaces between growth and reproduction/I. Nutritional modulation of gonadotropin, prolactin, and growth hormone secretion in the growth limited female lamb. Endocrinology 125: 342–350.

Foucher, J.L., Le Bail, P.Y. and Le Gac, F. 1992. Influence of hypophysectomy, castration, fasting, and spermiation on SBP concentration in male rainbow trout (*Oncorhynchus mykiss*). Gen. Comp. Endocrinol. 85: 101–110.

Foucher, J.L., Niu, P.D., Mourot, B., Vaillant, C. and Le Gac, F. 1991. *In vivo* and *in vitro* studies on sex steroid binding protein (SBP) regulation in rainbow trout (*Oncorhynchus mykiss*): influence of sex steroid hormones and of factors linked to growth and metabolism. J. Ster. Biochem. Molec. Biol. 39: 975–986.

Gjerde, B. 1986. Growth and reproduction in fish and shellfish. Aquaculture 57: 37–55.

Gong, J.G., Bramley, T. and Webb, R. 1991. The effect of recombinant bovine somatotropin on ovarian function in heifers: follicular populations and peripheral hormones. Biol. reprod. 45: 941–949.

Gutierrez, J., Parrizas, M., Carneiro, N., Maestro, M. and Planas, J. 1992. Insulin and IGF-I receptors and tyrosine kinase activity in carp ovaries: changes with reproductive stage. Fish Physiol. Biochem. 11: 247–254.

Hammond, J.M., Mondschein, J.S., Samaras, S.E. and Canning, S.F. 1991. The ovarian insulin-like growth factors a local amplification mechanism for steroidogenesis and hormone action. J. Steroid. Biochem. Molec. Biol. 40: 411–416.

Hansson, H.A., Billig, H. and Isgaard, J. 1989. Insulin-like growth factor I in the developing and mature rat testis: immunohistochemical aspects. Biol. Reprod. 40: 1321–1328.

Hernandez, E.R., Hurwitz, A., Vera, A., Pellicer, A., Adashi, E.Y., Le Roith, D. and Roberts, C.T. 1992. Expression of the genes encoding the insulin-like growth factors and their receptors in the human ovary. J. Clin. Endocrinol. Metab. 74: 419–425.

Higgs, D.A., Donaldson, E.M., Dye, H.M. and McBride, J.R. 1976. Influence of bovine growth hormone and L-thyroxine on growth, muscle composition, and histological structure of the gonads, thyroid, pancreas, and pituitary of coho salmon (*Oncorhynchus kisutch*). J. Fish. Board Can. 33: 1585–1603.

Higgs, D.A., Fagerlund, U.H.M., Eales, J.G. and McBride, J.R. 1982. Application of thyroid and steroid hormones as anabolic agents in fish culture. Comp. Biochem. Physiol. 73: 143–176.

Ho, K.Y., Evans, W.S., Blizzard, R.M., Veldhuis, J.D., Merriam, G.R., Samojlik, E., Furlanetto, R., Rogol, A.D., Kaiser, D.L. and Thorner, M.O. 1987. Effects of sex and age on the 24-hour profile of growth hormone secretion in man: importance of endogenous estradiol concentrations. J. Clin. Endocr. Metab. 64: 51–58.

Homburg, R., West, C., Torresani, T. and Jacobs, H.S. 1990. A comparative study of single-dose growth hormone therapy as an adjuvant to gonadotrophin treatment for ovulation induction. Clin. Endocrinol. 32: 781–785.

Hong, H. and Herington, A.C. 1991. Differentiation between the effects of IGF-I and GH on PMSG-induced progesterone production by rat granulosa cells. Growth Reg. 1: 65–71.

Horikawa, R., Asakawa, K., Hizuka, N., Takano, K. and Shizume, K. 1989. Growth hormone and insulin-like growth factor I stimulate Leydig cell steroidogenesis. Eur. J. Pharmacol. 166: 87–94.

Hsu, C.J. and Hammond, J.M. 1987. Concomitant effects of growth hormone on secretion of insulin like growth factor I and progesterone by cultured porcine granulosa cells. Endocrinology 121: 1343–1348.

Hunt, S.M.V., Simpson, T.H. and Wright, R.S. 1982. Seasonal changes in the levels of 11-oxotestosterone and testosterone in the serum of male salmon, *Salmo salar* L, and their relationship to growth and maturation cycle. J. Fish Biol. 20: 105–119.

Hutchinson, L.A., Findlay, J.K. and Herington, A.C. 1988. Growth hormone and insulin-like growth factor-I accelerate PMSG-induced differentiation of granulosa cells. Mol. Cell. Endocrinol. 55: 61–69.

Huybrechts, L.M., Decuypere, E. and Kühn, E.R. 1991. Granulosa cells of the preovulatory follicles of the domestic fowl contain an insulin-like growth factor (IGF) receptor. Med. Sci. Res. 19: 699–700.

Ivankov, V.N. 1983. Causes of variation in fecundity and age of sexual maturation in monocyclic fishes with examples from Salmon, Genus *Oncorhynchus*. J. Ichthyol. 23: 84–93.

Jacobs, H.S., Bouchard, P., Conway, G.S., Homburg, R., Lahlou, N., Mason, B., Ostergaard, H. and Owen, E.J. 1991. Role of growth hormone in infertility. Horm. Res. 36 (suppl 1): 61–65.

Jalabert, B., Fostier, A. and Breton, B. 1982. Controle endocrinien de la croissance chez les poissons téléostéens: données majeures et applications. Oceanis 8: 551–575.

Jalabert, B., Fostier, A., Breton, B. and Weil, C. 1991. Oocyte maturation in vertebrates. *In* Vertebrate Endocrinology: Fundamentals and Biomedical Implications. Vol 3, pp. 23–90. Edited by P.K.T. Pang and M.P. Schreibman, Academic press, New York.

Jansson, J.O. and Frohman, L.A. 1987. Inhibitory effect of the ovaries on neonatal androgen imprinting of growth hormone secretion in female rats. Endocrinology 121: 1417–1423.

Jansson, J.O., Ekberg, S., Isaksson, O., Mode, A. and Gustafsson, J.A. 1985. Imprinting of growth hormone secretion, body growth, and hepatic steroid metabolism by neonatal testosterone. Endocrinology 117: 1881–1889.

Jansson, J.O., Ekberg, S., Isaksson, O.G.P. and Eden, S. 1984. Influence of gonadal steroids on age and sex related secretory patterns of growth hormone in the rat. Endocrinology 114: 1287–1294.

Jégou, B. 1992. The Sertoli cell. *In* The Testes. Vol. 6, pp. 273–311. Edited by D.M. de Kretser. Belliere's Clinical Endocrinology and Metabolism. Bailliere Tindall.

Jia, X.C., Kalminjn, J. and Hsueh, A.J.W. 1986. Growth hormone enhances follicle stimulating hormone induced differentiation of cultured rat granulosa cells. Endocrinology 118: 1401–1409.

Jobin, R.M. and Chang, J.P. 1992. Differences in extracellular calcium involvement mediating the secretion of gonadotropin and growth hormone stimulated by 2 closely related endogenous GnRH peptides in Goldfish pituitary cells. Neuroendocrinology 2: 156–166.

Lanzone, A., Di Simone, N., Castellani, R., Fulghesu, A.M., Caruso, A. and Mancuso, S. 1992. Human growth hormone enhances progesterone production by human luteal cells *in vitro*: evidence of a synergistic effect with human chorionic gonadotropin. Fertil. Steril. 57: 92–96.

Lawrence, N.R. and Davies, A.G. 1977. Stimulation of testicular protein synthesis *in vivo* by gonadotrophins and growth hormone in hypophysectomized adult mice. J. Reprod. Fert. 49: 41–45.

Le Bail, P.Y. 1988. Growth-reproduction interaction in salmonids. *In* Reproduction in Fish, Basic and Applied Aspects in Endocrinology and Genetics, pp. 91–108. Edited by Y. Zohar and B. Breton; INRA, Paris Les Colloques de l'INRA, n°44.

Le Gac, F. and Loir, M. 1988. Control of testis function in fish: *in vitro* studies of gonadotropic regulation in the trout (*Salmo gairdneri*). Reprod. Nutr. Dev. 28: 1031–1046.

Le Gac, F., Ollitrault, M., Loir, M. and Le Bail, P.Y. 1991. Binding and action of salmon growth hormone (sGH) in the mature trout testis. *In* Reproductive Physiology of Fish. pp. 117–119. Edited by A.P. Scott, J.P. Sumpter, D.E. Kime and M.S. Rolf. FishSymp 91, Sheffield.

Le Gac, F., Ollitrault, M., Loir, M. and Le Bail, P.Y. 1992. Evidence for binding and action of growth hormone in trout testis. Biol. Reprod. 46: 949–957.

Lewis, K.M. and Sower, S.A. 1992. Effects of dietary testosterone on growth and sex ratio in juvenile atlantic salmon (*Salmo salar*). Fish Physiol. Biochem. 9: 513–517.

Lin, T., Blaisdell, J. and Haskell, J.F. 1988. Hormonal regulation of type I Insulin-like growth factor receptors of Leydig cells in hypophysectomized rats. Endocrinology 123: 134–139.

Lin, T., Haskell, J., Vinson, N. and Terracio, L. 1986. Characterization of insulin and insulin-like growth factor I receptors of purified Leydig cells and their role in steroidogenesis in primary culture: a comparative study. Endocrinology 119: 1641–1647.

Lobie, P.E., Breipohl, W., Aragon, J.G. and Waters, M.J. 1990. Cellular localization of the growth hormone receptor/binding protein in the male and female reproductive systems. Endocrinology 126: 2214–2221.

Loir, M. and Le Bail, P.Y. 1991. *In vitro* control of spermatogonial proliferation in the trout: preliminary data. Int. Congr. Res. Aquaculture: Fundamental and Applied aspects; pp. 175. Antibes, France.

Lucier, G.W., Slaughter, S.R., Thompson, C., Lamartiniere, C.A. and Powell-Jones, W. 1981. Selective actions of growth hormone on rat liver estrogen binding proteins. Biochem. Biophys. Res. Comm. 103: 872–879.

Maeda, K., Kato, Y., Yamaguchi, N., Chihara, K., Ohgo, S., Iwasaki, Y., Yoshimoto, Y., Moridera, K., Kuromaru, S. and Imaru, H. 1976. Growth hormone release following thyrotrophin-releasing hormone injection into patients with anorexia nervosa. Acta Endocrinol. 81: 1–8.

Maestro, J.L., Parrizas, M., Navarro, I. and Gutierrez, J. 1991. Insulin and IGF-1 receptors in carp oocytes. *In* Proc. Int. Congr. Res. Aquaculture: Fundamental and Applied Aspects pp. 4–5. Antibes, France.

Marchant, T.A. and Peter, R.E. 1986. Seasonal variations in body growth rates and circulating levels of growth hormone in the goldfish, *Carassius auratus*. J. Exp. Zool. 237: 231–239.

Marchant, T.A., Chang, J.P., Nahorniak, C.S. and Peter, R.E. 1989. Evidence that gonadotropin-releasing hormone also functions as a growth hormone-releasing factor in the goldfish. Endocrinology 124: 2509–2518.

Marchant, T.A. and Peter, R.E. 1989. Hypothalamic peptide influencing growth hormone secretion in the goldfish, *Carassius auratus*. Fish Physiol. Biochem. 7: 133–140.

Mason, H.D., Martikainen, H., Beard, R.W., Anyaoku, V. and Franks, S. 1990. Direct gonadotrophic effect of growth hormone on oestradiol production by human granulosa cells *in vitro*. J. Endocrinol. 126: R1–R4.

Mathews, L.S., Enberg, B., Norstedt, G. 1989. Regulation of rat growth hormone receptor gene expression. J. Biol. Chem. 264: 9905–9910.

Mita, M., Borland, K., Price, J.M. and Hall, P.F. 1985. The influence of insulin-like growth factor I on hexose transport by Sertoli cells. Endocrinology 116: 987–992.

Monniaux, D. and Pisselet, C. 1992. Control of proliferation and differentiation of ovine granulosa cells by insulin-like growth factor-I and follicle-stimulating hormone *in vitro*. Biol. Reprod. 46: 109–119.

Moore, A., Chen, C. and Morris, I.D. 1992. IGF-I mRNA expression in isolated testicular interstitial cells. *In* Proc. 7th Eur. Workshop on Mol. Cell. Endocrinol. Testis. Castel-Elmeau, Germany.

Moretti, C., Bagnato, A., Solan, N., Frajese, G. and Catt, J. 1990. Receptor-mediated actions of growth hormone releasing factor on granulosa cell differentiation. Endocrinology 127: 2117–2126.

Mourot, B., Fostier, A., Yao, K., Le Gac, F. and Le Bail, P.Y. 1992. Specific binding of salmonid growth hormone in rainbow trout (*Oncorrhynchus mykiss*) ovary. *In*: Proc. 2nd Int. Symp. Fish Endocrinology, St. Malo, France. p. 73.

Murphy, M.G., Rath, M., O'Callagan, D., Austin, F.H. and Roche, J.F. 1991. Effect of bovine somatotropin on production and reproduction in prepubertal friesian heifers. Dairy Sci. 74: 2165–2171.

Olivereau, M. and Olivereau, J. 1979. Effect of estradiol-17β on the cytology of the liver, gonads and pituitary, and on plasma electrolytes in the female freshwater eel. Cell Tiss. Res. 199: 431–454.

Ovesen, P., Moller, J. and Moller, N. 1992. Growth hormone secretory capacity and serum insulin-like growth factor I levels in primary infertile, anovulatory women with regular menses. Fertil. Steril. 57: 97–101.

Painson, J.C., Tannenbaum, G.S. 1991. Sexual dimorphism of somatostatin and growth hormone-releasing factor signaling in the control of pulsatile growth hormone secretion in the rat. Endocrinology 128: 2858–2866.

Painson, J.C., Thorner, M.O., Krieg, R.J. and Shaffer-Tannenbaum, D.G. 1992. Short term exposure to estradiol feminizes the male pattern of spontaneous and growth hormone-releasing factor-stimulated growth hormone secretion in the rat. Endocrinology 130: 511–519.

Pickford, G.E., Lofts, B., Bara, G. and Atz, J. 1972. Testis stimulation in hypophysectomized male killifish, *Fundulus heteroclitus*, treated with mammalian growth hormone and/or luteinizing hormone. Biol. Reprod. 7: 370–386.

Piferrer, F., Redding, M., Jorgensen, J., Dubois, W. and Callard, G. 1992. Stimulatory and inhibitory regulation of DNA synthesis during spermatogenesis: studies in *Squalus acanthias*. Fish Physiol. Biochem. 11: 293–298.

Planas, J., Swanson, P., Rand-Weaver, M. and Dickhoff, W.W. 1992. Somatolactin stimulates *in vitro* gonadal steroidogenesis in coho salmon, *Oncorhynchus kisutch*. Gen. Comp. Endocrinol. 87: 1–5.

Power, D.M. 1992. Immunocytochemical identification of growth hormone, prolactin, and gonadotropin cells in the pituitary of male plaice (*Pleuronectes platessa*) during gonadal maturation. Gen. Comp. Endocrinol. 85: 358–366.

Pursel, V.G., Pinkert, C.A., Miller, K.F., Bolt, D.J., Campbell, R.G., Palmiter, R.D., Brinster, R.L. and Hammer, R.E. 1989. Genetic engineering of livestock. Science 244: 1281–1288.

Ramaley, J.A. and Phares, C.K. 1980. Delay of puberty onset in female due to suppression of growth hormone. Endocrinology 106: 1989–2019.

Ramasharma, K. and Li, C.H. 1987. Human pituitary and placental hormones controle human insulin like growth factor 2 secretion in human granulosa cells. Proc. Nat. Acad. Sci. U.S.A. 84: 2643–2647.

Rand-Weaver, M., Swanson, P., Kawauchi, H. and Dickhoff, W.W. 1992. Increase in somatolactin levels during reproductive maturation in coho salmon (*Oncorhynchus kisutch*). Fish Physiol. Biochem. 11: 175–182.

Sadler, S.E. 1991. Inhibitors of phosphodiesterase III block stimulation of *Xenopus laevis* oocytes ribosomal S6 kinase activity by insulin-like growth factor-I. Mol. Endocrinol. 5: 1947–1954.

Schemm, S.R., Deaver, D.R., Griel, L.C. and Muller, L.D. 1990. Effects of recombinant bovine somatotropin on luteinizing hormone and ovarian function in lactating dairy cow. Biol. Reprod. 42: 815–821.

Schreck, C.B. and Fowler, L.G. 1982. Growth and reproductive development in fall chinook salmon: effects of sex hormones and their antagonists. Aquaculture 26: 253–263.

Sheikholislan, B.M. and Stempfel, R.S. 1972. Hereditary isolated somatotropin deficiency: effects of human growth hormone administration. Pediatrics 49: 362.

Shoham, Z., Conway, G.S., Ostergaard, H., Lahlou, N., Bouchard, P. and Jacobs, H.S. 1992. Cotreatment with growth hormone for induction of spermatogenesis in patients with hypogonadotropic hypogonadism. Fertil. Steril. 57: 1044–1051.

Shulman, D.I., Sweetland, M., Duckett, G. and Root, A.W. 1987. Effect of estrogen on the growth hormone (GH) secretory response to GH-releasing factor in the castrate adult female rat *in vivo*. Endocrinology 120: 1047–1051.

Singh, H., Griffith, R.W., Takahashi, A., Kawauchi, H., Thomas, P. and Stegeman, J.J. 1988. Regulation of gonadal steroidogenesis in *Fundulus heteroclitus* by recombinant salmon growth hormone and purified salmon prolactin. Gen. Comp. Endocrinol. 72: 144–153.

Singh, H. and Thomas, P. 1991. Mechanism of stimulatory action of Growth hormone on ovarian steroidogenesis in spotted seatrout. *In* Reproductive Physiology of Fish p. 104. Edited by A.P. Scott, J.P. Sumpter, D.E. Kime and M.S. Rolfe. FishSymp 91, Sheffield.

Skinner, M.K. 1991. Cell-cell interactions in the testis. Endocr. Rev. 12: 45–77.

Skottner, A., Clark, G., Ryklund, L. and Robinson, I.C.A.F. 1989. Growth responses in a mutant dwarf rat to human growth hormone and recombinant human insulin-like growth factor I. Endocrinology 124: 2519–2526.

Smals, A.E.M., Pieters, G.F.F.M., Smals, A.G.H., Hermus, A.R.M.M., Benraad, T.J. and Kloppenborg, P.W.C. 1987. Growth hormone responses to the releasing hormones GHRH and GnRH and the inhibitors somatostatin and bromocriptine in TRH-responsive and non-responsive acromegalics. Acta Endocrinol. (Copenh) 116: 53–58.

Smith, E.P., Svoboda, M.E., Van Wyk, J.J., Kierszenbaum, A.L. and Tres, L.L. 1988. Partial characterization of somatomedin-like peptide from the medium of cultured rat Sertoli cells. Endocrinology 120: 186–193.

Spicer, L.J. and Langhout, D.J. 1991. Effects of bovine somatotropin on ovarian function in cattle. An. Sci. Res. Rep. MP134: 31–34.

Spiteri-Grech, J., Bartlett, J.M.S. and Nieschlag, E. 1991a. Hormonal regulation of epidermal growth factor and insulin-like growth factor-I in adult male hypophysectomized rats treated with ethane dimethane sulphonate. J. Endocrinol. 129: 109–117.

Spiteri-Grech, J., Bartlett, J.M.S. and Nieschlag, E. 1991b. Regulation of testicular insulin-like growth factor-I in pubertal growth hormone-deficient male rats. J. Endocrinol. 131: 279–285.

Spiteri-Grech, J., Bartlett, J.M.S., Behre, H.M. and Nieschlag, E. 1992. GH administration to neonatal and prepubertal GH deficient (Dw) rats affects initiation of spermatogenesis and testicular IGF-1. *In* Proc. 7th Eur. Workshop on Mol. Cell. Endocrinol. Testis. p. 83.

Stacey, N.E., MacKenzie, D.S., Marchant, T.A., Kyle, A.L. and Peter, R.E. 1984. Endocrine changes during natural spawning in the white sucker, *Catostomus commersoni*. Gen. Comp. Endocrinol. 56: 333–348.

Stearns, C. and Crandall, R. 1984. Plasticity for age and size at sexual maturity: a life-history response to unavoidable stress. *In* Fish Reproduction: Strategies and Tactics pp. 13–33. Edited by G.W. Potts and R.H. Wootton. Academic Press, London.

Sumpter, J.P., Lincoln, R.F., Bye, V.J., Carragher, J.F. and Le Bail, P.Y. 1991. Plasma growth hormone levels during sexual maturation in diploid and triploid rainbow trout (*Oncorhynchus mykiss*). Gen. Comp. Endocrinol. 83: 103–110.

Swerdloff, R.S., Odell, W.D. 1977. Modulating influences of FSH, GH and prolactin on LH stimulated testosterone secretion. *In* The Testis in Normal and Infertile Men. pp. 395–401. Edited by P. Trohen and H.R. Nankin. Raven Press, New York.

Takano, K., Yamashita, N., Kojima, I., Kitaoke, M., Teramoto, A. and Ogato, E. 1991. Effects of activin-A and somatostatin on intact FSH secretion and intracellular Ca^{2+} concentration in human FSH-secreting pituitary adenoma cells. Biochem. Biophys. Res. Comm. 14: 1408–1415.

Tilemans, D., Andries, M. and Denef, C. 1992. Luteinizing hormone-releasing hormone and neuropeptide Y influence deoxyribonucleic acid replication in three anterior pituitary cell types. Evidence for mediation by growth factors released from gonadotrophs. Endocrinology 130: 882–894.

Tres, L.L., Smith, E.P., Van Wyk, J.J. and Kierszenbaum, A.L. 1986. Immunoreactive sites and accumulation of somatomedin-C in rat Sertoli-spermatogenic cell co-cultures. Exp. Cell. Res. 162: 33–50.

Trudeau, V.L., Somoza, G.M., Nahorniak, C.S. and Peter, R.E. 1992. Interactions of estradiol with gonadotropin-releasing hormone in the control of growth hormone secretion in the goldfish. Neuroendocrinology 56: 483–490.

Valotaire, Y., Le Roux, M. and Jego, P. 1993. Estrogen receptor gene: structure and expression in rainbow trout. *In* Biochemistry and Molecular Biology of Fishes. Vol 2. Edited by P. Hochachka and T.P. Mommsen. Elsevier, Amsterdam (In press).

Van Der Kraak, G., Rosenbloom, P. and Peter, R.E. 1990. Growth hormone dependent potentiation of gonadotropin stimulated steroid production by ovarian follicles of the goldfish. Gen. Comp. Endocrinol. 79: 233–239.

Vanelli, B.G., Barni, T., Orlando, C., Natali, A., Serio, M. and Balboni, G.C. 1988. Insulin-like growth factor-1 and IGF-1 receptor in human testis: an immunohistochemical study. Fertil. Steril. 49: 666–669.

Von Schoultz, B. and Carlström, K. 1989. On the regulation of sex-hormone binding globulin – A challenge of an old dogma and outlines of an alternative mechanism. J. Ster. Biochem. 32: 327–334.

Wehrenberg, W.B., Baird, A., Ying, S.Y. and Ling, N. 1985. The effects of testosterone and estrogen on the pituitary growth hormone response to growth hormone-releasing factor. Biol. Reprod. 32: 369–375.

Weigent, D.A. and Blalock, J.E. 1991. The production of growth hormone by subpopulations of rat mononuclear leukocytes. Cell. Immunol. 135: 55–65.

Wennink, J.M.B., Delemarre-van de Waal, A., Schoemaker, R., Blaauw, G., van den Braken, C. and Schoemaker, J. 1990. Growth hormone secretion patterns in relation to LH and testosterone secretion throughout normal male puberty. Acta Endocrinol. (Copenh) 23: 263–270.

Werner, H., Koch, Y., Baldino, F. and Gozes, I. 1988. Steroid regulation of somatostatin mRNA in the rat hypothalamus. J. Biol. Chem. 263: 7366–7671.

Yao, K., Niu, P.D., Le Gac, F. and Le Bail, P.-Y. 1991. Presence of GH specific binding sites in rainbow trout (*Oncorhynchus mykiss*) tissues: characterisation of the hepatic receptor. Gen. Comp. Endocrinol. 81: 72–82.

Yoshida, S. and Plant, S. 1991. A potassium current evoked by growth hormone-releasing hormone in follicular oocytes of *Xenopus laevis*. J. Physiol. 443: 651–667.

Young, G. and Ball, J.N. 1979. Effects of ovariectomy and oestrogen treatment on the ultrastructure of the adenohypophysis in the teleost *Poecilia latipinna*. J. Endocrinol. 83: P30.

Young, G., Ueda, H. and Nagahawa, Y. 1983. Estradiol-17β and 17α,20β-dihydroxy-4-pregnen-3-one production by isolated ovarian follicles of amago salmon (*Oncorhynchus rhodurus*) in response to mammalian pituitary and placental hormones and salmon gonadotropin. Gen. Comp. Endocrinol. 52: 329–335.

Yu, K.L., Peng, C. and Peter, R.E. 1991. Changes in brain levels of gonadotropin-releasing hormone and serum levels of gonadotropin and growth hormone in goldfish during spawning. Can. J. Zool. 69: 182–188.

Zhou, J., Chin, E. and Bondy, C. 1991. Cellular pattern of insulin-like growth factor-I (IGF-I) and IGF-I receptor gene expression in the developing and mature ovarian follicle. Endocrinology 129: 3281–3288.

Zipf, W.B., Payne, A.H., Kelch, R.P. 1978. Prolactin, growth hormone, and luteinizing hormone in the maintenance of testicular luteinizing hormone receptors. Endocrinology 103: 595–600.