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Overview of fish growth hormone family. New insights in genomic organization and heterogeneity of growth hormone receptors

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Abstract

Growth hormone (GH), prolactin (PRL) and somatolactin (SL) are single chain proteins structurally and functionally related. Fish PRL and GH receptors (PRLR, GHR) have been characterized in several fish species. There is limited evidence of fish PRLR isoforms, but emerging data support the existence of different GHR variants. In gilthead sea bream, black sea bream, turbot and fugu, but not in zebrafish, GHR has retained an exclusive fish intron (10/10A). In gilthead sea bream and turbot, this intron is not alternatively spliced, but the black sea bream intron is either removed or retained during mRNA processing, resulting in a long GHR isoform with a 31 amino acid insertion that does not alter the open reading frame. This or any other GHR variant are not found in gilthead sea bream, but a truncated anchored form has been reported in turbot. The latter GHR isoform comprises extracellular and trans-membrane domains, the first 28 amino acids of the intracellular domain and 21 divergent amino acids before a stop codon. This GHR variant is the result of alternative splicing, being the 3′ UTR and the divergent sequence identical to the sequence of the 5′ end of the 9/10 intron. The physiological significance of different fish GHR isoforms remains unclear, but emerging data provide suitable evidence for season and nutrition related changes in the somatototropic axis activity. The up-regulation of circulating GH together with the decrease of plasma titres of insulin-like growth factor-I (IGF-I), an altered pattern of serum IGF binding proteins and a reduced expression of hepatic IGF-I and GHRs represent a mechanism conserved through vertebrate evolution. It secures the preferential utilization of mobilized substrates to maintain energy homeostasis rather than tissue growth. Somatolactin also changes as a function of season, ration size, dietary amino acid profile and dietary protein source creating opposite plasma GH and SL profiles. There is now direct evidence for a lipolytic effect of fish SL, acting at the same time as an inhibitory factor of voluntary food intake. Indeed, long-term feeding restriction results in the enlargement of the summer GH peak, whereas the SL rise coincident with shortened day length is delayed in juvenile fish until late autumn. These findings agree with the idea that SL may act as a marker of energy surplus, priming some particular process such as puberty onset. However, it remains unclear whether SL works through specific receptors and/or dimers or heterodimers of GH and PRL receptors.

Introduction

Seasonally-changing photoperiod is the primary environmental cue responsible for the endogenous process of parr-smolt transformation in salmonids and growth-reproductive events in most temperate fish species. The pineal gland is known to be involved in the photo-endocrine transduction, and circulating melatonin synthesized from serotonin by photoreceptor cells of the fish pineal gland reflects the prevailing light/dark cycle and calendar time (reviewed in Falcon 1999). Indeed, administered intraperitoneally but not centrally,

melatonin inhibits food intake in goldfish, which suggests its role as a peripheral satiety signal (Pinillos et al. 2001).

The entire system of melanocortin and MCH (melanin-concentrating hormone) receptors has also been conserved through the evolution of vertebrates (Logan et al. 2003), and, in fish, melanin-stimulating hormone (α-MSH) and MCH peptides have retained an antagonistic function in color change and perhaps energy homeostasis (Pissios and Maratos-Flier 2003). More confusing is the occurrence and nature of fish adipostat signals. Tumor necrosis factor (α-TNF) has been cloned and sequenced in several fish species (García-Castillo et al. 2002; Hirono et al. 2000; Laing et al. 2001), but it remains unclear whether mammalian leptin and leptin receptor counterparts exist in fish. Doyon et al. (2001) failed to clone rainbow trout, American eel or goldfish analogues of leptin. No effect of mammalian leptin preparations was found in coho salmon (Baker et al. 2000) and catfish (Silverstein and Plisetskaya 2000). However, murine leptin injections in lizards increased body temperature and metabolic rate (Niewiarowski et al. 2000). Leptin injections also affected cocaine and amphetamine-regulated transcript (CART) levels in goldfish (Volkoff and Peter, 2001), and fatty acid binding protein activity in green sunfish (Londraville and Duvall 2002). Besides, leptin was able to stimulate *in vitro* pituitary LH (luteinizing hormone) secretion in European sea bass (Peyon et al. 2001), and both LH and FSH (follicle-stimulating hormone) secretion in rainbow trout (Weil et al. 2003). One possibility for these contradictory results may be that the amino acid sequence of leptin is less conserved than previously expected, and the effect of mammalian leptin preparations on weight and fat losses in fish requires higher doses and/or a longer time scale. If so, target tissue responsiveness and even biological properties of leptin would have evolved in fish in a different fashion, as the pressure to store energy efficiently at times of abundance may be especially advantageous for vertebrate species having low costs of locomotion and thermoregulation.

In this scenario, the aim of this article is to review recent data about the role of the growth hormone (GH)/prolactin (PRL)/somatolactin (SL) family in fish growth and energy homeostasis. Additionally, attention is focused on the structure and co-evolution of hormones and receptors of GH and PRL, with special reference to genomic organization of GH receptors in relation to their emerging heterogeneity among fish species.

GH and PRL family

Evolutionary origin

GH and PRL are single chain proteins of about 190–209 amino acids that were recognized as members of the same protein family many years ago. Subsequently, this family expanded with the discovery of mammalian placental lactogens (PLs) (reviewed in Walker et al. 1991), fish SL (Rand-Weaver et al. 1991), and more recently with a SL-like protein (Yang and Chen 2003) that shares 56% homology with trout SL. The evolutionary origin of PLs remains controversial, and alternate genes are proposed for primate PLs arising from the GH branch, and non-primate PLs evolving from the PRL lineage (reviewed in Forsyth and Wallis 2002). However, the question of whether SL evolved from already established GH and PRL genes, or independently from the ancestral molecule, remains unresolved (Chen et al. 1995). Furthermore, data from chum salmon and eel hormones suggest that SL evolved from the GH gene (May et al. 1997), whereas comparisons of goldfish, lungfish and European sea bass SL hormones support a PRL origin or an independent evolution (Cheng et al. 1997; Company et al. 2000; May et al. 1999). It is then of special relevance that cysteine residues involved in disulphide bridges, one linking distant parts of the polypeptide chain and another forming a loop close to the C-terminus, are strictly retained in all the members of the GH/PRL family. An additional N-terminal disulphide loop in SLs occurs in PRLs of tetrapods, lungfish and sturgeon, but not in teleostean PRLs or in any GH (Noso et al. 1993a, b). This supports the idea that SL appeared prior to the divergence of bony fish from the lineage leading to tetrapods, and specific gene deletion events most likely occurred between lungfish and the amphibian lineages that lack SL-like peptides (Forsyth and Wallis 2002).

In the latter scenario, the rate of evolution of fish SL was slower than that reported for GH and PRL, which suggested that SL remained more akin to the ancestral protein. Indeed, fish GH and PRL sequences differ markedly from one species to another, especially from eel, and from hormone sequences of lungfish and a primitive actinopterygian fish, the sturgeon (Rand-Weaver and Kawauchi 1993). This presumably explains the lack of activity of teleostean GHs in mammals, although the reverse is not true, and mammalian preparations of GH, PRL and PL potently compete for

fish GH and PRL binding sites (Le Bail et al. 1993; Sandowski et al. 2000).

Genomic organization

As in mammals, the genomic organization of GH genes in channel catfish (Tang et al. 1993) and Cypriniformes such as common carp (Chiou et al. 1990), silver carp (Hong and Schartl 1993) and grass carp (Zhu et al. 1992) reveals the occurrence of five exons and four introns. In rainbow trout (Agellon et al. 1988; Yang et al. 1997), Atlantic salmon (Johansen et al. 1989), tilapia (Ber and Daniel, 1992), flounder (Tanaka et al. 1995), barramundi (Yowe and Epping, 1995) and yellowtail (Ohkubo et al. 1996), the GH gene has an additional intron which probably evolved by independent insertion events. In contrast, in higher vertebrates and in all fish studied so far, including common carp (Chen et al. 1991), chinook salmon (Xiong et al. 1992), tilapia (Swennen et al. 1992) and gilthead sea bream (Astola et al. 2003b), the PRL gene has retained five exons and four introns. This exon-intron organization has also been found in SL genes of chum salmon (Takayama et al. 1991) and gilthead sea bream (Astola et al. 2003a), but they contain large introns in comparison to teleost GH or PRL genes.

GH and PRL receptors

Structural features. Mammalian receptor heterogeneity

More than two decades ago, GH receptors (GHR) and PRL receptors (PRLR) were first characterised in mammals as specific and high affinity membrane-anchored proteins (Boutin et al. 1988; Leung et al. 1987). Both receptors are single trans-membrane spanning proteins and, despite a relatively low degree of sequence identity, share several structural and functional features in common with other unrelated receptors (Kopchick and Andry 2000). All these receptors are now integrated in the superfamily of class 1 cytokine receptors, which includes among others interleukins, granulocyte-colony stimulating factor (G-CSF), granulocyte macrophage-colony stimulating factor (GM-CSF), leukaemia inhibitor factor (LIF), oncostatin M (OM), erythropoietin (EPO), thrombopoietin (TPO), gp 130 and leptin receptors. All of them have retained two pairs of disulphide-linked cysteines in the N-terminal extracellular domain involved in maintaining structural and functional properties. Close to the trans-membrane domain, a conserved WS motif (Trp-Ser-any amino acid-Trp-Ser), substituted in GHRs by the YGEFS (Tyr-Gly-Glu-Phe-Ser) motif, is conserved and probably required for cellular trafficking and correct folding and binding. In the intracellular domain, the greatest degree of sequence homology is found in box 1, a hydrophobic proline-rich segment of eight amino acids proximal to the trans-membrane domain. Box 2, a cluster of hydrophobic and acidic amino acids ending with one or two basic residues, is less conserved and situated towards the C-terminus, approximately 30 residues downstream from box 1. Deletions or mutations in these intracellular boxes prevent activation of cytoplasmatic tyrosine kinases of the Janus (JAK) family, and consequently other signalling pathways that occur after receptor dimerization and JAK phosphorylation (Moutoussamy et al. 1998; Skoda 1999; Zhu et al. 2001).

Transcripts that encode deletions/truncations of trans-membrane or intracellular domains yield soluble forms (GH and PRL binding proteins; GHBP, PRLBP) and different intracellular isoforms (reviewed in Bole-Feysot 1998; Edens and Talamantes 1998). Box 1 but not box 2 is conserved in all membrane PRLR isoforms described so far. In contrast, truncated variants of mammalian GHRs do not retain box 1, and the mechanisms which generate GHBPs can differ from one species to another (Figures 1A and 1B).

Short cDNA clones identical in sequence to the full receptor but few bases before the hydrophobic trans-membrane domain are found in mouse and rat (Smith et al. 1989; Zhou et al. 1996). At this point, the trans-membrane and intracellular encoding-domains are replaced by a short hydrophilic C-terminus (17–27 amino acids) and a divergent 3′ UTR that are encoded by an alternative exon-intron (between exons 7 and 8). Same as mice and rats, monkeys express an alternative GHR transcript that diverges in sequence 8 bp before the beginning of the trans-membrane encoding-domain (Martini et al. 1997). Downstream of this divergent point, the sequence of the monkey GHBP transcript is identical to the 5′ end of intron 7/8. This GHBP, however, can also be generated by proteolytic cleavage of the full-length GHR. Indeed, in other species like humans, proteolytic cleavage is considered the only GHBP generating mechanism, although no specific proteases intervening in this process have been identified (Bauman and Frank 2002). Truncated GHRs appear to be more susceptible to this post-translational processing, and the presence of different GHR

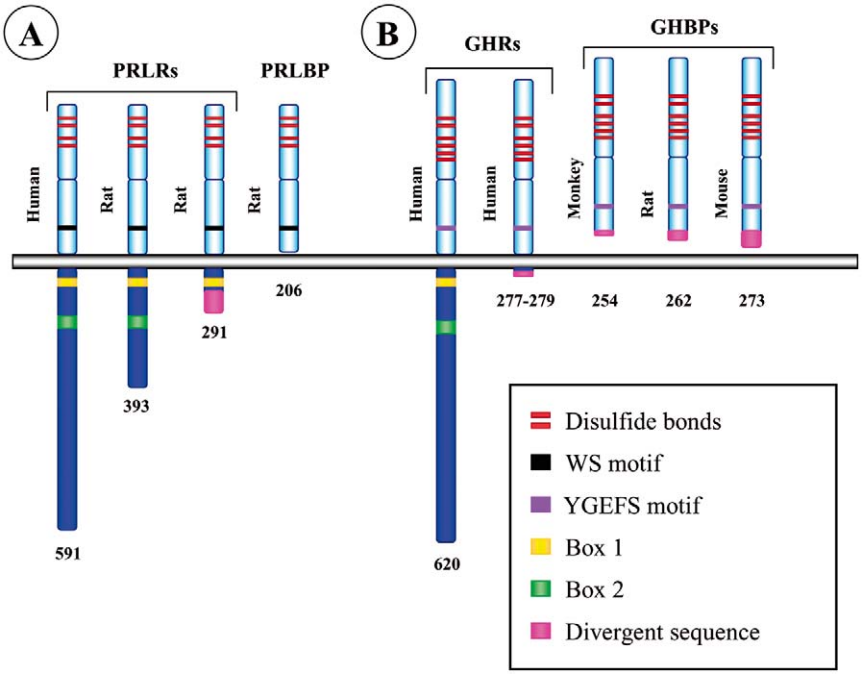


Figure 1. (A) Diagrammatic representation of prolactin receptors (PRLR) and prolactin binding proteins (PRLBP) in mammals (modified from Bole-Feysot et al. 1998). (B) Diagrammatic representation of growth hormone receptors (GHR) and growth hormone binding proteins (GHBP) in mammals (modified from Moutoussamy et al. 1998).

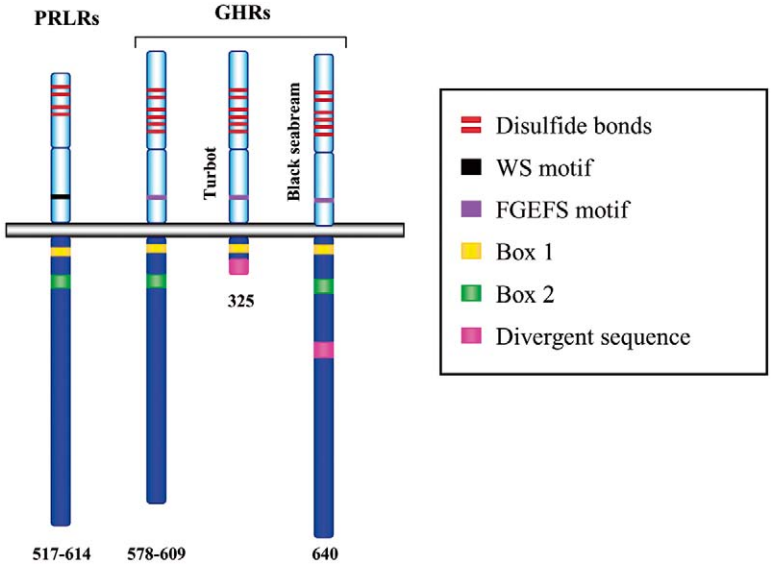


Figure 2. Diagrammatic representation of fish prolactin receptors (modified from Manzon 2002) and fish growth hormone receptors with truncated and long isoforms of turbot (Calduch-Giner et al. 2001) and black seabream (Tse et al. 2003), respectively.

transcripts encoding membrane anchored GHR isoforms has been confirmed in humans by means of PCR (Dastot et al. 1996). Cloning and sequencing of these GHR transcripts reveals that deletion of the first 26 bp of exon 9 would give rise to a protein with the first 273 amino acids of GHR (the 246-amino acid of the extracellular domain, the 24-amino acid transmembrane domain, and the first 3 amino acids of the intracellular domain), followed by 6 novel intracellular amino acids before a stop codon (GHR_{279}). A second related GHR messenger has been isolated from the same human hepatic cDNA library. In this transcript, exon 9 is absent due to direct joining of exon 8 and exon 10, with a resulting frame shift that would produce a GHR protein with a divergent 7-amino acid intracellular domain (GHR_{277}).

Fish GHRs and PRLRs. Genomic organization and alternative splicing

The first full-length PRLR cDNA was cloned and sequenced in tilapia (Sandra et al. 1995). Since this initial discovery, PRLRs from goldfish (Tse et al. 2000), rainbow trout (Le Rouzic et al. 2001), gilthead sea bream (Santos et al. 2001) and Japanese flounder (Higashimoto et al. 2001) have been cloned and sequenced. All of them retain the characteristic features of PRLRs, and the homology between fish and higher vertebrate PRLRs is equal to the homology between fish and mammalian PRLs (37%), which suggests coevolution of PRL and its receptor (see Manzon 2002). However, it is of interest that the most divergent sequence is that of gilthead bream, which is 70–100 amino acids shorter that any other PRLR, and several gaps should be introduced for a proper alignment of the cytoplasmatic region. Thus, cytoplasmatic tyrosines and key regions like box 1 and box 2 are highly conserved, but distances among these landmark domains are highly variable as was also reported for fish GHRs.

Fish GHRs were first cloned and sequence in goldfish (Lee et al. 2001) and turbot (Calduch-Giner et al. 2001). More recently, full-length GHRs have been cloned and sequenced in two sparid fish: black sea bream (Tse et al. 2003), and gilthead sea bream (Calduch-Giner et al. 2003). The amino acid sequence identity between these two closely related species is near to 96%, and decreases to 76%, 52% and 27% when comparisons are made with turbot, goldfish and human GHR sequences, respectively. Therefore, phylogenetic trees based on GHR sequences display clustering similar to that found for the hierarchy of vertebrate species, and sequence homologies parallel GH sequences of Sparidae (Martínez-Barberá et al. 1994), Cypriniformes (Law et al. 1996) and Pleuronectiformes (Pendón et al. 1994). The consensus sequence also shows conservation of all the characteristic features of GHRs, with three pairs of extracellular cysteine residues that establish disulphide bonds (Fuh et al. 1990). These cysteine residues are also present in unpublished sequences of halibut (GenBank accession number, AB058418), grass carp (GenBank, AY283778) and catfish (GenBank, AY336104) GHRs. Three other unpublished GHR sequences of salmonids (GenBank AB071216; AF403539; AF403540), lack the fifth and sixth cysteine residues. Nevertheless, partial cloning and sequencing of GHR in rainbow trout reveals strict conservation of extracellular cysteine residues (GenBank, AF438178). The unpaired cysteine that participates in the human GHR dimerization, forming an intermolecular disulphide bond (Zhang et al. 1999), is present in all vertebrates studied so far. Nevertheless, in *Xenopus* and fish species, this seventh cysteine is located upstream instead of downstream of the FGEFS motif.

Northern blot analysis shows that the sizes of GHR transcripts in goldfish (Lee et al. 2001) and gilthead sea bream (Calduch-Giner et al. 2003) are close to 4–5 Kb. However, a shorter alternative transcript is found in turbot (Calduch-Giner et al. 2001), and it encodes a membrane anchored protein that comprises extracellular and trans-membrane domains, the first 28 amino acids of the intracellular domain and 21 divergent amino acids before a stop codon is reached (GHR_{325}). In black sea bream, Tse et al. (2003) also reported an alternatively spliced intron of 93 bp that is either removed or retained during mRNA processing. This short DNA insertion, encompassing 106 amino acids downstream of the trans-membrane domain, does not alter the open reading frame and the lack of alternative splicing should give rise to a longer GHR variant (GHR_{640}) (see Figure 2). Exhaustive searches for alternatively spliced GHR variants in gilthead sea bream by means of Northern blot, 3′ RACE, and PCR screening failed to detect transcripts encoding soluble forms or any other GHR variants, although cross linking GH assays show two bands as the result of a different degree of glycosylation of the same core protein – full GHR – (Calduch-Giner et al. 2003). Nevertheless, partial PCR mapping of genomic DNA with primers derived from cDNA sequences (Table 1) shows the same exon-intron organization of GHRs in Pleuronec-

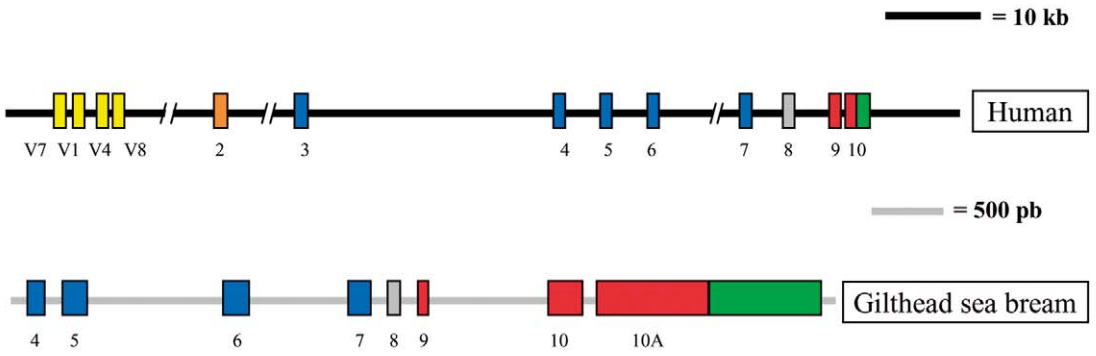
Table 1. Forward (f) and reverse (r) primers for PCR mapping (exon-intron organization) of GHRs genes of gilthead sea bream (fsb, rsb) and turbot (ft, rt). PCR consisted of 35 cycles of 1 min at 94 °C, 2 min at 55–57.5 °C and 3 min at 72 °C

Primer	cDNA position
4fsb: 5′-CGC ATT TCA CGG AGT GCA TAT CG	53–75
5rsb: 5′-CTA CGG TGA AAC AGT AGT CCT CGT CCA G	304–331
5fsb: 5′-CCA ACA GTG AAT GGA AAG AGT GTC CG	176–201
6rsb: 5′-GGC TCC CAG TTG ACC ATG ACA TCA TAA C	404–431
6fsb: 5′-CCC TCT GGG CTC AGT TAT GAT GTC ATG G	391–418
7rsb: 5′-TCT CAG TCA CTT GAA TGA ACA CGG AGT C	634–661
7fsb: 5′-GCC GCA CAC CCA GCA GAC AAT CTA C	531–555
8rsb: 5′-GCT GAG AGA TGC CAA TGA GCA AGA TGA G	730–757
8fsb: 5′-TTT GGG CAT CCT CAT ACT CAT CTT GCT C	714–741
9rsb: 5′-AGG AAC CGG CGG CAA CAG AAT C	774–795
9fsb: 5′-ATT CTG TTG CCG CCG GTT CCT G	775–796
10rsb: 5′-GTT GGC GCA CCC TGT GTT CAT G	1041–1062
10fsb: 5′-AGA CGA GCC ATG GGT GGA GTT CAT CGA	918–944
11rsb: 5′-CGT TGC TGA CCT GGG CAT AGA AGT C	1282–1306
12rsb: 5′-CCT AAA GTG GCA GTG TCA TTT CAT GGT G	1823-1850
4ft: 5′-GCC TCA TTT CAC TGA GTG CAT CTC AAG	57–83
5rt: 5′-GAA GAA GCA CTC CCG CTT CGA ATG	217–240
5ft: 5′-AGA GAG TGT CCA CAG TAC ATC CAT TCG AAC	196–225
6rt: 5′-GGG CTC CCA GTT GAC CAT GAC ATC	412–435
6ft: 5′-CAG TGT CTC TAA ACT GGA CCC TCC TGA AC	359–387
7rt: 5′-CAC GTG AAT GAA GAT GGA ACT GCT GAA C	630–657
7ft: 5′-CCC AGA GTC AGC AGA CAA TCT TCG G	536–560
8rt: 5′-CAT GAT GAG TAT GAG GAT GCC CAC AAT C	714–741
8ft: 5′-TTC CCT CTC GCG GTT GTT CTT G	685–706
9t: 5′-CAG GAA CTG GTG GCA GCA GAA TCA TC	774–779
9ft: 5′-GAT TCT GCT GCC ACC AGT TCC TGC	777–800
10rt: 5′-ACC CTA TGT TCA TGT GGT GGC TGA CG	1032–1057
10ft: 5′-AGA CGA GCC ATG GGT GGA GTT CAT CGA	921–947
11rt: 5′-CAT TGC TGA CCT GCG CAT AGA AGT C	1285–1309
12rt: 5′-CAC CCA TAG GTC CAT TGG CAT TGT C	1834–1858

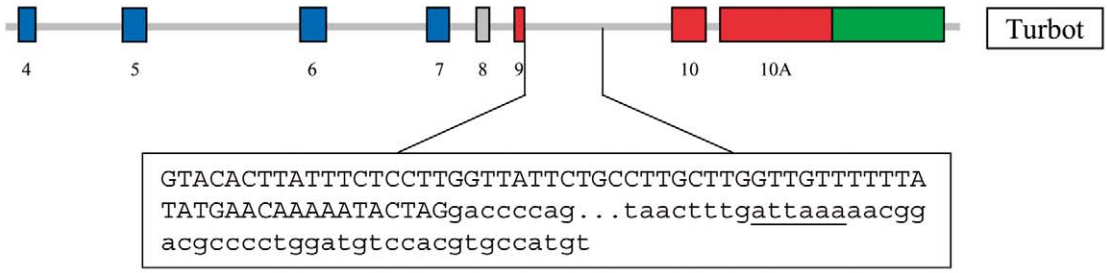
tiformes (turbot; GenBank, AY345330) and Perciformes (gilthead sea bream; GenBank, AY345329).

The results of PCR amplification of turbot and gilthead sea bream genomic DNA yields several clones that cover 6 different exons, homologous to exons 4–9 of the human GHR gene. Besides, the divergence sequence and the 3′ UTR of the truncated variant of turbot GHR is identical to the sequence of the 5′ end of the 9/10 intron. The alternative spliced intron (10/10A) of black sea bream also exists in gilthead sea bream and turbot. In gilthead sea bream, this intron (non spliced) has the same length (93 bp) as that of black sea bream, but with a relative low degree of amino acid identity (60%). In turbot, the 10/10A intron (113 bp) contains stop codons, which indicate that longer GHR isoforms are not feasible. Indeed, all intron-exon boundary sequences conform to the GT-AT rule, and surrounding nucleotides closely relate to consensus sequences found near spliced junctions. Fish introns are, however, much shorter than those found in higher vertebrates, and the major part of the translated GHR sequence extends over 6 Kb, with exons 4–7 coding for the extracellular domain, exon 8 coding for the trans-membrane domain, and exons 9, 10 and 10A coding for intracellular and 3′ UTR domains (Figure 3).

The screening of zebrafish and fugu genome databases (http://www.ensembl.org) for the analysis of assembled DNA sequences of GHRs show a strict conservation of exons 4–9. Indeed, the exclusive fish intron (10/10A) is retained in fugu but is absent from zebrafish (Figure 4). The evolutionary significance of intron 10/10A is now unclear, although probably this intron evolved from different DNA insertion events



Exon	Exon size	cDNA position	Exon-intron junctions	Intron	Intron size
4	>118	53-170	...AAGAAAGA**gt**gagtgt	4/5	109
5	170	171-340	tacgtc**ag**CTCGCCCA...GAATATCG**gt**cagtga	5/6	993
6	179	341-519	cctggc**ag**TGCGTCCT...GGGAAGCA**gt**aagtcg	6/7	685
7	155	520-674	tactgc**ag**TTGGAGAT...CAGCCAGG**gt**aagatc	7/8	135
8	90	675-764	ttttt**ag**ACTCTAAT...CAGCCCAG**gt**acgtac	8/9	113
9	70	765-834	cgttgc**ag**ATTAATGA...TGTTAAAG**gt**acattt	9/10	844
10	236	835-1057	tcttgc**ag**AAGGGGAA...GCCGTCAG**gt**actgca	10/10A	93
10A	>780	1058-1837	gcctcc**ag**CTTTCCTG...TCACCG TGA ...		



Exon	Exon size	cDNA position	Exon-intron junctions	Intron	Intron size
4	>120	57-176	...AAGAAAGA**gt**gagtgc	4/5	594
5	167	177-343	tccacc**ag**GTCTCCAA...AAACATTG**gt**gagcaa	5/6	1056
6	179	344-522	cctggc**ag**TACGTCCG...GGGAAGCA**gt**gagtgt	6/7	695
7	154	523-676	tattgt**ag**TTGGAGAT...CAGCAGAG**gt**aaaatc	7/8	174
8	91	677-767	ttttt**ag**AGACTACT...CAGCACAG**gt**aggaac	8/9	146
9	70	768-837	tgctgc**ag**ACTCATGA...TGTTGAAG**gt**acactt	9/10	992
10	236	838-1073	acatgc**ag**AAGGGGAA...GCCATTAG**gt**actgca	10/10A	113
10A	>785	1074-1858	cccccc**ag**CTTCCCTGCACCA...		

Figure 3. Diagrammatic representation of exon-intron organization of human (GenBank, AH002706), gilthead sea bream (GenBank, AY345330) and turbot (GenBank, AY345329) growth hormone receptors. Exon 2 (orange) codes for signal peptide; exons 3–7 (blue) for extracellular domains; exon 8 (grey) for trans-membrane domain; exons 9, 10 and 10A for intracellular (red) and 3′ UTR (green) domains. Exon-intron junctions of turbot and gilthead sea bream GHRs are indicated. The alternative spliced region of intron 9/10 of turbot is noted.

after the divergence of fish and mammalian lineages approximately 450 million years ago. Further studies on primitive fish are needed to better understand the structure and evolution of fish GHRs, and their relationship with the new GHR isoforms being identified. The existence of these alternative GHR isoforms represents an additional level of regulation of GH action in target tissues, although a high degree of variability even for very close related species is suspected.

Functions and regulation of the hormones

Nutritional regulation of somatotropic axis: molecular and physiological aspects

Nutritional status plays a major role in regulating circulating levels of GH, insulin-like growth factor-I (IGF-I), and their respective binding proteins (GHBP, IGFBP) as well as cell membrane receptors. In gilthead sea bream, as in other fish species, fasting is accompanied by the elevation of plasma GH levels. An increase in plasma GH is also observed following decrease of ration size and dietary energy content (Pérez-Sánchez et al. 1995; Company et al. 1999). However, the amount of dietary proteins seems to be the most important factor regulating GH availability and GH-liver responsiveness in the gilthead sea bream, which has high dietary protein requirements (Martí-Palanca et al. 1996; Company et al. 1999). A pronounced increase in circulating GH was also observed in gilthead sea bream fed diets with poorly balanced amino acid profiles (Gómez-Requeni et al. 2003b), and a high level of fish meal replacement by plant proteins (Gómez-Requeni et al. 2003a). This observation was related to decrease in plasma IGF-I levels in concurrence with a reduced expression of hepatic IGF-I and GHR genes, the features characteristic for catabolic state. Therefore, liver GH desensitization and the inverse relationships between plasma GH and IGF-I concentrations represent, a conserved mechanism for the preferential utilization of mobilized substrates to maintain energy homeostasis, rather than cell growth and proliferation, under either reduced nutrition or malnutrition (reviewed in Renaville et al. 2002).

In tilapia, an inverse relationship between food intake and circulating GH levels has also been reported (Toguyeni et al. 1996), but studies in salmonids often fail to demonstrate the down-regulation of GH at greater than maintenance rations (Pierce et al. 2001; Storebakken et al. 1991). Indeed, feeding during winter is required to maintain sensitivity of the GH-IGF-I axis (Larsen et al. 2001), although fine-tuning of the somatotropic axis varies among fish species and perhaps fish strains (Valente et al. 2003), which, in turn, would reflect changes in basal GH release, metabolic clearance rate of GH, and IGF-I mediated feedback. Interestingly, a recent study on rainbow trout shows that the concurrent increase of temperature and ration size promotes growth through the enhancement of hepatic synthesis and release of IGF-I (Gabillard et al. 2003). However, these authors also found that white muscle expression of IGF-I and IGF-II remained unaltered irrespective of growth rates, so, they concluded that the paracrine/autocrine expression of IGFs does not play a key role in the growth promoting effects of temperature and nutrient supply.

Current understanding of the physiological role of fish IGFBPs is also gaining momentum: There is now evidence for at least three serum IGFBPs, including a high molecular weight form (40–50 kDa) and two IGFBPs in the 31–24 kDa size range (Kelley et al. 1992; Niu and Le Bail 1993; Park et al. 2000). A 41 kDa IGFBP has been purified from chinook salmon serum (Shimizu et al. 2003), and a complementary tilapia cDNA with a 50% homology to mammalian IGFBP-3 has also been cloned and sequenced (Cheng et al. 2002). As in mammals, this higher MW IGFBP is the most abundant circulating IGF carrier under normal physiological conditions, up-regulated by feeding and GH treatment. In contrast, lower MW IGFBPs are often at or below the limit of detection in fed fish, and up-regulated several folds under catabolic conditions (Kelley et al. 2001, 2002). After gilthead sea bream IGFBP-2 (Funkenstein et al. 2002) and zebrafish IGFBP-1 and -2 (Duan et al. 1999; Maures and Duan 2002) have been cloned and sequenced, it became very likely that the ≤ 31 kDa IGFBPs, originally identified by Western ligand blotting, might indeed be IGFBP-1 and -2. Alternatively, doublets of higher molecular weight proteins might represent different glycosylated forms of IGFBP-3.

In mammalian IGFBPs, two glycosylation sites are always utilised, and the incorporated carbohydrates account for an estimated 4–4.5 kDa increase in molecular weight. The third alternative glycosylation site incorporates 5 kDa of carbohydrates, accounting for the characteristic doublet (40–45 kDa) with a core protein size of 29 kDa (reviewed in Firth and Baxter 2002). Fish IGFBP-3 also exists as glycosylated protein (Shimizu et al. 2003), and Shimizu et al. (1999) found in coho salmon serum a doublet of 45–34 kDa.

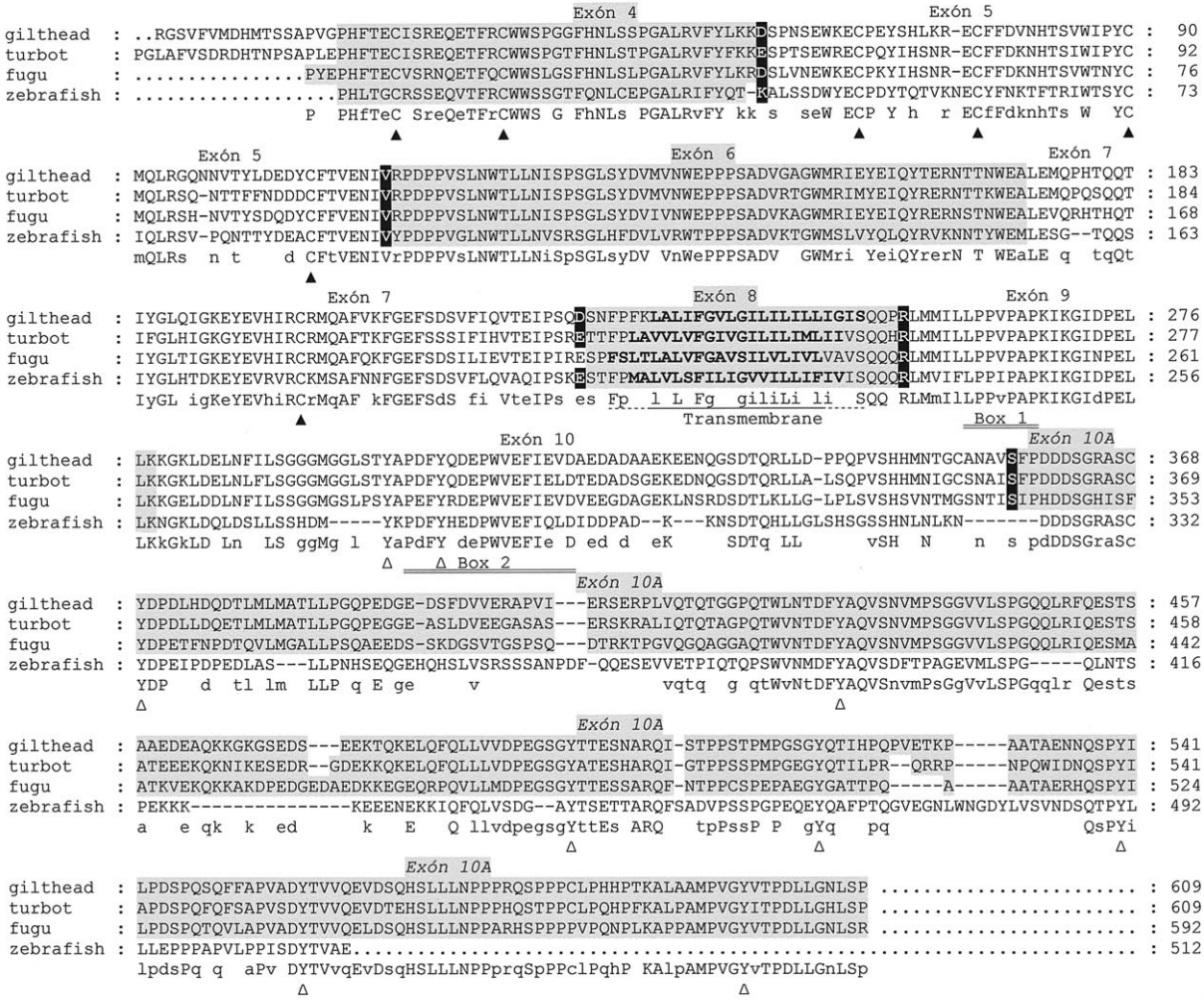


Figure 4. Alignment of deduced amino acid sequences of mature gilthead sea bream, turbot, fugu and zebrafish growth hormone receptors. Exon alternatig is shown by changing background color. Amino acid residue overlap is shown by a black background. Fugu and zebrafish sequences are the result of the predicted assembled analysis (htpp://www.ensembl.org). The precise start of exon 4 is unresolved in gilthead sea bream and turbot (cDNA position: < 53–57). Note that exons 10 and 10A exist as a single exon in zebrafish (exon 10). Trans-membrane (bold letters), Box 1 and Box 2 domains are indicated. Conserved cysteines and cytoplasmatic tyrosines are indicated by black and white triangles, respectively.

Using trout IGF-I as a radioligand, we also detected by Western ligand blot two bands in trout serum, and the 45/34 kDa IGFBP ratio increased when more plant protein was supplied by fish meal replacement. Total circulating levels of IGF-I, and hepatic expression of IGF-I and GHRs remained unaltered, but the reduction of growth rates with a plant proteins implies that the nutritionally regulated IGFBP-3 ratio can play an important role in target tissue responsiveness to IGF action (Gómez-Requeni et al. unpublished results). However, the regulation of metabolic needs to enhance animal growth by somatotropic axis is based not only on the nutritional supply, but also on the genetic background. Unfortunately, few studies exist on a possible relationship between gene polymorphism and fish metabolism, and future investigations are needed to forward these studies in relation to fish enhanced growth and well-being.

GH and SL paradigm

In mammals, leptin is part of the negative feedback loop of GH, stimulating GH release through the down-regulation of hypothalamic neuropeptide Y (NPY) (reviewed in Harris 2000). There is no data about the

effect of mammalian leptin on fish GH, but a recent *in vitro* study shows a stimulatory effect of murine leptin upon European sea bass somatolactin (Peyon et al. 2003). The physiological significance of this leptin effect remains unclear. However, it highlights the complex regulation of the fish pituitary axis, and the emerging role of SL in maintaining energy homeostasis. In this context, the nutritional regulation of fish SL has been addressed in gilthead sea bream, and there is now evidence for an inverse relationship between plasma GH and SL levels. Thus, plasma SL levels elevate with the increase in ration size and fatness, and this SL responsiveness often parallels the increase in circulating IGF-I levels (Company et al. 2001). However, a single intraperitoneal injection of GH, but not of SL, increases circulating levels of IGF-I in juvenile gilthead sea bream (Vega-Rubín de Celis et al. 2003a). This lack of enhancement of IGF-I by SL is consistent with previous *in vitro* studies in salmonids (Duan et al. 1993, 1994), reinforcing the idea that SL has not retained a growth promoting effect through fish evolution. To the contrary, both GH and SL decrease the respiratory quotient (CO_2 output per O_2 uptake) in juvenile gilthead sea bream, inhibiting the hepatic activity of acetyl-coenzyme A carboxylase, a key lipogenic enzyme (Vega-Rubín de Celis et al. 2003a). These findings provide direct evidence for a lypolytic action of both GH and SL, which agrees with the involvement of SL in energy mobilisation as has been proposed in salmonids on the basis of plasma changes during reproduction (Kakizawa et al. 1995b; Rand-Weaver et al. 1992; Taniyama et al. 1999), acute stress (Rand-Weaver et al. 1993) and exhaustive exercise (Kakizawa et al. 1995a).

Changes in growth associated with changes in dietary amino acid profiles and protein sources also affect plasma SL availability in gilthead sea bream. In a characteristic pattern, plasma SL levels decrease with impaired growth performance, confirming the different regulation of SL and GH (Vega-Rubín de Celis et al. 2003b). The post-prandial regulation of these two hormones also differs: plasma GH levels are higher following overnight fasting than few hours after feeding (Gómez-Requeni et al. 2003b), while plasma SL levels are higher at six hours after feeding than following overnight fasting (Vega-Rubín de Celis et al. 2003b). Therefore, for a given nutritional condition and particular fish size, the increase of circulating GH levels would reflect some energy deficit, whereas plasma SL levels are up-regulated in a direct or indirect manner by energy surplus and perhaps adipostat signals.

Seasonal timing

Light is considered to be a determining factor that adjusts circannual rhythms by delaying and/or shortening periods of reduced growth. In salmonids, a growth-promoting effect of continuous light has been reported on fish maintained either in freshwater (Handeland and Stefansson 2001) or seawater environment (Hansen et al. 1992; Endal et al. 2000; Handeland et al. 2003). Similar results have been documented in marine fish, e.g. turbot (Boeuf et al. 1999), cod (Otterlei et al. 1999), halibut (Jonassen et al. 2000), European sea bass (Rodríguez et al. 2001) and gilthead sea bream (Silva-García, 1996; Kissil et al. 2001). This has led to the use of seasonally compressed photocycles or phase advanced photoperiods to inhibit sexual maturation or advance the timing of smoltification in farmed fish stocks (Berrill et al. 2003; Komourdjian et al. 1976; Porter et al. 1999).

Life-history decisions are, however, not fixed and often depend on critical size and sufficient energy at a specific stage 'opportunity window' several months prior to transformation itself. For instance, the decision in salmonids to become smolts or to sexually mature is linked to growth and fat deposition at mid summer and spring (Shearer and Swanson 2000; Silverstein et al. 1997, 1998). The factors underlying the fine tuning of these decisions need to be investigated, but circumstantial evidence indicates that the GH-IGF-I axis provides an integrated signal for growth and nutrient partitioning year-round. Thus, plasma GH levels commonly peaked at late spring and early summer (Beckman and Dickhoff 1998; Einarsdottir et al. 2002; Pérez-Sánchez et al. 1994), whereas ongoing studies on gilthead sea bream revealed that the plasma peak of PRL is delayed in non-mature fish to midsummer. The time of SL increase was further delayed until autumn, although juvenile growing fish need to attain a threshold size before they can up-regulate plasma SL during day shortening period in the autumn (Mingarro et al. 2002). It appears therefore in gilthead sea bream, that the regulation of the annual cycle of GH, PRL and SL is different for each hormone irrespective of some overlapping functions (Figure 5). In agreement with this, pituitary expression of GH, PRL and SL in growing and maturing masu salmon is sensitive to GnRH during different seasons (Bhandari et al. 2003).

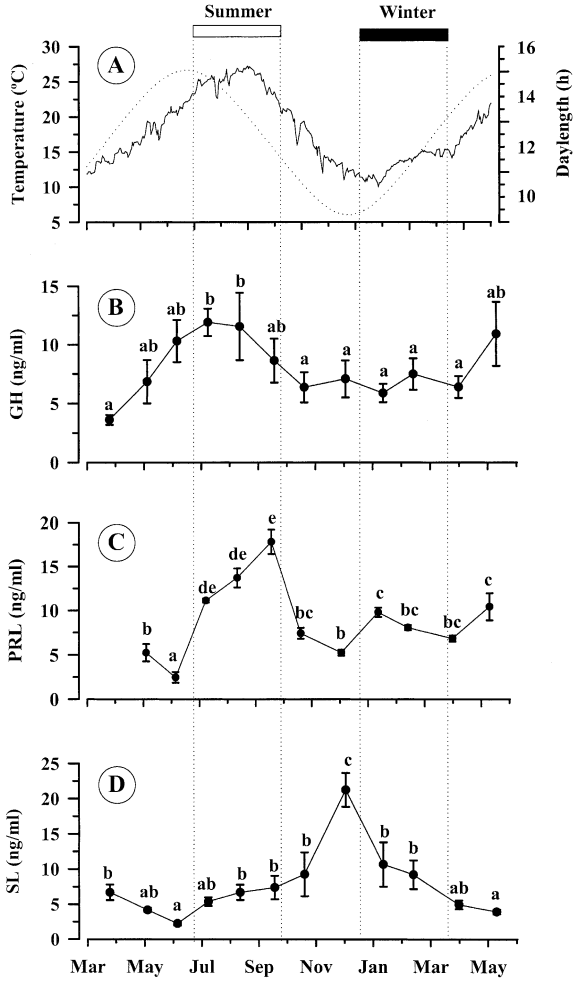


Figure 5. Annual changes of plasma levels of growth hormone (A), prolactin (B) and somatolactin (C) in juvenile gilthead sea bream (modified from Mingarro et al. 2002). Fish were fed restricted diets over experimental period. Prolactin was measured by an enzyme-linked immunosorbent assay based on the use of recombinant gilthead sea bream prolactin as a ligand. The ED_{50} value was 6.5 ng ml^{-1}. Data are the mean $\pm$SEM of 12–15 animals. Different case letters indicate significant differences at $P < 0.05$ (Student-Newman-keuls). Black and white bars at the top of the figure refer to summer and winter period.

Of particular interest is the different effect of IGF-I on fish GH and PRL secretion. The inhibitory action of IGF-I on pituitary GH release was demonstrated several years ago (Pérez-Sánchez et al. 1992; Weil et al. 1999). In contrast, there is an emerging evidence for a stimulatory action of IGF-I on PRL secretion (Fruchtman et al. 2000, 2001). Since the summer increase in circulating IGF-I is often delayed in relation to the seasonal GH peak, it is tempting to suggest that IGF-I mediates, at least in part, the summer spurt of PRL in non-maturing gilthead sea bream. Fish PRL has been traditionally considered a lipolytic factor (Sheridan and Kao 1998; Leena et al. 2001), but literature provides evidence that lactogenic hormones may have lipogenic as well as lipolytic effects *in vivo.* It has been reported that: a) PRL stimulates food intake and fat deposition in female rats (Byatt et al. 1993; Sauve and Woodside, 1996) and contributes to the seasonal fattening of birds in preparation for migration (Sharp et al. 1998; Sharp and Blache 2003); b) hyperprolactinemia in men and non-pregnant women may be accompanied by weight gain (Greenman et al. 1998; Ferreira et al. 1998). Finally, PRL knockout mice show hypoleptinemia and reduced weight gain and abdominal fat mass (Freemark et al. 2001). If so, we cannot exclude a role for PRL in the replenishment of body fat stores of fast growing gilthead sea bream over the course of the second half of the summer period. After this, the autumn rise of SL may reflect a state of energy surplus, acting perhaps as a trigger of different processes, like reproductive onset, if the required energy status is reached at the precise time of the year.

Several studies have been performed to confirm this hypothesis of nutritionally regulated hormone responsiveness, the results of which suggest that there is a critical window for GH and SL release that can be overridden by changes in the metabolic energy balance. Attention was focused on feeding regimens and there is evidence for an improved growth performance and immunological status in fish on long-term restricted feed (Sitjà-Bobadilla et al. 2003). In these fish some kind of compensatory growth occurs during the summer growth spurt. At the same time, fish fed *ad libitum* show the higher amplitude of the summer GH peak whereas the autumn rise of SL is delayed (Figure 6). Besides, our studies in progress have indicated that a single intraperitoneal injection of SL (0.1 μg g^{-1} fish) provokes a transitory inhibition of voluntary food intake in gilthead sea bream. These findings suggest that SL could act not only as a marker of energy surplus, but also as a peripheral satiety factor. However, further studies are needed to better understand the nutritional regulation of SL and somatotropic axis. Also, it remains to be established whether fish SL works through specific receptors and/or dimers or heterodimers of GH and PRL receptors. Solving these problems would represent a key step for the understanding of the regulation of fish growth and adiposity year-round.

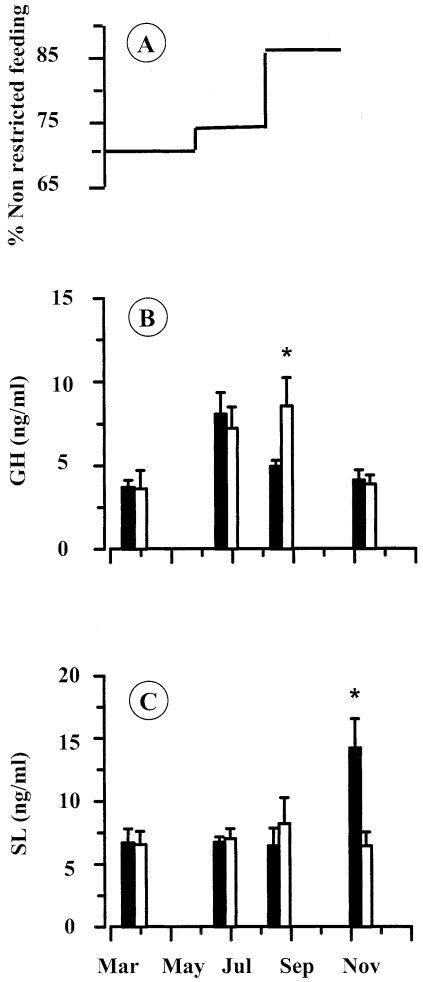


Figure 6. Effect of long-term feed restriction on plasma levels of growth hormone (B) and somatolactin in juvenile gilthead sea bream (C). Graph at the top of the figure (A) refers to food intake in restricted fed fish (percentage of non-restricted feeding). Values of growth hormone and somatolactin are the mean ± SEM (n = 12–15). Restricted diet (white bars); non-restricted diet (black bars). *, Significant differences between restricted and non-restricted fish (Student *t*-test, $P < 0.05$).

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