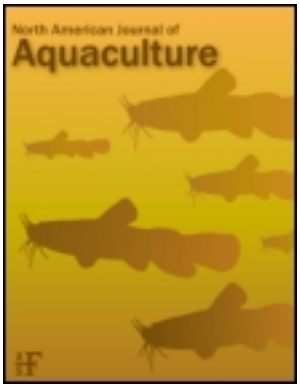

North American Journal of Aquaculture
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/unaj20

Endocrine Biomarkers of Growth and Applications to Aquaculture: A Minireview of Growth Hormone, Insulin-Like Growth Factor (IGF)-I, and IGF-Binding Proteins as Potential Growth Indicators in Fish

Matthew E. Picha [a] , Marc J. Turano [b] , Brian R. Beckman [c] & Russell J. Borski [a]

[a] Department of Zoology, North Carolina State University, Raleigh, North Carolina, 27695, USA

[b] North Carolina Sea Grant, North Carolina State University, Raleigh, North Carolina, 27695, USA

[c] NOAA Fisheries, Northwest Fisheries Science Center, 2725 Montlake Boulevard East, Seattle, Washington, 98112, USA

Version of record first published: 09 Jan 2011.

To cite this article: Matthew E. Picha, Marc J. Turano, Brian R. Beckman & Russell J. Borski (2008): Endocrine Biomarkers of Growth and Applications to Aquaculture: A Minireview of Growth Hormone, Insulin-Like Growth Factor (IGF)-I, and IGF-Binding Proteins as Potential Growth Indicators in Fish, North American Journal of Aquaculture, 70:2, 196-211

To link to this article: http://dx.doi.org/10.1577/A07-038.1

North American Journal of Aquaculture 70:196–211, 2008

DOI: 10.1577/A07-038.1

[Article]

Endocrine Biomarkers of Growth and Applications to Aquaculture: A Minireview of Growth Hormone, Insulin-Like Growth Factor (IGF)-I, and IGF-Binding Proteins as Potential Growth Indicators in Fish

MATTHEW E. PICHA
Department of Zoology, North Carolina State University, Raleigh, North Carolina 27695, USA

MARC J. TURANO
North Carolina Sea Grant, North Carolina State University, Raleigh, North Carolina 27695, USA

BRIAN R. BECKMAN
NOAA Fisheries, Northwest Fisheries Science Center, 2725 Montlake Boulevard East, Seattle, Washington 98112, USA

RUSSELL J. BORSKI*
Department of Zoology, North Carolina State University, Raleigh, North Carolina 27695, USA

Abstract.—Growth in fish and other vertebrates is under endocrine control, particularly through the growth hormone (GH)–insulin-like growth factor (IGF) axis. For this reason, it has been of interest to aquaculture researchers and the industry to establish endocrine biomarkers that can both reflect and predict growth rates in fish subject to various biotic and abiotic manipulations. Ultimately, by understanding the hormones that control growth and utilizing them as biomarkers, we hope to achieve optimal growth conditions in the aquaculture environment with less need for lengthy and costly grow-out trials. While the most appropriate endocrine biomarkers for growth can be both species and situation specific, IGF-I may be the most promising candidate for measuring instantaneous growth in fish. This is based on the direct contributions of IGF-I in regulating cell proliferation and ultimately somatic growth, along with its previously established correlations with the specific growth rate in fish under various conditions that alter growth. However, other endocrine indices, such as GH and IGF-binding proteins (IGFBPs), are also important contributors and may in some instances prove a strong corollary to growth rate. This review discusses the potential utility of GH, IGF-I, and IGFBPs as growth biomarkers for those manipulations most relevant to the aquaculture industry, namely, feeding regimen, diet composition, temperature, photoperiod, and stress.

For aquaculture producers, the ability to minimize production costs is critical to competing in a global market place. Since endocrine responses to both environmental and genetic variables ultimately control growth in fish and other vertebrates, evaluation of these hormonal indices could prove useful in establishing biomarkers for growth. Therefore, we will build the case that endocrine indices might provide not only useful biomarkers for growth but also an endocrine foundation for understanding the variation in growth that will help producers design efficient rearing regimens for cultured fish. To do this, we will review the utility of certain endocrine factors as potential growth biomarkers in warm- and coolwater aquacultured fishes and analyze their practicality for use in the industry.

In fish, as in mammals, the endocrine control of growth works through the growth hormone (GH)–insulin-like growth factor (IGF) axis (Figure 1; reviewed by Oksbjerg et al. 2004; Wood et al. 2005; Reinecke 2006). Endogenous (nutritional state and humoral factors) and exogenous (temperature and photoperiod) cues integrated by the hypothalamus lead to the subsequent release of either stimulatory (GH-releasing hormone) or inhibitory (somatostatins) signals onto somatotrophs (GH-producing cells) in the anterior pituitary (see Björnsson et al. 2002 and Canosa et al. 2007 for reviews). Under anabolic conditions, GH released from the pituitary enters the circulation and binds to hepatic GH receptors, stimulating the synthesis and release of IGF-I into the bloodstream. Insulin-like growth factor-I, a 7.5-kDa single-chain polypeptide, is responsible for cell differentiation and

* Corresponding author: russell_borski@ncsu.edu

Received April 12, 2007; accepted July 25, 2007
Published online March 27, 2008

proliferation, the stimulation of processes related to skeletal elongation, and ultimately for body growth (see Duan 1997 and Le Bail et al. 1998 for reviews). Plasma IGF-I, in turn, acts in a negative feedback fashion to inhibit GH secretion from the pituitary (Fruchtman et al. 2000). Hence, GH and IGF levels are tightly controlled to maintain the appropriate growth homeostasis. While hepatically derived IGF-I accounts for the majority of the circulating peptide (Shamblott et al. 1995), GH can also stimulate the synthesis of IGF-I in nonhepatic tissues such as skeletal muscle (Kajimura et al. 2001). If translated, this locally produced IGF-I can act in a paracrine–autocrine manner to initiate cell proliferation (Chauvigné et al. 2003; Pedroso et al. 2005). Additional evidence also suggests that GH has anabolic effects on these tissues independent of IGF-I, at least in mammals (reviewed by Ohlsson et al. 1998). Since the majority of IGF-I in the extracellular space and plasma is bound to IGF-binding proteins (IGFBPs), they are central modulators of IGF actions. These carrier proteins not only increase the IGF half-life but can mediate their transport from the vascular space to target tissues, determine tissue distribution, and inhibit or potentiate IGF activities. They also bind IGF-I with affinities similar to those of the type-1 IGF receptor (IGFR; reviewed by Kelley et al. 2002, 2006; Duan and Xu 2005). Approximately four IGFBP homologs of mammalian IGFBPs have been identified in fish at the protein level (IGFBP-1, -2, -3, and -5), while five full IGFBP coding sequences (IGFBP-1, -2, -3, -5, and -6) and a partial sequence for a sixth (IGFBP-4) have been reported at the molecular level (Kamangar et al. 2006). In general, in accordance with their functions in mammals, IGFBP-1 (20–29 kDa) and IGFBP-2 (31–39 kDa) are typically up-regulated in catabolic states, potentially sequestering plasma IGF-I and thus preventing any anabolic effects (Duan et al. 1999; Bauchat et al. 2001; Maures and Duan 2002; Shimizu et al. 2005). On the other hand, IGFBP-3 (40–50 kDa) is associated with anabolic states and may facilitate IGF actions (Shimizu et al. 2003b), while the actions of IGFBP-5 (76–90 kDa) are less clear (Johnson et al. 2003). It should be noted that while the 40–50-kDa IGFBP is most similar to mammalian IGFBP-3 based on physiological responses, molecular weight, and type of glycosylation, (Shimizu et al. 2003b), its amino acid sequence is most homologous with human IGFBP-2 (Kamangar et al. 2006). For the purpose of this review, the 40–50-kDa IGFBP will be referred to as IGFBP-3.

The endocrine control of growth is complex, and for this reason this article is not intended to be an exhaustive review of the GH–IGF axis or its control of growth in fish. Rather, it will focus on some of the major factors that are most applicable to the aquaculture industry with respect to growth improvement. Since IGF-I is ultimately responsible for body growth (McCormick et al. 1992; Negatu and Meier 1995), this growth factor would seem to be a most appropriate candidate for a growth biomarker, and the evidence discussed herein suggests that this is the case. However, the efficacy of specific endocrine factors as growth indicators is likely both species and situation specific and dependent on various components within the GH–IGF axis. In this review we will focus on the major circulating proteins within the growth endocrine system, specifically GH, IGF-I, and IGFBPs; their utility in assessing disparities in growth rate due to feeding regimen, diet composition, temperature, photoperiod and stress will be discussed. Since protein levels determine phenotype, we will focus primarily on plasma hormone measurements rather than tissue mRNA levels.

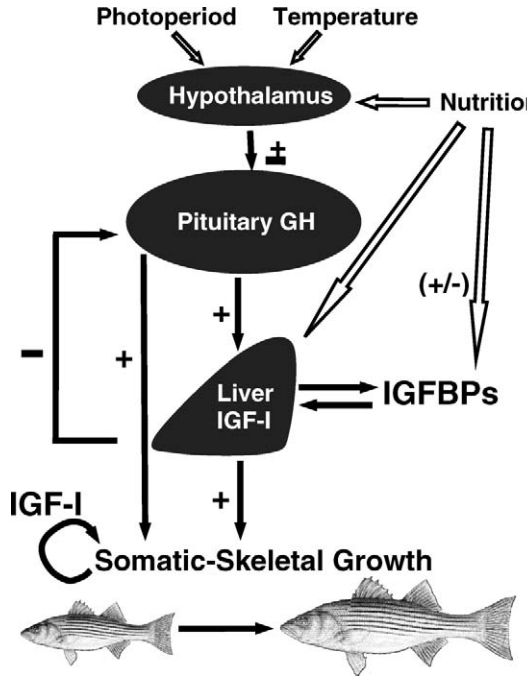

FIGURE 1.—Endocrine control of growth in teleost fish. In response to various exogenous and endogenous cues, pituitary growth hormone (GH) stimulates the synthesis and secretion of insulin-like growth factor-I (IGF-I), which causes the proliferation of target tissues. Increases in IGF-I, in turn, lead to an inhibition of GH synthesis and secretion through a classic negative feedback loop. Locally produced IGF-I may also contribute to cell proliferation. Insulin-like growth factor–binding proteins (IGFBPs) from hepatic and nonhepatic sources can inhibit or potentiate the biological actions of IGF-I.

TABLE 1.—Correlations (r^2) between plasma IGF-I and specific growth rate (weight) in fish induced through specific manipulations. All correlations are statistically significant. Other studies discussed in the text but not included in the table because of lack of correlative analysis also showed similar patterns regarding the fluctuations in IGF-I and growth.

Species	Feeding regimen	Nutrient composition	Temperature × photoperiod	Crude protein (%)	Genetic strain × fish meal (%)
Mozambique tilapia[a]	0.55				
Hybrid striped bass[b]	0.56				
Coho salmon[c–f]	0.72, 0.68, 0.72, 0.47				
Atlantic salmon[g]		0.67			
Rainbow trout[h]			0.78		
Gilthead seabream[i]			0.67		
Atlantic cod[j]			0.73		
Barramundi[g]				0.65	
Channel catfish[k]					0.70

[a] Uchida et al. (2003).
[b] Picha et al. (2006).
[c] Pierce et al. (2001).
[d] Beckman et al. (2004a).
[e] Beckman et al. (2004b).
[f] Beckman et al. (2004c).
[g] Dyer et al. (2004a).
[h] Taylor et al. (2005).
[i] Mingarro et al. (2002).
[j] Davie et al. (2007).
[k] Li et al. (2006).

While the ability to use these endocrine indices as growth biomarkers hinges on deducing correlations with specific growth rate (SGR, defined as $\{[\log_e W_2 - \log_e W_1]/[t_2 - t_1]\} \times 100$, where W_1 and W_2 represent fish weight at times 1 and 2 [t_1 and t_2], respectively) under the conditions being tested, surprisingly few correlations have been made between plasma IGF-I and SGR (Table 1). Even fewer have been made between SGR and IGFBPs or GH (see discussion below for examples). For this reason, well-planned quantitative studies will have to be performed to determine whether the lack of correlations is simply due to a deficiency of studies designed specifically for this purpose or to the absence of physiological relationships. With this in mind, it is hoped that researchers will fill these voids to expedite the use of endocrine biomarkers for facilitating growth improvement in aquacultured fishes.

Feeding Regimen

Optimizing feeding regimen with respect to growth and metabolic efficiency is a goal of any aquaculture producer. Feeding rate and frequency, for instance, not only vary with species but with water temperature and body size. However, feeding tables that consider these variables have not been developed or optimized for many aquacultured fishes. Furthermore, alternative feeding regimens that deviate from typical daily feeding recommendations, such as those that might elicit compensatory growth responses or maximize feed utilization, are in some instances proving to be more appropriate. Based on measures of plasma IGF-I, IGFBPs, and perhaps GH, it may be possible to develop these optimal feeding regimens on a species-specific basis.

Feed Restriction

A common initial means of assessing the relationship of a hormone to nutritional status and thus growth is to measure its concentration in fed versus feed-deprived fish. In adult channel catfish *Ictalurus punctatus*, 2 weeks of fasting resulted in a significant depression in plasma IGF-I, while plasma GH showed no change. It was not until 4 weeks of fasting that plasma GH displayed the canonical increases associated with catabolism in fish (Table 2; Small and Peterson 2005). This initially paradoxical relationship of elevated circulating GH during episodes of poor or negative growth (Duan and Plisetskaya 1993; Pérez-Sánchez and Le Bail 1999) is likely due, in part, to a state of GH resistance. That is, elevated plasma GH is accompanied by a reduction in the number of hepatic GH receptors (Gray et al. 1992; Mori et al. 1992), preventing GH from stimulating the production of hepatic-derived IGF-I and ultimately depressing somatic growth (reviewed by MacKenzie et al. 1998; Thissen et al. 1999). Depressed plasma IGF-I during catabolism may also facilitate the elevation in plasma GH through a reduction in negative feedback by IGF-I on GH synthesis and secretion in the pituitary (Fruchtman et al. 2000; Figure 1). Meanwhile, the elevated levels of circulating GH may still promote lipolysis for energy utilization and protein-sparing purposes (MacKenzie et al. 1998). These results in adult channel catfish are consistent with those of a similar study in fingerling channel catfish in which 3 weeks of fasting resulted in a significant reduction in plasma IGF-I and no change in circulating GH (Small 2005). The earlier response of plasma IGF-I was also observed in freshwater-acclimated Mozambique tilapia *Oreochromis mossambicus*, where 2 weeks of fasting resulted in

TABLE 2.—Dynamics of the GH–IGF system relative to altered states of growth elicited by various manipulations. Upward arrows reflect positive relations between the hormone and the variable, downward arrows negative relationships; horizontal arrows indicate no relationship. Multiple indicator arrows represent differing results between studies. Binding protein numbers are based on their putative mammalian homologs. IGFBP-1 and -2 are typically associated with a catabolic state and IGFBP-3 with an anabolic state.

Manipulation	SGR	Plasma IGF-I	Plasma GH	IGFBPs
Feed				
Restriction–deprivation	↓	↓	↑↔	(IGFBP-3) ↓
Increased ration size	↑	↑	↓	(IGFBP-1) ↓; (IGFBP-3) ↑
Compensatory growth	↑	↑		
Increased crude protein (%)	↑	↑	↓	
Plant protein supplementation	↓	↓	↑	
Optimal rearing temperature[a]	↑	↑	↑	
Increasing day length	↑	↑	↑	
Stress				
Cortisol injections	↓	↓		(IGFBP-1) ↑
Stress	↓	↑↓↔	↑	(IGFBP-1, -2) ↑; (IGFBP-3) ↓

[a] The effects of temperature on growth may be confounded by those of photoperiod and vice versa.

significant reductions in IGF-I and growth but no change in GH (Uchida et al. 2003). Strong correlations between IGF-I and SGR were demonstrated in this as well as other studies (Table 1). In seawater-acclimated Mozambique tilapia, decreases in plasma IGF-I coincided with increases in plasma GH after 4 weeks of fasting (Fox et al. 2006), although specific correlations between growth and endocrine factors were not determined in this study. Thus, the circulating level of IGF-I appears to be a more acute biomarker for disparities in growth due to feed restriction than plasma GH in both channel catfish and Mozambique tilapia. In hybrid striped bass (white bass *Morone chrysops* × striped bass *Morone saxatilis*), a considerable catabolic state induced by 4 weeks of partial feed restriction (fish were fed twice over 4 weeks) rendered depressed concentrations of circulating IGF-I along with a significant correlation between IGF-I and SGR (Table 1; Picha et al. 2006). Three weeks of complete feed restriction in this same species resulted in depressed plasma IGF-I and elevated plasma GH relative to fed controls (M. Picha, unpublished results; Turano 2006).

While the trends discussed above suggest roles for both plasma IGF-I and GH during catabolic and anabolic states, the earliest samples in all cases were taken after 2 weeks of feed restriction. Much information would be gained if, instead, the temporal dynamics of IGF-I and GH were established through more frequent sampling. This would allow determination of the earliest point at which changes in feeding frequency coincided with changes in endocrine indices and the point at which these biomarkers may become viable. In Chinook salmon *Oncorhynchus tshawytscha*, for instance, increases in plasma GH were detected by day 3 of fasting while IGF-I and IGFBP-3 decreases were detected after 4 d (Pierce et al. 2005). After 4 weeks of fasting in rainbow trout *O. mykiss*, immediate changes in plasma IGF-I and GH were also observed upon refeeding. Specifically, significant increases in previously depressed plasma IGF-I values were recorded after 4 d of realimentation while only 1 d of refeeding was required for previously elevated plasma GH levels to be reduced to control values (Gabillard et al. 2006). Therefore, unlike in channel catfish and Mozambique tilapia, in salmonids either plasma GH or IGF-I may be an effective indicator of the differences in growth due to feeding regimen (Table 2). Indeed, based on these previous studies, it appears that a combination of elevated GH and depressed plasma IGF-I may serve as a biomarker for the catabolic state (negative energy balance) induced through fasting. It would be both interesting and informative, however, to assess whether graded degrees (lengths) of fasting in fact resulted in graded changes in either of these hormones or whether a threshold level of catabolism resulted in dramatic, all-or-nothing endocrine changes. It should also be noted that while this approach to hormone assessment may be appropriate for evaluating feeding regimens that utilize "on-and-off" feeding or catabolic versus anabolic states, comparing the hormone levels of fed and fasted fish may not be an appropriate general approach to assessing a growth biomarker. Rather, assessing the endocrine correlates of growth in animals showing graded degrees of weight gain should be distinguished from those looking at positive growth (weight gain) versus negative growth (weight loss).

Ration Size

Positive correlations between SGR and plasma IGF-I have also been made by feeding variable ration sizes to achieve a broad range of positive growth rates, at least

in coho salmon *Oncorhynchus kisutch* (Table 1; Pierce et al. 2001; Beckman et al. 2004a, 2004b, 2004c) and hybrid striped bass ($r^2 = 0.86$; M. Picha, unpublished data). Collectively, the strongest correlations from these studies were derived from growth rates that reflected the most recent growth stanzas (2–6 weeks), establishing IGF-I as a biomarker of recent growth. In one instance it was even found that plasma IGF-I was more strongly related to growth rate than either size or condition factor (Beckman et al. 2004a). Within these studies, moderate changes in nutritional plane (feeding level) resulted in parallel changes in plasma IGF-I and IGFBP-3, with additional positive correlations between plasma IGF-I and IGFBP-3 (Beckman et al. 2004b, 2004c). In Chinook salmon, mild reductions in nutritional plane produced increases in IGFBP-1. Specifically, increases in IGFBP-1 were seen 2 weeks after a reduction in ration from 2% to 0.5% of body weight per day (BW/d), and 4 weeks after a reduction from 1% to 0.5% BW/d (Shimizu et al. 2006). Interestingly, no changes in plasma IGF-I were detected following the 1–0.5% BW/d reduction (Shimizu et al. 2006). Variable ration sizes given to Nile tilapia *Oreochromis niloticus* also yielded a gradient of SGR values that were positively correlated to hepatic IGF-I mRNA expression (Vera Cruz et al. 2006). Collectively, these results among the different fish species indicate that plasma IGF-I, IGFBP-3 and possibly hepatic IGF-I mRNA may prove useful as positive and rapid (within 2 weeks) indicators of growth (Table 2), while IGFBP-1 may serve as a negative indicator. In fact, IGFBP-1 may be the most sensitive of these factors, at least based on studies of salmonids.

Growth hormone either changed little or showed an inverse relationship to feed consumption and growth in response to different ration sizes in salmonids (Table 2; Pierce et al. 2001; Beckman et al. 2004b). Similarly, gilthead seabream (also known as gilthead bream) *Sparus auratus* fed graded ration sizes showed an inverse relationship between positive SGR and plasma GH (Company et al. 1999a). These results are consistent with those of other studies that assessed suboptimal but positive growth in gilthead seabream (Pérez-Sánchez et al. 1995; Marti-Palanca et al. 1996; see also the section on diet composition below). The disparity between GH and growth rate may very well be mediated by the prevailing levels of IGF-I and its negative feedback effects on the pituitary. That is, as plasma IGF-I increases with higher growth rates, GH levels decline owing to an amplified negative feedback, the opposite trends occurring during the lower growth states observed with reduced ration size.

Compensatory Growth

An important aspect to the validity of growth biomarkers is the capacity to assess differences between poor, normal, and rapid growth states. Compensatory growth, an example of the latter, is the phenomenon by which animals exhibit growth that exceeds normal rates after experiencing growth-stunting conditions. Compensatory growth (CG) has been well studied in fish (see Ali et al. 2003 for review) and has potential benefits for aquaculturists in the form of improved overall growth rates and feed efficiencies, along with reduced labor costs and improved water quality. The CG model also allows one to assess the utility of potential bioindicators and the underlying endocrine mechanisms mediating poor, normal, and rapid growth. Additionally, since CG is typically preceded by a period of negative growth, biomarkers can be evaluated in animals exposed to sequential shifts in metabolic state (e.g., from catabolism to extreme anabolism) in comparison with those reared under continuous conditions. These types of measurements may better reflect the naturally fluctuating conditions that fish often experience as part of their life history in the wild or when cultured under ambient conditions in seasonal environments.

While some CG studies have focused on manipulating temperature, salinity, density, and oxygen level as a means of inducing the response, the vast majority involve some form of feeding manipulation, typically a period of feed restriction followed by refeeding (reviewed by Ali et al. 2003). The overwhelming majority of studies, however, have not addressed physiological indicators of CG, particularly the endocrine mediators of the accelerated growth response in fishes. Studies in hybrid striped bass show that animals subjected to an initial period of feed restriction exhibit a robust CG response upon refeeding (Skalski et al. 2005; Picha et al. 2006; Turano et al. 2007). During the catabolic state induced by restricted feeding, circulating levels of IGF-I declined, but they rebounded dramatically during the subsequent CG response. The most dramatic increase in plasma IGF-I occurred during the initial 4 d of the 28-d response (Table 2), which also corresponded to the highest SGR observed among either controls (fish fed normally throughout) or animals on the CG regimen. Overall, there was a strong positive correlation between SGR and circulating IGF-I with compensatory growth (Table 1; Picha et al. 2006). Interestingly, while the CG response was characterized by elevated SGRs, IGF-I levels did not exceed those of control fish. Thus, while circulating IGF-I may be crucial to regulating growth rate, the relative change in plasma IGF-I may be a more critical

regulator of the accelerated growth response observed during CG than the absolute concentration. Indeed, there was an even stronger correlation between SGR and the change in plasma IGF-I level than between SGR and the absolute IGF-I concentration (Picha et al. 2006). It is well established that secretory pulses of hormones, including those within the endocrine–growth axis, may be more effective regulators of target organs than absolute hormone levels (Borski et al. 2000). This sensitivity of target tissues to bolus hormone release may well be mediated in part by changes in the hormone receptor(s) or amplification of the cellular transduction cascade. Supportive of this hypothesis are data from rainbow trout and gilthead seabream in which 4 weeks of fasting increases the specific binding for IGF-I in muscle tissue (Montserrat et al. 2007a, 2007b). Hence, heightened IGF receptor numbers or sensitivity may lead to disproportionate increases in mitogenic activity, particularly when IGF-I increases from a depressed or baseline level. Therefore, although the level of IGF-I is a good indicator of growth, it may be more critical to determine the relative changes in IGF-I to distinguish relative differences in growth rates under anabolic conditions (normal versus accelerated growth).

Collectively, changes in systemic IGF-I appear to be a good and reasonably rapid ($\leq$4 d) indicator of growth under feed manipulation protocols in which extreme shifts in metabolism occur. In addition to systemic IGF-I, it is also important to consider locally produced IGF-I. Muscle IGF-I mRNA is up-regulated in rainbow trout (Chauvigné et al. 2003; Montserrat et al. 2007a) and hybrid striped bass (M. Picha, unpublished data) following periods of fasting. Presumably, this IGF-I is being translated to act in a paracrine–autocrine manner, and hence this pool of IGF-I may also contribute to greater growth during CG, especially given the up-regulation of IGF-I binding in muscle tissue after catabolism (Montserrat et al. 2007a, 2007b).

Diet Composition

Feed formulation is critical to fish health and growth and to aquaculture economics. Carnivorous fish, for instance, generally require formulated feeds that contain 40–50% protein. Because of these high protein requirements, much of which is derived from costly fish meal, 40–70% of the variable (operational) costs for most cultured species can be attributed to feeds. Therefore, ongoing research is aimed at supplementing diets with lipid and carbohydrates to support maintenance metabolism to allow the maximal amount of protein for growth (protein sparing; Stickney 1994). Additionally, the incorporation of plant protein and oil in lieu of fish meal and fish oil is being extensively investigated. It would be highly useful to circumvent lengthy and costly grow-out trials by using endocrine biomarkers such as plasma IGF-I and GH for testing various feed formulations on growth performance during brief exposure to test diets.

Protein Levels

In barramundi (also known as barramundi perch) *Lates calcarifer* fed diets with variable amounts of crude protein for 6 weeks, strong correlations were found between plasma IGF-I and SGR with a single end point measure (Table 1; Dyer et al. 2004a). Consequently, it is possible that grow-out trials such as these could be reduced in length to the point where discernable and significant differences in plasma IGF-I are first detected and that these subtle endocrine changes may reflect current as well as future body weight gain. To design efficient (short) feed trials, however, it will be necessary initially to employ a serial sampling design in order to determine the temporal sequence of hormone changes and how this relates to differences in growth and size. In particular, do changes in IGF-I precede, coincide with, or follow divergences in size or growth rate? This barramundi study also showed that plasma IGF-I was positively correlated to dietary protein level, indicating that the growth factor may prove a reliable indicator of the optimal protein levels required for growth. Initial trials with this same species suggest that the effects of dietary energy level on growth might also be assessed by IGF-I measurements (Nankervis et al. 2000).

In contrast to circulating IGF-I, GH is generally negatively correlated to growth and dietary protein levels, as was observed in fingerling gilthead seabream (Pérez-Sánchez et al. 1995). Similarly, seabream fingerlings fed high protein–low lipid diets exhibited greater growth rates, better feed conversion, and lower plasma GH than those on a low protein–high lipid diet (Marti-Palanca et al. 1996). An additional study with this same species was less clear, as there was little effect of variable protein–lipid ratios (55:9 versus 46:17) on SGR and inconsistent changes in GH levels (Company et al. 1999a). Seabream fed isoproteic and isoenergetic diets with variable ratios of indispensable and dispensable amino acids displayed no differences in SGR (Gómez-Requeni et al. 2003). Despite this lack of effect on SGR, fish fed lower proportions of indispensable amino acids displayed hormone levels consistent with lower growth (low plasma IGF-I and elevated plasma GH) and had nutritional characteristics consistent with poorer growth efficiency (lower feed conversion and nitrogen retention). Thus, the endocrine characters of these fish reflected some disruption in the relationship between nutrition and growth even

though the growth rates, as measured, did not differ. This suggests that IGF-I and GH measures may be useful for making inferences about feeds and the nutritional condition of fish in terms of factors other than growth rate, including the efficiency of lipid utilization, protein-sparing effects, and nutrient retention (MacKenzie et al. 1998; Company et al. 1999b; Pérez-Sánchez and Le Bail 1999).

Plant Proteins and Oils

Because of the high cost and finite availability of fish meal for aquaculture feeds, research regarding its substitution with plant protein sources is increasing (Hardy 1996), as are the corresponding investigations on the effects of protein replacement on the GH–IGF system. Given the limitations of plant protein substitution in certain fish species, namely, carnivores, in terms of palatability, digestion, and disease (reviewed by Gatlin et al. 2007), it will be important to assess the suitability of such substitution on a species-by-species basis based on their effects on growth, for which endocrine biomarkers may serve as a proxy and potential predictor. In juvenile channel catfish, isoproteic diets (28%) containing various percentages of fish meal (0, 4, and 8%) supplemented accordingly with plant protein were evaluated for their effects on commercially important traits. In two of the three genetic strains tested (Mississippi "normal" and USDA 303), diets with higher levels of fish meal resulted in elevated SGRs and plasma IGF-I, along with generally improved feed conversion (Table 2; Li et al. 2006). In the third genetic strain (NWAC 103), however, fish meal percentage had no significant effect on SGR, coincident with steady levels of IGF-I. When all three strains were evaluated together, a significant and positive correlation was achieved between SGR and plasma IGF-I (Table 1). Thus, circulating IGF-I appears to be an appropriate biomarker for growth in all three genetic strains of this omnivorous species. In rainbow trout, a carnivore, diets with increasing levels of plant protein replacement (0, 50, 75, and 100%) resulted in graded declines in IGF-I and increasing levels of GH, along with significant decreases in growth rates and feed efficiency (Gómez-Requeni et al. 2005). In nearly identical experimental manipulations, gilthead seabream showed strikingly similar growth and endocrine trends. That is, 50, 75, and 100% plant protein replacement resulted in significant decreases in growth rate and feed efficiency that paralleled the increases in plasma GH (Gómez-Requeni et al. 2004). These decreases in growth rate also resulted in significant declines in plasma IGF-I, supporting the notion that IGF-I may also prove useful as an indicator of growth in these types of studies. Similarly, when gilthead seabream diets were formulated with graded levels of vegetable oil mixture to replace fish oil, the differences in growth corresponded to significant changes in plasma IGF-I. Specifically, diets containing 100% fish oil along with 33% and 66% vegetable oil replacement all resulted in similar weights and plasma IGF-I levels at the end of the 11-week study, while fish fed diets with 100% vegetable oil replacement had significantly reduced growth and depressed circulating IGF-I concentrations (Benedito-Palos et al. 2007). Taken together, both GH and IGF-I appear to provide relevant but discordant signals with regard to growth performance and diet formulation in these studies; that is, increases in plant protein and vegetable oil that resulted in decreased growth were also associated with lower IGF-I and higher GH.

While the trends seem clear for these studies on catfish, rainbow trout, and gilthead seabream, caution must be exercised in drawing direct conclusions about plant protein percentages and regulation of the endocrine–growth axis. Specifically, the elevated plasma GH or depressed plasma IGF-I may not be due to the effects of plant protein replacement on the somatotrophic axis directly but rather to the palatability of plant-based feeds. Indeed, in the channel catfish (Li et al. 2006) and gilthead seabream (Gómez-Requeni et al. 2004) studies, increasing the percentage of plant protein replacement resulted in significant decreases in feed intake, which in and of itself may be directing the endocrine and growth changes. Thus, it appears that measures of IGF-I and GH do not provide answers as to why a feed performed poorly (i.e., through palatability or protein quality); instead, they reliably indicate differences in growth regardless of differences in diet composition. This is an essential characteristic for a growth biomarker to be useful for comparative feed trials.

Temperature

With unlimited feed availability, increases in temperature often enhance growth up to a species-specific physiological limit. However, the mechanisms mediating the effects of temperature on the growth and regulation of the GH–IGF axis are not well understood (Mommsen 2001). Isolating the effects of temperature alone on the growth axis has proven to be difficult because studies that employ satiation feeding result in variable feed intake and growth rates based on water temperature. However, a good growth biomarker should detect changes in growth regardless of whether it is mediated by an environmental factor (e.g., temperature) alone, feed intake, or both. To this end, we review the literature on the effects of temperature

on growth where it may be mediated by alterations in feed intake or not.

Temperature and GH

Growth hormone regulation by rearing temperature has not been clearly established in fish or any other vertebrate. Indeed, as most work on endocrine growth physiology has occurred in homeothermic mammals and birds, investigations into the relationship between temperature, growth, and the GH–IGF-I system are almost unique to fish. In an effort to determine the role of temperature in hormone regulation in rainbow trout, plasma GH levels were compared in fish maintained at similar growth rates through feed manipulations and exposed to rearing temperatures of 8, 12, and 16°C (Gabillard et al. 2003a). It was found that low temperature reduces plasma GH, indicating that temperature affects circulating GH levels independent of any effects on growth. In gilthead seabream and smolting Atlantic salmon *Salmo salar*, increasing water temperatures were associated with increases in feed intake, growth, and plasma GH (McCormick et al. 2000; Mingarro et al. 2002), with significant positive correlations between plasma GH and feed intake in the gilthead seabream study (Mingarro et al. 2002). It should be noted that while seabream were on a natural photoperiod and increases in GH coincided with increases in day length, smolting Atlantic salmon were held on a constant photoperiod. Taken together, it appears that GH may, in part, drive alterations in growth under different water temperatures. This positive relationship between circulating GH, feed intake and growth rate contrasts with the discordance between GH and growth discussed earlier for catabolic versus anabolic states but is similar to that associated with photoperiod discussed in a later section.

Temperature and the IGF System

Increasing environmental temperatures resulted in increased growth and plasma IGF-I levels in Chinook salmon (Beckman et al. 1998), Atlantic salmon (McCormick et al. 2000), rainbow trout (Gabillard et al. 2003b; Taylor et al. 2005), coho salmon (Larsen et al. 2001) and gilthead seabream (Mingarro et al. 2002). In these studies, significant correlations between plasma IGF-I and SGR were established in gilthead seabream, although natural photoperiod may have contributed to the effect of temperature on growth seen in this species (Table 1; Mingarro et al. 2002). Hepatic IGF-I mRNA was positively correlated to growth rates of Nile tilapia reared at temperatures ranging from approximately 18°C to 32°C (Vera Cruz et al. 2006). Furthermore, correlated increases in growth rates and plasma IGF-I levels were also reported in southern flounder *Paralichthys lethostigma* grown at 23°C versus 28°C (Luckenbach et al. 2007). In a 3-year study in Atlantic cod *Gadus morhua*, mean plasma IGF-I levels showed a annual pattern that positively correlated with ambient water temperature under ambient photoperiod conditions. Correlations of IGF-I with individual growth rates were relatively weak, but this may have been due to the longer-term measure of growth activity and IGF-I levels (around every 3 months) relative to the fluctuations in ambient temperature to which fish were exposed between sampling intervals (Davie et al. 2007). In rainbow trout, positive correlations in plasma IGF-I, growth rate, and water temperature were found when fish were raised for 6 months under ambient water temperatures that gradually fluctuated between 2°C and 16°C and were sampled at monthly intervals (Taylor et al. 2005). It is possible that the elevations in growth and IGF-I seen in these studies are mediated by differences in feed consumption, as feed intake was shown to increase with temperature. Consistent with this, little change was observed in plasma IGF-I in rainbow trout reared at different temperatures (8, 12, and 16°C) but given feeding rations that resulted in similar growth rates (Gabillard et al. 2003b).

Direct tests of whether IGF-I or 41-kDa IGFBP (IGFBP-3) can be used as growth biomarkers for fish reared at different temperatures have been conducted with juvenile coho salmon (Beckman et al. 2004c). The growth of individually tagged fish was monitored at 2–3-week intervals over a 9-week period as one group of fish experienced a temperature decrease from 11°C to 7°C while control fish remained at 11°C. Positive and significant correlations were found between growth and both IGF-I and 41-kDa IGFBP on all four sampling dates for control fish (Table 1). While the correlations between growth and either IGF-I or 41-kDa IGFBP were disrupted on the first two sampling dates for fish subjected to the temperature decrease, positive and significant correlations between both IGF-I and 41-kDa IGFBP and growth were subsequently reestablished for the fish held at cooler temperatures. This indicates that IGF-I and 41-kDa IGFBP may be used as biomarkers for growth in fish regardless of differences in rearing temperature, although a sufficient temporal period of acclimation may be required before comparisons are made. However, since this is only one study with one species, further work is needed to assess the efficacy of IGF-I and 41-kDa IGFBP as growth biomarkers across temperatures.

Collectively, studies in various salmonid and non-salmonid species point to IGF-I as a potentially effective biomarker for growth rates under varying rearing temperatures. It would appear that its useful-

ness extends to gradual and seasonal changes in temperature, although a brief period of acclimation may be required prior to analysis when abrupt temperature shifts are made. It would also appear that much of the change in plasma IGF-I and growth that occurs with temperature are mediated through alterations in temperature-dependent feed consumption. Interestingly, unlike that observed with the state of "GH resistance" associated with episodes of feed restriction, GH and IGF-I both show positive correlations to growth with seasonal temperature variation. From this perspective, circulating GH and IGF-I together might prove useful in assessing and predicting growth in fish under variable temperature regimes in which feed availability is unlimited (Table 2).

Photoperiod

Photoperiod and changes in it clearly have strong effects on growth in some fishes (Boeuf and Le Bail 1999). Consequently, light cycle manipulations are becoming common in many commercial aquaculture programs to directly increase growth, change the seasonal timing of smolting (introduction into seawater), and inhibit maturation (which maintains investment in somatic rather than gonadal tissue). Early work suggests that at least some photoperiod-driven changes in growth can be traced to changes in the GH–IGF axis (Kourmandjian et al. 1976; Marchant and Peter 1986). Thus, a key test for a putative growth index is how photoperiod manipulation affects the status of GH and IGF-I as biomarkers for growth.

Spring Equinox

Some of the earliest work on photoperiod, growth, and GH took place in salmonids and was directly concerned with the mechanisms controlling smolting. However, identifying the effects of photoperiod on the relationship between GH level and growth in salmonids during smoltification is difficult because of GH's overlapping osmoregulatory, behavioral, metabolic, and growth-stimulating actions (Stefansson et al. 1991; McCormick et al. 1995). This may be further compounded by interactions with other seasonal cues such as varying water temperature and feeding rates (Björnsson et al. 1989; McCormick et al. 2000). Nevertheless, it is now well established that plasma GH levels increase during the spring par–smolt transformation and that the increasing day length is of overriding importance as a zeitgeber for these increases in GH levels (for review see Björnsson 1997). The increase in plasma GH during smolting results in a strong, positive, nonlinear correlation between plasma GH and SGR (Björnsson et al. 1995). Thus, the relationships between GH and growth are the opposite of those described previously (see the sections on feeding regimen and diet composition). However, a negative correlation was found between GH and growth rate in adult salmon over the course of the summer and fall (both natural and manipulated photoperiods; Nordgarden et al. 2005), demonstrating that a positive correlation between GH and growth is not a common feature in adult salmon. Finally, a late spring–summer increase in GH in gilthead seabream appears to correlate with seasonal increases in growth rate (Pérez-Sánchez et al. 1994; Mingarro et al. 2002). This work, together with that in goldfish *Carassius auratus* (Marchant and Peter 1986), suggests that spring increases in GH and growth are not limited to salmon smolts and that there may be a disruption of the "normal" relationship between GH and growth during the spring equinox, at least in some fishes.

Unlike with GH, the relationship between IGF-I and growth rate remains positive during the spring increase in photoperiod and smolting in salmon (Beckman et al. 1998; Larsen et al. 2001). Similarly, IGF-I and the growth rate are positively correlated (see Table 1) in gilthead seabream through the spring–summer period (Pérez-Sánchez et al. 1994; Mingarro et al. 2002).

Autumn Equinox

Autumnal changes in IGF-I and GH have been described in Chinook salmon (Pierce et al. 2001) and gilthead seabream (Mingarro et al. 2002) that appear to be dissociated from feeding rates and temperature along with developmental events such as smolting and reproduction. Both studies suggest that seasonally changing photoperiod provides the cue for these altered hormone levels. Autumnal peaks in IGF-I were found in rainbow trout, but it was suggested that the peaks were not photoperiod induced as fish held under constant photoperiod also displayed an IGF-I peak in September (Taylor et al. 2005). Instead, it was suggested that the IGF-I peak was related to the changes in water temperature and feeding rate found in their experiment. In postsmolt coho salmon, the relationship between individual growth rates and plasma IGF-I levels was assessed on four occasions from July through September (Beckman et al. 2004b). On each date, a positive and significant relationship between IGF-I and growth was found. However, plasma IGF-I levels increased from July to September even though temperature and ration were held constant, resulting in a shift in the relationship between IGF-I and growth as fish approached the autumn equinox. Together, these studies suggest that while IGF-I and growth are generally positively related, the exact nature of this relation may change seasonally. Thus, one should be cautious in using IGF-I as a growth index

when comparing samples taken during different seasons.

Multiple Photoperiods

In addition to experiencing naturally changing photoperiods, fish in aquaculture are subjected to a number of constant photoperiod regimes, ranging from constant short and long days to to continuous (24-h) light. In hybrid striped bass, 3 weeks of exposure to long-day (16 h light : 8 h dark) or short-day (8 h light : 16 h dark) light cycles resulted in insignificant differences in both growth and plasma IGF-I (Davis and McEntire 2006). Indeed, it appears that in many cases a treatment period of months rather than weeks is required before variable photoperiod regimens result in appreciable changes in body weight (Boeuf and Le Bail 1999). This may be an opportunity, however, to gauge whether noticeable changes in plasma IGF-I precede significant changes in growth, which ultimately could allow for shortened photoperiod experiments. In rainbow trout, IGF-I and growth rates were compared in two experiments (Taylor et al. 2005). In the first, fish were subjected to a natural photoperiod, a constant short day, or a constant long day from June to December with naturally fluctuating temperatures and the resulting variations in feed intake. A positive and significant correlation between mean plasma IGF-I values and growth rates was found for samples taken at approximately monthly intervals and compared among all treatments (see Table 1). A second experiment employing natural photoperiod, short-day, and continuous light treatments from April to October found similar results: mean IGF-I was positively correlated to mean growth rate for all samples combined (although $P = 0.07$). To examine the effects of photoperiod on growth in Atlantic cod, eight different photoperiod treatments were used that utilized different combinations of long-day constant and natural photoperiods with a seasonally varying temperature (Davie et al. 2007). When the relationship between growth and plasma IGF-I was compared over two periods (January–April and April–July), the researchers found positive (both trials) and significant (first trial) relationships between mean IGF-I (measured at the end of the growth period) and mean growth over each 3-month period (Davie et al. 2007; Table 1).

These studies demonstrate a common positive relationship between IGF-I and growth for fish held under different photoperiods, suggesting that IGF-I acts as a growth index regardless of photoperiod. A cautionary note is necessary, as these studies were conducted with seasonally varying temperatures and concomitantly varying feeding rates. It is therefore difficult to isolate the effect of photoperiod in these studies (Taylor et al. 2005). Studies specifically designed to test whether the relationships between growth and IGF-I are consistent regardless of photoperiod will have to be conducted to clearly demonstrate whether IGF-I provides a stable growth index.

Stress

Owing to the intimate association with their aquatic medium, fish are inherently susceptible and sensitive to a wide range of stressors that disrupt homeostasis and ultimately lead to growth suppression (for review, see Conte 2004). In aquaculture settings, stressors include high density, poor water quality, handling, transport, and acclimation, among others. The stress response in fish involves the release of catecholamines (norepinephrine and epinephrine) and glucocorticoids (cortisol) (reviewed by Perry and Bernier 1999; Barton 2002), cortisol being the most frequently utilized indicator of stress despite the resistance in cortisol responses that often occurs with acute or chronic stress. There is likely cross talk between the stress and growth axes; in particular, cortisol is linked to inhibition of various components of the IGF axis and thereby to the attenuation of growth (Pankhurst and Van Der Kraak 1997; Mommsen et al. 1999; Davis 2006). Likewise, in salmonids glucocorticoids have been shown to stimulate the synthesis and production of IGFBP-1 from hepatocytes (Pierce et al. 2006), a protein whose expression is up-regulated during poor growth states such as those associated with stress (Kelley et al. 2001). Therefore, while cortisol may be an appropriate biomarker for the portion of the stress response concerning energy metabolism and hydromineral balance (Vijayan et al. 1993; Reid et al. 1998), plasma IGF-I, IGFBPs, and perhaps GH may represent a direct indicator of the effects of acute and chronic stressors on growth. If so, protocols for aquaculture operations that result in stress responses, such as handling and transport, could be optimized to minimize the stress-induced effects on growth. Interestingly, in rainbow trout the relationships between growth and plasma GH, IGF-I, and cortisol are also being used for genetic selection of stress responses associated with better growth performance (Lankford and Weber 2006; Weber and Silverstein 2007).

In Mozambique tilapia, intraperitoneal cortisol injections caused an initially rapid (<2-h) increase in IGFBPs with low molecular weights (MWs; potential IGFBP-1 and -2) and decreases of higher-MW IGFBPs (potential IGFBP-3), followed by recovery at 24 h (Kajimura et al. 2003). The putative roles of these variably sized IGFBPs in fish are generally consistent with those in their mammalian counterparts, whereby low-MW IGFBPs increase under catabolic conditions

while higher-MW IGFBPs increase with anabolic states (Kajimura et al. 2003; review in Kelley et al. 2006). Cortisol was also effective in reducing circulating IGF-I within 24 h, albeit fivefold higher concentrations of cortisol were used than in regulating IGFBPs (Kajimura et al. 2003). In channel catfish, dietary cortisol treatment for 4 weeks suppresses growth by 50% and feed intake by 30%, reduces circulating IGF-I levels, and up-regulates a low-MW (~20-kDa) IGFBP (Peterson and Small 2005; Small et al. 2006). Thus, it would appear that exogenous treatment with the stress hormone cortisol leads to a consistent inhibition of IGF-I and a high-MW IGFBP while stimulating low-MW IGFBP(s). Surprisingly, few studies other than those on catfish have assessed growth alongside the endocrine–growth responses to exogenous cortisol.

In Atlantic salmon parr subjected to once-daily handling stress for 40 d (e.g., long-term chronic stress), plasma GH was significantly higher than in unstressed controls both before and 7 h after an acute handling stress on day 40 (McCormick et al. 1998). Since chronic stress was associated with lower growth rates, these elevated GH concentrations may be involved in energy mobilization to accommodate the increased energetic demands of stress. At the same time, however, plasma IGF-I was higher than in controls 3 and 7 h after the stressor on day 40 (McCormick et al. 1998). Similarly, dramatic elevations in cortisol but no changes in plasma IGF-I were observed immediately after a 3-h confinement stress in yearling steelhead trout (anadromous rainbow trout; Liebert and Schreck 2006). While it may be that up-regulation of low-MW IGFBPs is suppressing the growth-promoting effects of elevated or sustained levels of circulating IGF-I, it indicates that measures of a single hormone during stressful situations may not always be representative of short- and long-term growth status and that more comprehensive measures (i.e., cortisol, IGF-I, and IGFBPs) will provide a clearer picture. In contrast to salmonids, hybrid striped bass subjected to a 15-min low-water stress showed significant depression in both plasma IGF-I and a 33-kDa IGFBP (potential IGFBP-3), along with considerable increases in low-MW IGFBPs (putative IGFBP-1 and -2) 2–6 h poststress (Davis and Peterson 2006). Interestingly, plasma cortisol was only elevated for 1 h following the stressor, suggesting that changes in plasma IGF-I and IGFBPs are more appropriate biomarkers for gauging the temporal effects that acute stressors exert on somatic growth, if any. Additional studies involving handling or confinement stress in southern bluefin tuna *Thunnus maccoyii*, and the Australian fishes silver perch *Bidyanus bidyanus* and black bream *Acanthopagrus butcherii* (alternatively known as southern black bream) also led to depressions in plasma IGF-I, some within 12 h of the stressor (Dyer et al. 2004b). Furthermore, jack mackerel *Trachurus symmetricus* subjected to confinement stress followed by handling stress showed strong increases in low-MW IGFBPs 60 s after the handling stress, similar to the response observed for plasma cortisol (Kelley et al. 2001).

The results to date suggest that IGFBPs are a sensitive indicator of stress (increase in low-MW IGFBPs, reduction in a high-MW IGFBP) and, along with IGF-I, could provide an accurate indication of the long-term effects of stress on growth. Detailed studies analyzing the temporal patterns of plasma cortisol, IGF-I, and IGFBPs in direct relation to growth will be required before growth biomarkers reflecting the effects of specific stressors are established.

Conclusion

Establishing endocrine biomarkers responsible for or reflective of fish growth has broad implications for aquaculture researchers and the industry. In particular, establishing correlations between hormonal indices and specific growth rates under various biological conditions obviates the need for lengthy grow-out trials to establish optimal diet formulations, feeding regimens, handling protocols, or rearing conditions (i.e., temperature, photoperiod, and salinity). It also provides valuable endocrine data regarding the underlying control of growth in fish that may ultimately be required for optimizing growth.

It would appear that among all the hormones controlling somatic growth IGF-I is the most promising candidate as a measure of instantaneous growth in fish. This is due to the direct role that the growth factor plays in regulating cellular proliferation and ultimately somatic growth in vertebrates. A recent study in domesticated dogs *Canis familiaris* shows that IGF-I is crucial to regulating body size (Sutter et al. 2007), and previous investigations using IGF-I knockout mice established that IGF-I is responsible for much of postnatal growth (Lupu et al. 2001). Of the numerous studies on growth regulation in fish, relatively few have established a correlation between plasma IGF-I and SGR (Table 1), which would be a criterion for biomarker efficacy. However, it will have to be determined whether the lack of correlation is due simply to the lack of studies designed specifically for this purpose or to the absence of an actual physiological relationship. The development and validation of a commercial IGF-I radioimmunoassay (RIA; GroPep, Adelaide, Australia; Shimizu et al. 1999, 2000; Dyer et al. 2004b) in the past decade with the highly conserved IGF-I ligand and a "universal" antibody for fish (GroPep, Adelaide, Australia) should prove highly

useful for IGF-I biomarker testing in various fish species. Furthermore, the recent development of homologous RIAs for salmon IGFBP-1 and -3 (Shimizu et al. 1999, 2003a, 2003b, 2006) should enable decisive testing of these carrier proteins for biomarker potential, especially since RIAs have greater precision and enable one to process a larger number of samples than traditional Western IGFBP ligand blot analyses. Based on current literature, it appears that IGF-I, and possibly GH or IGFBPs where appropriate (see Table 2), would best serve as putative biomarkers for growth when the variables of interest (ration size, diet composition, temperature, etc.) are held relatively constant, and particularly when they are not confounded by multiple environmental factors (as in simultaneous temperature and photoperiod manipulations).

Clearly, the utility of growth biomarkers should be based not only on their relationship to current growth status but also ideally on their ability to predict future growth rates, assuming that the variable being tested is held relatively constant. The predictive value of early endocrine measures with respect to subsequent growth performance has yet to be established for any of the components of the GH–IGF growth axis. Additionally, if one is to predict or assess the relative quality of a test variable it is important to know how rapidly the endocrine biomarker might change. Based on this review, it would appear that changes in IGF-I can occur within days and that the correlations reflect growth rates within the last 2 weeks. With more frequent sampling rather than end point analysis, however, a better resolution of the temporal dynamics between endocrine parameters and growth rates can be established. An additional point to consider is whether subtle changes in growth are reflected in distinguishable changes in the biomarker. This feature in particular could support the practicality of endocrine biomarker use over that of direct weight measures, although it may require using larger sample sizes to reduce the standard errors and establish statistical significance.

While this review has intentionally been limited in scope, it is important to note that hormonal factors that were not discussed herein (i.e., IGF-II and neuropeptide Y) might also reflect growth status, whether directly through the regulation of tissue proliferation or indirectly through the control of appetite. Indeed, the heritability of appetite seems to be a driving force behind the divergent growth rates between different strains of the same fish species (Silverstein 2002). Likewise, as pointed out in this review, many of the variables regulating IGF-I, GH, or IGFBPs and growth might also be doing so through changes in feed intake.

Acknowledgments

Research in the authors' laboratories was funded by grants from the National Science Foundation (IBN-0215205), North Carolina Sea Grant (NA16RG2251, RA/F-41, RA/F-46), North Carolina Fisheries Resource Program, U.S. Department of Agriculture, and the National Marine Fisheries Service.

References

Ali, M., A. Nicieza, and R. J. Wootton. 2003. Compensatory growth in fishes: a response to growth depression. Fish and Fisheries 4:147–190.

Barton, B. A. 2002. Stress in fishes: a diversity of responses with particular reference to changes in circulating corticosteroids. Integrative and Comparative Biology 42:517–525.

Bauchat, J. R., W. H. Busby, A. Garmong, P. Swanson, J. Moore, M. Lin, and C. Duan. 2001. Biochemical and functional analysis of a conserved IGF-binding protein isolated from rainbow trout (*Oncorhynchus mykiss*) heptoma cells. Journal of Endocrinology 170:619–628.

Beckman, B. R., W. Fairgrieve, K. A. Cooper, C. V. W. Mahnken, and R. J. Beamish. 2004a. Evaluation of endocrine indices and growth in individual postsmolt coho salmon. Transactions of the American Fisheries Society 133:1057–1067.

Beckman, B. R., D. A. Larsen, S. Moriyama, B. Lee-Pawlak, and W. W. Dickhoff. 1998. Insulin-like growth factor-I and environmental modulation of growth during smoltification of spring Chinook salmon (*Oncorhynchus tshawytscha*). General and Comparative Endocrinology 109:325–335.

Beckman, B. R., M. Shimizu, B. A. Gadberry, and K. A. Cooper. 2004b. Response of the somatotropic axis of juvenile coho salmon to alterations in plane of nutrition with an analysis of the relationships among growth rate and circulating IGF-I and 41-kDa IGFBP. General and Comparative Endocrinology 135:334–344.

Beckman, B. R., M. Shimizu, B. A. Gadberry, P. J. Parkins, and K. A. Cooper. 2004c. The effect of temperature change on the relations among plasma IGF-1, 41-kDa IGFBP, and growth rate in postsmolt coho salmon. Aquaculture 241:601–619.

Benedito-Palos, L., A. Saera-Vila, J.-A. Calduch-Giner, S. Kaushik, and J. Pérez-Sanchez. 2007. Combined replacement of fish meal and oil in practical diets for fast-growing juveniles of gilthead sea bream (*Sparus aurata* L.): networking of systemic and local components of GH–IGF axis. Aquaculture. 267:199–212.

Björnsson, B. T. 1997. The biology of salmon growth hormone: from daylight to dominance. Fish Physiology and Biochemistry 17:9–24.

Björnsson, B. T., V. Johansson, S. Benedet, I. E. Einarsdottir, J. Hildahl, T. Agustsson, and E. Jonsson. 2002. Growth hormone endocrinology of salmonids: regulatory mechanisms and mode of action. Fish Physiology and Biochemistry 27:227–242.

Björnsson, B. T., S. O. Stefansson, and T. Hansen. 1995. Photoperiod regulation of plasma growth hormone levels during parr–smolt transformation of Atlantic salmon:

implications for hypoosmoregulatory ability and growth. General and Comparative Endocrinology 100:73–82.

Björnsson, B. T., H. Thorarensen, T. Hirano, T. Ogasawara, and J. B. Kristinsson. 1989. Photoperiod and temperature affect plasma growth hormone levels, growth, condition factor, and hypoosmoregulatory ability of juvenile Atlantic salmon (*Salmo salar*) during parr–smolt transformation. Aquaculture 82:77–91.

Boeuf, G., and P. Y. Le Bail. 1999. Does light have an influence on fish growth? Aquaculture 177:129–152.

Borski, R. J., W. Tsai, R. Demott-Friberg, and A. L. Barkan. 2000. Induction of growth hormone (GH) mRNA by pulsatile GH-releasing hormone in rats is pattern specific. American Journal of Physiology 278:E885–E891.

Canosa, L. F., J. P. Chang, and R. E. Peter. 2007. Neuroendocrine control of growth hormone in fish. General and Comparative Endocrinology 151:1–26.

Chauvigné, J., C. Gabillard, C. Weil, and P. Y. Rescan. 2003. Effect of refeeding on IGFI, IGFII, IGF receptors, FGF2, FGF6, and myostatin mRNA in rainbow trout myotomal muscle. General and Comparative Endocrinology 132:209–215.

Company, R., J. A. Calduch-Giner, S. J. Kaushik, and J. Pérez-Sánchez. 1999a. Growth performance and adiposity in gilthead sea bream (*Sparus aurata*): risks and benefits of high-energy diets. Aquaculture 171:279–292.

Company, R., J. A. Calduch-Giner, J. Pérez-Sánchez, and S. J. Kaushik. 1999b. Protein sparing effect of dietary lipids in common dentex (*Dentex dentex*): a comparative study with sea bream (*Sparus aurata*) and sea bass (*Dicentrarchus labrax)*. Aquatic Living Resources 12:23–30.

Conte, F. S. 2004. Stress and the welfare of cultured fish. Applied Animal Behavior Science 86:205–223.

Davie, A., M. J. R. Porter, N. R. Bromage, and H. Migaud. 2007. The role of seasonally altering photoperiod in regulating physiology in Atlantic cod (*Gadu morhua*), part II. Somatic growth. Canadian Journal of Fisheries and Aquatic Sciences 64:98–112.

Davis, K. B. 2006. Management of physiological stress in finfish aquaculture. North American Journal of Aquaculture 68:116–121.

Davis, K. B., and B. McEntire. 2006. Effect of photoperiod on feeding, intraperitoneal fat, and insulin-like growth factor-I in sunshine bass. Journal of the World Aquaculture Society 37:431–436.

Davis, K. B., and B. C. Peterson. 2006. The effects of temperature, stress, and cortisol on plasma IGF-I and IGFBPs in sunshine bass. General and Comparative Endocrinology 149:219–225.

Duan, C. 1997. The insulin-like growth factor system and its biological actions in fish. American Zoologist 37: 491–503.

Duan, C., J. Ding, Q. Li, W. Tsai, and K. Pozios. 1999. Insulin-like growth factor binding protein 2 is a growth inhibitory protein conserved in zebrafish. Proceedings of the National Academy of Sciences of the USA 96:15274–15279.

Duan, C., and E. M. Plisetskaya. 1993. Nutritional regulation of insulin-like growth factor-I mRNA expression in salmon tissues. Journal of Endocrinology 139:243–252.

Duan, C., and Q. Xu. 2005. Roles of insulin-like growth factor (IGF) binding proteins in regulating IGF actions. General and Comparative Endocrinology 142:44–52.

Dyer, A. R., C. G. Barlow, M. P. Bransden, C. G. Carter, B. D. Glencross, N. Richardson, P. M. Thomas, K. C. Williams, and J. F. Carragher. 2004a. Correlation of plasma IGF-I concentrations and growth rate in aquacultured finfish: a tool for assessing the potential of new diets. Aquaculture 236:583–592.

Dyer, A. R., Z. Upton, D. Stone, P. M. Thomas, K. L. Soole, N. Higgs, K. Quinn, and J. F. Carragher. 2004b. Development and validation of a radioimmunoassay for fish insulin-like growth factor-I (IGF-I) and the effect of aquaculture-related stressors on circulating IGF-I levels. General and Comparative Endocrinology 135:268–275.

Fox, B. K., L. G. Riley, T. Hirano, and E. G. Grau. 2006. Effects of fasting on growth hormone, growth hormone receptor, and insulin-like growth factor-I axis in seawater-acclimated tilapia, *Oreochromis mossambicus*. General and Comparative Endocrinology 148:340–347.

Fruchtman, S., L. Jackson, and R. J. Borski. 2000. Insulin-like growth factor-I disparately regulates prolactin and growth hormone synthesis and secretion: studies utilizing the teleost pituitary model. Endocrinology 141:2886–2894.

Gabillard, J. C., B. B. Kamangar, and N. Montserrat. 2006. Coordinated regulation of the GH/IGF system genes during refeeding in rainbow trout (*Oncorhynchus mykiss*). Journal of Endocrinology 191:15–24.

Gabillard, J. C., C. Weil, P. Y. Rescan, I. Navarro, J. Gutierrez, and P. Y. Le Bail. 2003a. Environmental temperature increases plasma GH levels independently of nutritional status in rainbow trout (*Oncorhynchus mykiss*). General and Comparative Endocrinology 133:17–26.

Gabillard, J. C., C. Weil, P.Y. Rescan, I. Navarro, J. Gutierrez, and P. Y. Le Bail. 2003b. Effects of environmental temperature on IGF-I, IGF-II, and IGF type I receptor expression in rainbow trout (*Oncorhynchus mykiss*). General and Comparative Endocrinology 133:233–242.

Gatlin, D. M., III, F. T. Barrows, P. Brown, K. Dabrowski, T. G. Gaylord, R. W. Hardy, E. Herman, G. Hu, A. Krogdahl, R. Nelson, K. Overturf, M. Rust, W. Seale, D. Skonberg, E. J. Souza, D. Stone, R. Wilson, and E. Wurtele. 2007. Expanding the utilization of sustainable plant products in aquafeeds: a review. Aquaculture Research 38:551–579.

Gómez-Requeni, P., J. Calduch-Giner, S. Vega-Rubín de Celis, F. Médale, S. J. Kaushik, and J. Pérez-Sánchez. 2005. Regulation of the somatotropic axis by dietary factors in rainbow trout (*Oncorhynchus mykiss)*. British Journal of Nutrition 94:353–361.

Gómez-Requeni, P., M. Mingarro, S. Kirchner, J. A. Calduch-Giner, F. Médale, G. Corraze, S. Panserat, S. A. M. Martin, D. F. Houlihan, S. J. Kaushik, and J. Pérez-Sánchez. 2003. Effects of dietary amino acid profile on growth performance, key metabolic enzymes, and somatotropic axis responsiveness of gilthead sea bream (*Sparus aurata*). Aquaculture 220:749–767.

Gómez-Requeni, P., M. Mingarro, S. Kirchner, J. A. Calduch-Giner, F. Médale, G. Corraze, S. Panserat, S. A. M. Martin, D. F. Houlihan, S. J. Kaushik, and J. Pérez-Sánchez. 2004. Protein growth performance, amino acid utilization, and somatotropic axis responsiveness to fish

meal replacement by plant protein sources in gilthead sea bream (*Sparus aurata)*. Aquaculture 232:493–510.

Gray, E. S., K. M. Kelley, S. Law, R. Tsai, G. Young, and H. A. Bern. 1992. Regulation of hepatic growth hormone receptors in coho salmon (*Oncorhynchus kisutch*). General and Comparative Endocrinology 88:243–252.

Hardy, R. W. 1996. Alternate protein sources for salmon and trout diets. Animal Feed Science and Technology 59: 71–80.

Johnson, J., J. Silverstein, W. R. Wolters, M. Shimizu, W. W. Dickhoff, and B. S. Shepherd. 2003. Disparate regulation of insulin-like growth factor–binding proteins in a primitive ictalurid teleost (*Ictalurus punctatus*). General and Comparative Endocrinology 134:122–130.

Kajimura, S., T. Hirano, N. Visitacion, S. Moriyama, K. Aida, and E. G. Grau. 2003. Dual mode of cortisol action on GH/IGF-I/IGF binding proteins in the tilapia, *Oreochromis mossambicus*. Journal of Endocrinology 178:91–99.

Kajimura, S., K. Uchida, T. Yada, L. G. Riley, J. C. Byatt, R. J. Collier, K. Aida, T. Hirano, and E. G. Grau. 2001. Stimulation of insulin-like growth factor-I production by recombinant bovine growth hormone in Mozambique tilapia, *Oreochromis mossambicus*. Fish Physiology and Biochemistry 25:221–230.

Kamangar, B. B., J.-C. Gabillard, and J. Bobe. 2006. Insulin-like growth factor–binding protein (IGFBP)-1, -2, -3, -4, -5, and -6 and IGFBP-related protein 1 during rainbow trout postvitellogenesis and oocyte maturation: molecular characterization, expression profiles, and hormonal regulation. Endocrinology 147:2399–2410.

Kelley, K. M., J. T. Haigwood, M. Perez, and M. M. Galima. 2001. Serum insulin-like growth factor binding proteins (IGFBPs) as markers for anabolic/catabolic condition in fishes. Comparative Biochemistry and Physiology 129B:229–236.

Kelley, K. M., T. D. Price, M. M. Galima, K. Sak, J. A. Reyes, O. Zepeda, R. K. Hagstrom, T. A. Truong, and C. Lowe. 2006. Insulin-like growth factor–binding proteins (IGFBPs) in fish: beacons for (disrupted) growth endocrine physiology. Pages 167–195 *in* M. Reinecke, G. Zaccone, and B. G. Kapoor, editors. Fish endocrinology. Science Publishers, Enfield, New Hampshire.

Kelley, K. M., K. E. Schmidt, L. Berg, K. Sak, M. M. Galima, C. Gillespie, L. Balogh, A. Hawayek, J. A. Reyes, and M. Jamison. 2002. Comparative endocrinology of the insulin-like growth factor–binding protein. Journal of Endocrinology 175:3–18.

Komourdjian, M. P., R. L. Saunders, and J. C. Fenwick. 1976. Evidence for the role of growth hormone as a part of a 'light–pituitary axis' in growth and smoltification of Atlantic salmon (*Salmo salar*). Canadian Journal of Zoology 54:544–551.

Lankford, S. E., and G. M. Weber. 2006. Associations between plasma growth hormone, insulin-like growth factor-I, and cortisol with stress responsiveness and growth performance in a selective breeding program for rainbow trout. North American Journal of Aquaculture 68:151–159.

Larsen, D. A., B. R. Beckman, and W. W. Dickhoff. 2001. The effect of low temperature and fasting during the winter on metabolic stores and endocrine physiology (insulin, IGF-I, and thyroxine) of coho salmon, *Oncorhynchus kisutch*. General and Comparative Endocrinology 123:308–323.

Le Bail, P. Y., V. Gentil, O. Noel, J. M. Gomez, F. Carre, P. Le Goff, and C. Weil. 1998. Structure, function, and regulation of insulin-like growth factors in fish. Pages 157–161 *in* H. Vaundry, M. C. Tonon, E. W. Roubos, and A. de Loof. editors, Trends in comparative endocrinology and neurobiology: from molecular to integrative biology. New York Academy of Sciences, New York.

Li, M. H., B. C. Peterson, C. L. Janes, and E. H. Robinson. 2006. Comparison of diets containing various fish meal levels on growth performance, body composition, and insulin-like growth factor-I of juvenile channel catfish *Ictalurus punctatus* of different strains. Aquaculture 253:628–635.

Liebert, A. M., and C. B. Schreck. 2006. Effects of acute stress on osmoregulation, feed intake, IGF-1, and cortisol in yearling steelhead trout (*Oncorhynchus mykiss*) during seawater adaptation. General and Comparative Endocrinology 148:195–202.

Luckenbach, J. A., M. Murashige, H. V. Daniels, J. Godwin, and R. J. Borski. 2007. Temperature affects insulin-like growth factor-I and growth of juvenile southern flounder, *Paralichthys lethostigma*. Comparative Biochemistry and Physiology 146A:95–104.

Lupu, F., J. D. Terwilliger, K. Lee, G. V. Segre, and A. Efstratiadis. 2001. Roles of growth hormone and insulin-like growth factor 1 in mouse postnatal growth. Developmental Biology 229:141–162.

MacKenzie, D. S., C. M. VanPutte, and K. A. Leiner. 1998. Nutrient regulation of endocrine function in fish. Aquaculture 161:3–25.

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

Marti-Palanca, H., J. P. Martinez-Barbera, C. Pendon, M. M. Valdivia, J. Pérez-Sánchez, and S. Kaushik. 1996. Growth hormone as a function of age and dietary protein: energy ration in a marine teleost, the gilthead sea bream (*Sparus aurata*). Growth Regulation 6:253–259.

Maures, T. J., and C. Duan. 2002. Structure, developmental expression, and physiological regulation of zebrafish IGF binding protein-1. Endocrinology 143:2722–2731.

McCormick, S. D., B. T. Björnsson, M. Sheridan, C. Eilertson, J. B. Carey, and M. Odea. 1995. Increased day length stimulates plasma growth hormone and gill Na^+,K^+-ATPase in Atlantic salmon (*Salmo salar*). Journal of Comparative Physiology 165B:245–254.

McCormick, S. D., K. M. Kelley, G. Young, R. S. Nishioka, and H. A. Bern. 1992. Stimulation of coho salmon growth by insulin-like growth factor-1. General and Comparative Endocrinology 86:398–406.

McCormick, S. D., S. Moriyama, and B. T. Björnsson. 2000. Low temperature limits photoperiod control of smolting in Atlantic salmon through endocrine mechanisms. American Journal of Physiology 278:R1352–R1361.

McCormick, S. D., J. M. Shrimpton, J. B. Carey, M. F. O'Dea, K. E. Sloan, S. Moriyama, and B. T. Björnsson. 1998. Repeated acute stress reduces growth rate of Atlantic salmon parr and alters plasma levels of growth

hormone, insulin-like growth factor-I, and cortisol. Aquaculture 168:221–235.

Mingarro, M., S. Vega-Rubín de Celis, A. Astola, C. Pendón, M. M. Valdivia, and J. Pérez-Sánchez. 2002. Endocrine mediators of seasonal growth in gilthead sea bream (*Sparus aurata*): the growth hormone and somatolactin paradigm. General and Comparative Endocrinology 128:102–111.

Mommsen, T. P. 2001. Paradigms of growth in fish. Comparative Biochemistry and Physiology 129B:207–219.

Mommsen, T. P., M. M. Vijayan, and T. W. Moon. 1999. Cortisol in teleosts: dynamics, mechanisms of action, and metabolic regulation. Reviews in Fish Biology and Fisheries 9:211–268.

Montserrat, N., J. C. Gabillard, E. Capilla, M. I. Navarro, and J. Gutiérrez. 2007a. Role of insulin, insulin-like growth factors, and muscle regulatory factors in the compensatory growth of the trout (*Oncorhynchus mykiss)*. General and Comparative Endocrinology 150:462–472.

Montserrat, N., P. Gómez-Requeni, G. Bellini, E. Capilla, J. Pérez-Sánchez, I. Navarro, and J. Gutierrez. 2007b. Distinct role of insulin and IGF-I and its receptors in white skeletal muscle during compensatory growth of gilthead sea bream (*Sparus aurata*). Aquaculture 267:188–198.

Mori, I., T. Sakamoto, and T. Hirano. 1992. Growth hormone (GH)-dependent GH receptors in the Japanese eel, *Anguilla japonica*: effects of hypophysectomy and GH injection. General and Comparative Endocrinology 85:385–391.

Nankervis, L., S. J. Matthews, and P. Appleford. 2000. Effect of dietary nonprotein energy source on growth, nutrient retention, and circulating insulin-like growth factor-I and triiodothyronine levels in juvenile barramundi, *Lates calcarifer*. Aquaculture 191:323–335.

Negatu, Z., and A. H. Meier. 1995. In vitro incorporation of [^{14}C] glycine into muscle protein of Gulf killifish (*Fundulus grandis*) in response in insulin-like growth factor-I. General and Comparative Endocrinology 98:193–201.

Nordgarden, U., T. Hansen, G. I. Hmre, A. Sundby, and B. T. Björnsson. 2005. Endocrine growth regulation of adult Atlantic salmon in seawater: the effects of light regime on plasma growth hormone, insulin-like growth factor-I, and insulin levels. Aquaculture 250:862–871.

Ohlsson, C., B.-A. Bengtsson, O. G. P. Isaksson, T. T. Andreassen, and M. C. Slootweg. 1998. Growth hormone and bone. Endocrine Reviews 19:55–79.

Oksbjerg, N., F. Gondret, and M. Vestergaard. 2004. Basic principles of muscle development and growth in meat-producing mammals as affected by the insulin-like growth factor system. Domestic Animal Endocrinology 27:219–240.

Pankhurst, N.W., and G. Van Der Kraak. 1997. Effects of stress on reproduction and growth of fish. Pages 73–94 *in* G. K. Iwama, A. D. Pickering, J. P. Sumpter, and C. B. Schreck, editors. Fish stress and health in aquaculture. Cambridge University Press, Cambridge, UK.

Pedroso, F. L., E. G. T. de Jesus-Ayson, H. H. Cortado, S. Hyodo, and F. G. Ayson. 2005. Changes in mRNA expression of grouper (*Epinephelus coioides*) growth hormone and insulin-like growth factor-I in response to nutritional status. General and Comparative Endocrinology 145:237–246.

Pérez-Sánchez, J., H. Marti-Palanca, and S. J. Kaushik. 1995. Ration size and protein intake affect circulating growth hormone concentration, hepatic growth hormone binding and plasma insulin-like growth-factor-I immunoreactivity in a marine teleost, the gilthead sea bream (*Sparus aurata*). Journal of Nutrition 125:546–552.

Pérez-Sánchez, J., H. Marti-Palanca, and P.-Y. Le Bail. 1994. Seasonal changes in circulating growth hormone (GH), hepatic GH-binding plasma insulin-like growth factor-I immunoreactivity in a marine fish, gilthead sea bream, *Sparus aurata*. Fish Physiology and Biochemistry 13:199–208.

Pérez-Sánchez, J., and P.-Y. Le Bail. 1999. Growth hormone axis as marker of nutritional status and growth performance in fish. Aquaculture 177:117–128.

Perry, S. F., and N. J. Bernier. 1999. The acute humoral adrenergic stress response in fish: facts and fiction. Aquaculture 177:285–295.

Peterson, B. C., and B. C. Small. 2005. Effects of exogenous cortisol on the GH/IGF-I/IGFBP network in channel catfish. Domestic Animal Endocrinology 28:391–404.

Picha, M. E., J. T. Silverstein, and R. J. Borski. 2006. Discordant regulation of hepatic IGF-I mRNA and circulating IGF-I during compensatory growth in a teleost, the hybrid striped bass (*Morone chrysops* × *Morone saxatilis)*. General and Comparative Endocrinology 147:196–205.

Pierce, A. L., B. R. Beckman, K. D. Shearer, D. A. Larsen, and W. W. Dickhoff. 2001. Effects of ration on somatotropic hormones and growth in coho salmon. Comparative Biochemistry and Physiology 128B:255–264.

Pierce, A. L., M. Shimizu, B. R. Beckman, D. M. Baker, and W. W. Dickhoff. 2005. Time course of the GH–IGF axis response to fasting and increased ration in Chinook salmon (*Oncorhynchus tshawytscha*). General and Comparative Endocrinology 140:192–202.

Pierce, A. L., M. Shimizu, L. Felli, P. Swanson, and W. W. Dickhoff. 2006. Metabolic hormones regulate insulin-like growth factor binding protein-1 mRNA levels in primary cultured salmon hepatocytes; lack of inhibition by insulin. Journal of Endocrinology 191:379–386.

Reid, S. G., N. J. Bernier, and S. F. Perry. 1998. The adrenergic stress response in fish: control of catecholamine storage and release. Comparative Biochemistry and Physiology 120C:1–27.

Reinecke, M. 2006. Insulin-like growth factor-I and -II in fish. Pages 87–130 *in* M. Reinecke, G. Zaccone, and B. G. Kapoor, editors. Fish endocrinology. Science Publishers, Enfield, New Hampshire.

Shamblott, M. J., C. M. Cheng, D. Bolt, and T. T. Chen. 1995. Appearance of insulin-like growth factor mRNA in the liver and pyloric ceca of a teleost in response to exogenous growth hormone. Proceedings of the National Academy of Sciences of the USA 92:6943–6946.

Shimizu, M., B. R. Beckman, A. Hara, and W. W. Dickhoff. 2006. Measurement of circulating salmon IGF binding protein-1: assay development, response to feeding ration

and temperature, and relation to growth parameters. Journal of Endocrinology 188:101–110.

Shimizu, M., J. T. Dickey, H. Fukada, and W. W. Dickhoff. 2005. Salmon serum 22-kDa insulin-like growth factor–binding protein (IGFBP) is IGFBP-1. Journal of Endocrinology 184:267–276.

Shimizu, M., A. Hara, and W. W. Dickhoff. 2003a. Development of an RIA for salmon 41-kDa IGF-binding protein. Journal of Endocrinology 178:275–283.

Shimizu, M., P. Swanson, and W. W. Dickhoff. 1999. Free and protein-bound insulin-like growth factor-I (IGF-I) and IGF binding proteins in plasma of coho salmon, *Oncorhynchus kisutch*. General and Comparative Endocrinology 115:398–405.

Shimizu, M., P. Swanson, H. Fukada, A. Hara, and W. W. Dickhoff. 2000. Comparison of extraction methods and assay validation for salmon insulin-like growth factor-I using commercially available components. General and Comparative Endocrinology 119:26–36.

Shimizu, M., P. Swanson, A. Hara, and W. W. Dickhoff. 2003b. Purification of a 41-kDa insulin-like growth factor–binding protein from serum of Chinook salmon, *Oncorhynchus tshawytscha*. General and Comparative Endocrinology 132:103–111.

Silverstein, J. T. 2002. Using genetic variation to understand control of feed intake in fish. Fish Physiology and Biochemistry 27:173–178.

Skalski, G. T., M. E. Picha, J. F. Gilliam, and R. J. Borski. 2005. Variable intake, compensatory growth, and increased growth efficiency in fish: models and mechanisms. Ecology 86:1452–1462.

Small, B. C. 2005. Effect of fasting on nychthemeral concentrations of plasma growth hormone (GH), insulin-like growth factor-I (IGF-I), and cortisol in channel catfish (*Ictalurus punctatus)*. Comparative Biochemistry and Physiology 142B:217–223.

Small, B. C., C. A. Murdock, G. C. Waldbieser, and B. C. Peterson. 2006. Reduction in channel catfish hepatic growth hormone receptor expression in response to food deprivation and exogenous cortisol. Domestic Animal Endocrinology 31:340–356.

Small, B. C., and B. C. Peterson. 2005. Establishment of a time-resolved fluoroimmunoassay for measuring plasma insulin-like growth factor-I (IGF-I) in fish: effect of fasting on plasma concentrations and tissue mRNA expression of IGF-I and growth hormone (GH) in channel catfish (*Ictalurus punctatus)*. Domestic Animal Endocrinology 28:202–215.

Stefansson, S. O., B. T. Björnsson, T. Hansen, C. Haux, G. L. Taranger, and R. L. Saunders. 1991. Growth, parr–smolt transformation, and changes in growth hormone of Atlantic salmon (*Salmo salar*) reared under different photoperiods. Canadian Journal of Fisheries and Aquatic Sciences 48:2100–2108.

Stickney, R. R. 1994. Principles of aquaculture. Wiley, New York.

Sutter, N. B., C. D. Bustamante, K. Chase, M. M. Gray, K. Zhao, L. Zhu, B. Padhukasahasram, E. Karlins, S. Davis, P. G. Jones, P. Quignon, G. S. Johnson, H. G. Parker, N. Fretwell, D. S. Mosher, D. F. Lawler, E. Satyaraj, M. Nordborg, K. G. Lark, R. K. Wayne, and E. A. Ostrander. 2007. A single IGF-1 allele is a major determinant of small size in dogs. Science 316:112–115.

Taylor, J. F., H. Migaud, M. J. R. Porter, and N. R. Bromage. 2005. Photoperiod influences growth rate and plasma insulin-like growth factor-I levels in juvenile rainbow trout, *Oncorhynchus mykiss*. General and Comparative Endocrinology 142:169–185.

Thissen, J. P., L. E. Underwood, and J. M. Ketelslegers. 1999. Regulation of insulin-like growth factor-I in starvation and injury. Nutritional Reviews 57:167–176.

Turano, M. J. 2006. Effect of cyclic feeding on compensatory growth and water quality in hybrid striped bass, *Morone chrysops* × *M. saxatilis*, culture. Doctoral dissertation. North Carolina State University, Raleigh.

Turano, M. J., R. J. Borski, and H. V. Daniels. 2007. Compensatory growth of pond-reared hybrid striped bass (*Morone chrysops* × *M. saxatilis*) fingerlings. Journal of the World Aquaculture Society 38:250–261.

Uchida, K., S. Kajimura, L. G. Riley, T. Hirano, K. Aida, and E. G. Grau. 2003. Effects of fasting on growth hormone/insulin-like growth factor-I axis in the tilapia, *Oreochromis mossambicus*. Comparative Biochemistry and Physiology 134A:429–439.

Vera Cruz, E. M., C. L. Brown, J. A. Luckenbach, M. E. Picha, R. B. Bolivar, and R. J. Borski. 2006. Insulin-like growth factor-I cDNA cloning, gene expression, and potential use as a growth rate indicator in Nile tilapia, *Oreochromis niloticus*. Aquaculture 251:585–595.

Vijayan, M. M., G. D. Foster, and T. W. Moon. 1993. Effects of cortisol on hepatic carbohydrate metabolism and responsiveness to hormones in sea raven *Hemitripterus americanus*. Fish Physiology and Biochemistry 12:327–335.

Weber, G. M., and J. T. Silverstein. 2007. Evaluation of a stress response for use in a selective breeding program for improved growth and disease resistance in rainbow trout. North American Journal of Aquaculture 69:69–79.

Wood, A. W., C. M. Duan, and H. A. Bern. 2005. Insulin-like growth factor signaling in fish. International Review of Cytology 243:215–285.