NOTICE OF PUBLICATION

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RESEARCH REPORTS

Sustainable Aquaculture for a Secure Future

Title: **Leptin stimulates hepatic growth hormone receptor and insulin-like growth factor gene expression in a teleost fish, the hybrid striped bass**

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Leptin is an anorexigenic peptide hormone that circulates as an indicator of adiposity in mammals, and functions to maintain energy homeostasis by balancing feeding and energy expenditure. In fish, leptin tends to be predominantly expressed in the liver, another important energy storing tissue, rather than in fat depots as it is in mammals. The liver also produces the majority of circulating insulin-like growth factors (IGFs), which comprise the mitogenic component of the growth hormone (GH)-IGF endocrine growth axis. Based on similar regulatory patterns of leptin and IGFs that we have documented in previous studies on hybrid striped bass (HSB: *Morone saxatilis* × *M. chrysops*), and considering the co-localization of these peptides in the liver, we hypothesized that leptin might regulate the endocrine growth axis in a manner that helps coordinate somatic growth with energy availability. Using a HSB hepatocyte culture system to simulate autocrine or paracrine exposure that might occur within the liver, this study examines the potential for leptin to modulate metabolism and growth through regulation of IGF gene expression directly, or indirectly through the regulation of GH receptors (GHR), which mediate GH-induced IGF expression. First, we verified that GH (50 nM) has a classical stimulatory effect on IGF-1 and additionally show it stimulates IGF-2 transcription in hepatocytes. Leptin (5 and/or 50 nM) directly stimulated *in vitro* GHR2 gene expression within 8 hrs of exposure, and both GHR1 and GHR2 as well as IGF-1 and IGF-2 gene expression after 24 hrs. Cells were then co-incubated with submaximal concentrations of leptin and GH (25 nM each) to test if they had a synergistic effect on IGF gene expression, possibly through increased GH sensitivity following GHR upregulation by leptin. In combination, however, the treatments only had an additive effect on stimulating IGF-1 mRNA despite their capacity to increase GHR mRNA

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abundance. This suggests that leptin's stimulatory effect on GHRs may be limited to enhancing transcription or mRNA stability rather than inducing full translation of functional receptors, at least within a 24-h time frame. Finally, leptin was injected IP (100 ng/g and 1 ug/g BW) to test the *in vivo* regulation of hepatic IGF-1 and GHR1 gene expression. The 100 ng/g BW leptin dose significantly upregulated in vivo IGF-1 mRNA levels relative to controls after 24 hrs of fasting, but neither dosage was effective at regulating GHR1 gene expression. These studies suggest that stimulation of growth axis component transcripts by leptin may be an important mechanism for coordinating somatic growth with nutritional state in these and perhaps other fish or vertebrates, and represent the first evidence of leptin regulating GHRs in vertebrates.

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