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# Leptin – A Potential Tool for Enhancing the Feed Conversion in Aquaculture

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## ABSTRACT

This review delves into the evolving landscape of teleostean leptin physiology in the context of global obesity concerns. Leptin, a key regulator of body weight and energy homeostasis, takes center stage in this exploration, with a particular focus on teleostean fishes renowned for their metabolic adaptability. Unlike mammals, fish predominantly synthesize leptin in the liver, displaying species-specific expression patterns. The interaction between leptin and its receptor (LepR) exhibits structural variations, underscoring the importance of tailoring considerations to individual species. Leptin's effects on fish food intake and body weight are complex, and contradictory results call for more research. Leptin also emerges as a crucial modulator of metabolism, responding to environmental cues like hypoxia. In the realm of reproduction, leptin's role is unfolding, potentially influencing sexual maturation. Furthermore, a regulatory connection between leptin and the fish stress axis is evident, influencing cortisol release and contributing to hormonal balance. Despite substantial strides, lingering questions prompt ongoing research into leptin's interactions, receptor mechanisms, and the evolutionary underpinnings of energy homeostasis. Leveraging teleostean models remains pivotal, providing distinctive insights into vertebrate physiology and the adaptive evolution of systems critical for maintaining energy balance amid environmental challenges.

## KEYWORDS

Stress, leptin, metabolism, synthesis, food intake, energy balance.

## Introduction

The global surge in obesity rates, nearly doubling since 1980, has reached alarming proportions, affecting over half a billion adults and 40 million preschool children worldwide (WHO, 2013). Astonishingly, the repercussions of overweight and obesity now claim more lives globally than malnutrition. Extensive research has been conducted into the complex mechanisms governing energy balance and body weight regulation in response to the growing hazard to human health. An essential component of physiological balance, energy homeostasis requires a precise balance between energy expenditure (which includes basal metabolic rate, physical activity, and thermogenesis for endotherms) and energy intake (which includes food ingestion and digestion). The hormone leptin, which was identified about twenty years ago and named after the Greek word "leptoz," which means lean, is essential to maintaining this complex equilibrium. Alpha-melanophore stimulating hormone (α-MSH) and cocaine and amphetamine-regulated transcript (CART) are two anorexigenic pro-opiomelanocortin (POMC)-derived alpha-melanophore stimulating hormone (α-MSH) and leptin-stimulated specific neurons in the hypothalamus. In mammals, leptin is produced in proportion to white adipose tissue. Leptin regulates food intake and metabolism through these neural circuits and secondary neurons in the paraventricular nucleus, reestablishing the energy balance in situations of excess.

Beyond its central role in energy metabolism, leptin exhibits pleiotropic actions, impacting the development of bones, angiogenesis, immune system, and stress response. The diverse range of prime targets underscores the multifaceted nature of leptin's actions, posing a significant challenge for physiologists seeking to comprehend its well-known anorexigenic epithet. While in-depth analyses of leptin physiology in mammals have focused on metabolism and feeding behavior, here we highlight new developments in leptin physiology in teleosts. Taking a comparative stance, we make use of the various models provided by ectotherms, especially teleosts, which are recognized for having less strict metabolic homeostasis. Examining teleostean fishes, which are the earliest known vertebrates on Earth, could reveal additional 'original' uses for leptin. According to recent research, teleostean fishes have a different leptin physiology than mammals, opening up new research opportunities. Our goal in this review is to summarize recent findings on the physiology of teleostean leptin while also outlining potential future research obstacles.

## Synthesis

Fish exhibit leptin levels ranging from 0.05–5 mM, similar to those in mammals. While adipose tissue is the main source of leptin production in mammals, fish, with species-specific variations, primarily rely on their liver. Some exceptions include mandarin fish and chub mackerel where adipose tissue contributes. In certain species, the liver may express one leptin form more than the other, as seen in common carp and northern snakeheads. Leptin synthesis in fish responds to various factors, including fasting. Fasting can either decrease (as in green sunfish) or increase (as in rainbow trout) plasma leptin levels, showcasing diverse responses across species. Feeding induces changes opposite to those during fasting, with variations observed in different fish species. Diet composition also affects leptin levels in fish. Diets rich in carbohydrates or fats may increase leptin mRNA abundance in the liver, as seen in grass carp and Nile tilapia. Different species respond differently to environmental factors that modulate leptin expression, such as salinity, temperature, and hypoxia.

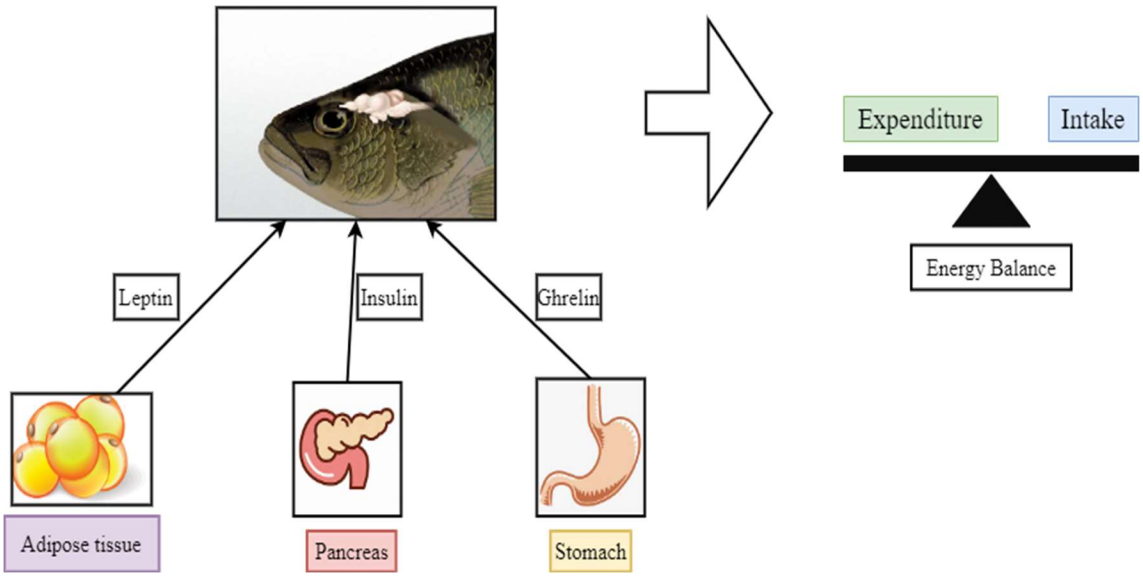
## Mechanism of action

The interaction between leptin and the leptin receptor (LepR), which belongs to the class I helical cytokine receptor family, is necessary for leptin to function. Teleost fish species, including zebrafish, medaka, goldfish, crucian carp, rainbow trout, Atlantic salmon, Nile tilapia, yellow catfish, orange-spotted grouper, European eel, and lined seahorse, exhibit an orthologous gene analogous to mammalian LepR. While Lepr is typically a singular orthologue, certain species like Atlantic salmon or European eel feature duplicate lepr paralogues. Additionally, some species manifest more than one isoform of LepR, as seen in Atlantic salmon, where four shorter LepR isoforms coexist with the long functional form due to alternative splicing, a phenomenon also observed in crucian carp and rainbow trout. Structure-wise, lepRs normally consist of a cytoplasmic tail that facilitates intracellular signaling upon leptin binding and an extracellular ligand-binding domain. Fish data are still scarce, but leptin binds to its receptors through three different binding sites (I–III) in mammals. Functional domains of salmon LepR remain conserved despite low sequence identity between their mammalian counterparts. However, there is a noticeable difference in the binding interface of leptin to LepR between fish and mammals. LepRs exhibit diverse expression patterns among different species and are widely distributed in fish tissues, specifically in the brain, pituitary, and gonads. Fish exhibit variable expression of lepr in response to reproductive hormones and nutritional status, indicating possible species-specific roles for leptin. The Jak/STAT pathway, which is a mechanism that is conserved in vertebrates, is how LepR signals. Although the precise mechanism in teleost fish is still not fully understood, evidence points to conserved mechanisms that are found to be similar in mammals. This is corroborated by similarities in important motifs that are essential for the recruitment and activation of the Jak/STAT protein. Nonetheless, caution is warranted in generalizing, given that current studies predominantly focus on specific fish species.

## Leptin's function in food consumption and body weight

Initial investigations into common carp demonstrated a distinct leptin physiology in comparison to mammals. Although there was a notable surge in hepatic leptin (-a) expression post-prandially, akin to mice, the levels of leptin-a mRNA remained unaltered during prolonged fasting. This underscores the liver's pivotal role in modulating short-term food intake in teleostean fish, given its direct link to the gut and responsiveness to post-prandial alterations in glucose and non-esterified fatty acids. The query of whether the heightened expression of leptin-a is directly governed by nutrients or other regulators like insulin or cholecystokinin (CCK) remains unresolved. Successive investigations into leptin and food intake in carp have produced diverse outcomes, with some indicating elevated leptin levels after fasting, suggesting an orexigenic mechanism. Nevertheless, consistent findings reveal that injections of leptin proteins diminish food intake in fish. Notably, contradictory discoveries regarding plasma leptin levels during fasting in rainbow trout and salmon underscore the necessity for supplementary assays to corroborate results. Novel tools, including a knock-down lep-a zebrafish and a medaka leptin receptor mutant, furnish valuable insights. The mutant medaka, comparable to the db/db mouse model, exhibited continual upregulation of orexigenic signals in the hypothalamus, leading to heightened feed intake and increased visceral fat deposition. Despite the limited expression of leptin in visceral fat, its role in signaling energy reserves remains uncertain. The observed correlation between insulin levels and visceral fat suggests a potential avenue for future research into the protracted regulation of food intake in fish and the interplay between

insulin and leptin. Moreover, fish models could contribute to comprehending the distinctions between visceral and subcutaneous fat and their respective implications for obesity-related pathology, considering the absence of isolated fat tissue in fish.




## Leptin and metabolic processes

Leptin assumes a pivotal role in the regulation of fish metabolism, especially in response to shifts in environmental factors such as decreases in water temperature or oxygen levels. These variations are commonplace in a fish's life, triggering a natural metabolic suppression. Fish employ diverse tactics, such as migrating to areas with optimal oxygen saturation or lower temperatures, to conserve energy and diminish oxygen consumption. In conditions of low oxygen (hypoxia), a notable response involves the inhibition of feeding, leading to growth impairment. Analogous to mammals, fish exhibit an elevation in leptin expression under hypoxic circumstances, facilitated by the oxygen-sensitive transcription factor HIF-1α. The HIF-1α pathway in fish mirrors that in mammals. The hypoxia-induced expression of leptin-a mRNA in zebrafish, along with the overexpression of hif-1α mRNA in developing zebrafish embryos, provides substantiation of HIF-1α's role in governing leptin-a. Acclimatization to hypoxia not only results in heightened leptin mRNA levels but also induces noteworthy changes in hematology and modifications in the expression levels of signals associated with the hypothalamic feeding circuitry. These alterations aim to curtail food intake, reduce metabolism, and conserve energy to adapt to the environmental shift. Studies also indicate that leptin plays a role in the anorexic response to hypoxia induced by disease. In trout infected with *Cryptobia salmositica*, a decline in appetite is regulated by increased hepatic leptin-a1 expression and a shift in gene expression in the hypothalamus from orexigenic to anorexigenic signals. Crucially, the primary stimulus for the upsurge in leptin-a expression is hypoxia itself, not the concomitant reduction in feed intake. Fish, particularly those renowned for high hypoxia tolerance, such as the crucian carp, can modulate their metabolic rate for extended durations without the necessity for thermoregulation. This adaptability enables them to confront food shortages without rigid signaling of nutrient deficit. Understanding the role of

leptin in fish physiology, especially in hypoxia-tolerant species like the crucian carp, can furnish valuable insights for anesthesiologists addressing temperature and metabolic instability during surgical procedures.

## Leptin and reproduction

Initial investigations utilizing elevated concentrations of recombinant human leptin (ranging from $10^8$ M to $10^6$ M) proposed a regulatory function for leptin in reproductive processes. Research conducted on European sea bass and rainbow trout suggested that the administration of high levels of recombinant human leptin could stimulate the secretion of LH and FSH hormones from pituitary gland cells in vitro. More recent investigations, employing sophisticated methodologies, identified an augmentation in the expression of a specific leptin variant, leptin-a1, in mature male Atlantic salmon parr. Nevertheless, these studies also indicated the absence of significant disparities in plasma leptin levels, implying the substantial contribution of other leptin variants to overall plasma concentrations. A study by Trombley et al. (2014) showcased an upsurge in the expression of both leptin-a paralogues in salmon, yet it did not furnish information on the expression levels of leptin-b genes or the total leptin plasma levels. Despite the absence of quantitative PCR (qPCR) data regarding the tissue expression patterns of leptin-b in salmon, the notable expression of leptin-b in zebrafish ovaries implies a potential involvement of leptin-b in the regulation of female reproduction. To encapsulate, although existing research has only begun to unravel the intricate role of leptin in the sexual maturation of fish, this area holds significant promise for future exploration.

## The stress-leptin axis

The association between leptin and the stress axis has been conclusively established in mammals. In fish, the stress axis is activated in the hypothalamic pre-optic area (POA), where corticotropin-releasing factor (CRF) is co-synthesized with CRF-binding protein (CRF-BP) and released by axons near corticotrope cells in the pars distalis. These cells respond to CRF stimulation by generating the pro-hormone pro-opiomelanocortin (POMC), which is further processed into adrenocorticotropic hormone (ACTH) in the pars distalis. In teleostean fish, cortisol, produced in response to ACTH, regulates hydromineral balance through the mineralocorticoid receptor (MR) and redirects energy flow to cope with specific stressors through the glucocorticoid receptor (GR). Observations in common carp have shown that recombinant human leptin can alleviate the stress axis (Gorissen et al., 2012). Increased leptin levels in the head kidney lead to a decrease in cortisol release, while the stimulation by ACTH remains unaffected. The pituitary gland exhibits high levels of leptin-a and leptin-b, along with significant leptin receptor expression, supporting the role of leptin in hormone output. In in-vitro perifusion, recombinant human leptin induces a rapid and prolonged decrease in ACTH release, regardless of its origin. Additionally, Tipsmark et al. (2008) found that leptin stimulates prolactin, and prolactin inhibits leptin, suggesting a substantial regulatory role for leptin in the pituitary gland's output, encompassing both the stress axis and the osmoregulatory axis (prolactin being crucial for fish survival in freshwater). Unpublished data and studies in salmon and tilapia further confirm leptin's regulatory role in osmoregulation (Baltzegar et al., 2014). As previously mentioned, leptin expression increases in hypoxic conditions. In situations of significantly reduced energy expenditure, inducing a robust stress response may be counterproductive due to the interconnectedness of cortisol and metabolism. Leptin may function to communicate the energy status and mitigate the stress response in such scenarios, contributing to

the delicate coordination between eustress and distress.

## Conclusion

In summary, a decade of teleostean model research has yielded valuable insights into the unique functions of leptin, a pivotal hormone in adapting to environmental challenges and energy reallocation. Fish leptin exhibits distinct physiological roles compared to mammals. Despite notable progress, key questions persist, particularly regarding interactions with other metabolic hormones and the intricacies of leptin receptor mechanisms. Recent advancements include the identification of the complete mammalian leptin system components in fish, enabling the creation of mutant models for comparative leptin research. Understanding vertebrate physiology requires an understanding of fish models, which provide unique insights into the evolution of systems essential to energy homeostasis.

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