Effects of Nutrients on Fish Appetite: Postprint

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Abstract

Identifying ideal fish meal substitutes has been a major research focus in animal nutrition over the past two decades. In carnivorous fish, replacement ratios of fish meal substitutes have remained low due to poor palatability, low digestibility, amino acid imbalance, and the presence of anti-nutritional factors. However, as the supply-demand imbalance of fish meal continues to intensify, replacing fish meal has become an imperative for the sustainable development of carnivorous fish aquaculture. Consequently, enhancing the utilization efficiency of fish meal substitutes in carnivorous fish has emerged as a critical bottleneck in fish meal replacement research. This review examines the influence of various nutrients on appetite from the perspective of appetite regulation, with the aim of manipulating fish appetite through nutritional interventions to improve feed utilization efficiency.

Full Text

Effect of Nutrients on Appetite of Fishes

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Abstract: Finding ideal fish meal substitutes has become one of the research hotspots in animal nutrition over the past two decades. In carnivorous fishes, fish meal substitutes are limited to low replacement ratios due to poor palatability, low digestibility, amino acid imbalance, and anti-nutritional factors. However, with the further imbalance between fish meal supply and demand, replacing fish meal has become an inevitable requirement for the sustainable development of carnivorous fish aquaculture. Therefore, improving the utilization efficiency of fish meal substitutes in carnivorous fishes has become the bottleneck of fish meal substitution research. This review examines the effects of various nutrients on appetite from the perspective of appetite regulation, aiming to utilize nutritional measures to artificially regulate fish appetite and thereby improve feed utilization efficiency.

Keywords: appetite; nutrients; regulation; fishes

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Introduction

With the rapid development of aquaculture, the demand for formulated feed ingredients has increased dramatically. The shortage of feed protein sources emerged as early as the 1990s, with fish meal being the most prominent case as the highest quality protein source. Consequently, finding ideal fish meal substitutes has become one of the research hotspots in animal nutrition over the past two decades [1-3]. Currently, numerous studies have reported on the use of inexpensive and readily available plant protein sources to replace fish meal in aquatic animals. Generally, non-carnivorous fishes can better utilize plant protein ingredients, allowing partial or complete replacement of fish meal in formulated feeds. However, in carnivorous fishes, plant protein ingredients substantially reduce appetite and cause negative effects (decreased production performance, reduced physiological and immune functions, deteriorated flesh quality), which greatly limits the application of plant protein sources in carnivorous fish farming [3-4]. Nevertheless, replacing fish meal has become an inevitable requirement for sustainable development of carnivorous fish aquaculture. Therefore, comprehensive and in-depth research on the physiological regulation mechanisms of fish appetite, and the use of nutritional measures to artificially regulate appetite and improve utilization efficiency of plant protein ingredients, will provide necessary theoretical basis and technical support for effectively solving the application problems of plant protein sources in carnivorous fishes. This review will focus on the effects of nutrients on fish appetite.

1. Concept of Appetite

Appetite refers to the natural motivation for feeding in animals, representing the desire that drives animals to engage in ingestion activities to obtain energy and nutrients for maintaining normal physiological functions. This constitutes the primary link in the digestive and metabolic process. The most important indicator reflecting appetite quality is voluntary feed intake, which results from complex interactions among numerous factors. These factors include intrinsic animal factors such as physiological status (sensory stimuli, gastrointestinal signals, circulating factors, and chemical signals), as well as extrinsic factors like feed characteristics (odor, shape, size, ingredient composition, nutritional content), water environment (temperature, dissolved oxygen, pH, metal ions, CO_2), stocking density, and disease prevention.

The basic regulatory process of fish feeding is illustrated in Figure 1 [Figure 1: see original paper] [5].

2.1 Effects of Protein and Amino Acids on Appetite

Animals require a certain amount of protein intake for growth and life maintenance, making dietary protein or amino acid levels extremely important for animal feeding. The hypothalamic feeding regulation center can monitor protein and amino acid levels in ingested food through neural and humoral pathways, thereby regulating animal appetite [6-7]. Research has confirmed that when dietary protein or even a single essential amino acid is insufficient, animals exhibit poor feeding behavior. When dietary protein or essential amino acids can only meet the minimum physiological requirements, animals increase feed intake to satisfy their needs. When dietary protein levels are too high, feed intake significantly decreases [8]. For example, when only 5%-8% of dietary energy comes from protein, mice show significantly increased feed intake compared to standard diets (where nutritional standards specify that 14% of required energy should be provided by protein). However, when protein provides less than 5% of energy, mice show significantly reduced feed intake [9]. Under conditions of constant carbohydrate content, increasing the proportion of energy from protein from 15% to 30% in diets can cause appetite suppression and significantly reduced feed intake in humans [10]. Numerous scholars have reported similar results [11-14].

Additionally, protein exhibits a feeding compensation effect [15]. This is mainly because protein, compared to carbohydrates and fats, more readily induces satiety in the short term, which relates to the stronger thermogenic effect of protein metabolism compared to carbohydrates and fats [16]. Moreover, protein is relatively more difficult to digest and decompose in the body than other major nutrients, thus requiring more time and energy for digestion and absorption and being less likely to cause hunger [17]. Some researchers have found that protein increases glucose "production" in the small intestine, and after analyzing glucose levels in the small intestine, the brain decides whether to send a "full" signal, which once issued, suppresses appetite [18-19]. Furthermore, protein affects appetite by influencing the secretion of appetite-related peptides such as leptin, ghrelin, cholecystokinin (CCK), and peptide YY (PYY) [10,20].

Compared to higher terrestrial animals, fishes have higher protein requirements, and protein plays extremely important physiological functions in fish growth. Fish protein is not only used for growth and self-repair of various tissues and organs but also constitutes many biologically active substances such as enzymes, hormones, and antibodies. Research has found that fish growth shows a significant positive correlation with protein gain, thus true fish growth refers to protein gain [21]. However, both excessively low and high dietary protein levels are generally considered to adversely affect feed intake, protein efficiency, and feed efficiency in fishes [22-23].

Fish-specific mechanistic research results show significant differences from higher animals. In Atlantic salmon, high plant protein diets showed no significant effect on mRNA expression levels of leptin, ghrelin, and CCK compared to fish meal [24-25]. In grass carp, neuropeptide Y (NPY) acts as an appetite-promoting regulatory factor [26], and dietary protein levels of 35%-40% significantly increased hypothalamic NPY mRNA expression levels [27]. In rainbow trout (*Oncorhynchus mykiss*), plant protein-based diets did not affect protein phosphorylation levels of TOR and ribosomal protein S6 (S6) in the TOR signaling pathway [28], but as the dietary protein-to-carbohydrate ratio decreased, the TOR signaling pathway was activated [29]. In soft-shelled turtle (*Pelodiscus sinensis*), replacing 60% of fish meal with soy protein concentrate significantly decreased protein phosphorylation levels of TOR, S6, and 4E-binding protein 1 (4E-BP1) [30]. These findings indicate that the fish TOR signaling pathway is regulated by dietary protein levels, and the effect of protein sources on the TOR signaling pathway depends on animal species.

Essentially, fish protein requirements are actually requirements for proportionally balanced amino acids in proteins. Therefore, in fish formulated feeds, attention should be paid not only to the effects of protein on appetite but also to the effects of amino acids. Amino acids are now widely recognized to have strong stimulatory effects on animal feeding behavior and serve as excellent feeding stimulants. Amino acids can be divided into L-type (levorotatory) and D-type (dextrorotatory). L-type amino acids are recognized as one of the most effective compounds for attracting fishes, crustaceans, and other aquatic animals. L-type amino acids (salts) have certain taste profiles: histidine, arginine, and phenylalanine taste bitter; alanine, proline, and threonine taste sweet; aspartic acid tastes sour; glutamate salts have umami flavor; branched-chain amino acids such as valine, leucine, and isoleucine have chocolate flavor; while methionine and its derivatives have fresh meat flavor [31]. Different fish species have different flavor preferences and show orientation toward specific flavors. Even the same amino acid or amino acid combination shows different feeding attractant activities in different fish species. Generally, non-carnivorous fishes prefer sweet tastes, while carnivorous fishes prefer fresh meat flavors [32-33]. Additionally, amino acid effects on fish appetite relate to their acid-base properties. Acidic amino acids include aspartic acid and glutamic acid, while basic amino acids include lysine, arginine, and histidine. Generally, carnivorous fishes are sensitive to basic and neutral amino acids, while herbivorous fishes are sensitive to acidic amino acids [34-35]. In mammals, oral receptors related to amino acid recognition belong to the taste receptor family 1 members (T1Rs), which are G protein-coupled receptors. T1R1 and T1R3 recognize amino acid tastes as heterodimers [36].

Research results on amino acid effects on feeding regulation differ among species and treatment methods. For example, after intracerebroventricular injection of leucine, rats showed significantly reduced feed intake and significantly decreased protein expression of appetite-promoting NPY and agouti-related protein (AgRP) [6]. However, dietary leucine supplementation did not affect feed intake, heat production, or body weight gain in lactating rats but significantly suppressed hypothalamic NPY and AgRP mRNA expression [37]. In recent years, central signaling pathways affecting appetite have become research hotspots. In weaned piglets, adding 0.55% L-leucine significantly increased protein phosphorylation levels of ribosomal protein S6 kinase 1 (S6K1) and 4E-BP1 in the mTOR signaling pathway compared to control and 0.27% L-leucine groups, thereby promoting protein synthesis capacity [38]. In fishes, research has mainly focused on transcriptional levels. In gibel carp, dietary supplementation of 0.54% arginine significantly decreased mRNA expression levels of TOR and S6K1 in liver and muscle but did not affect 4E-BP2 mRNA expression [39]. As dietary leucine levels increased, TOR mRNA expression levels in the liver of blunt snout bream significantly increased [40]. Leucine and arginine increased protein phosphorylation levels and mRNA expression levels of TOR and S6K1 in starved Chinese shrimp [41], while tryptophan inhibited TOR mRNA expression in muscle and liver of Jian carp but increased TOR and 4E-BP mRNA expression levels in midgut and hindgut [42]. TOR is a highly conserved protein kinase evolutionarily, widely present in various biological cells. Fish TOR genes share over 90% homology with humans, and carp TOR genes share over 97% homology with zebrafish [43]. In higher mammals, key upstream and downstream factors in the TOR signaling pathway such as protein kinase B (Akt), TOR, S6K1, S6, and 4E-BP1 generally do not show large changes at the transcriptional level (mRNA expression) but mainly manifest at the protein phosphorylation level. However, most studies on fishes have found differences at the transcriptional level, requiring further confirmation at the protein level to identify differences between fish and mammals.

2.2 Effects of Fat and Fatty Acids on Appetite

The primary need for animals to obtain nutrients from the external environment is to supply energy for life activities. As a high-energy nutrient, each gram of fat produces 2.3 and 1.7 times more heat in the body than carbohydrates and proteins, respectively (oxidation heat values: protein 23,640 J/g, fat 39,539 J/g, carbohydrate 17,154 J/g) [44]. Compared to protein and carbohydrates, animals have lower sensitivity to fat, which is the least likely to induce satiety [20]. Therefore, consuming the same mass of these three nutrients means more energy input from fat without appetite suppression due to energy excess, leading to fat deposition and obesity. Boyd et al. [45] believed that high-fat diets do not affect human feed intake or plasma CCK and glucagon-like peptide-I (GLP-I) levels. However, other researchers believe that long-term high-fat diets suppress appetite and increase levels of appetite-suppressing peptides such as CCK and somatostatin [46-47].

Recent physiological studies have found that humans and rodents can taste fatty acids orally but cannot taste triglycerides [48]. Recognizable fatty acids include polyunsaturated fatty acids (linoleic acid), monounsaturated fatty acids (oleic acid), and saturated fatty acids (C18:0, C12:0, C6:0) [49]. Receptors related to fat intake and metabolism are mainly distributed in oral taste receptor cells and the small intestine. Oral fatty acid sensitivity plays a key role in controlling fat intake. Studies show that long-term high-fat diets reduce oral fatty acid sensitivity. For example, diet-induced obesity-prone (DIO-P) rats have significantly lower oral fatty acid sensitivity than diet-induced obesity-resistant (DIO-R) rats. When fed the same high-fat diet, the former shows significantly higher appetite and feed intake than the latter [50]. Intestinal regulation of fat intake mainly occurs through modulating gastrointestinal motility and stimulating secretion of appetite-related hormones. When more fat is consumed, the small intestine slows gastrointestinal motility, prolongs gastric emptying time, and secretes appetite-suppressing hormones such as CCK and GLP-I, thereby reducing energy intake [51]. Similarly, fatty acids affect leptin and ghrelin secretion. For example, eicosapentaenoic acid (EPA) increases leptin secretion in mice [52], while increasing fatty acid chain length suppresses ghrelin secretion and promotes secretion of PYY, pancreatic polypeptide, and glucagon-like peptide-2 (GLP-2) [53].

In fishes, the efficiency of converting digestible and metabolic energy from fat to net energy is 5%-10% higher than that from carbohydrates and proteins. Free fatty acids and triglycerides from direct dietary sources or internal metabolism are important energy substances for fish growth, especially in marine fish. Due to their poor carbohydrate utilization, the energy-supplying role of fat is more important in marine fish nutrition, and appropriate fat levels can promote feed intake and spare protein [44]. Research has found that fish feeding rates can adjust according to dietary lipid levels. In non-isocaloric diets, some fish species show feeding rates that initially increase with dietary lipid levels but significantly decrease when lipid levels exceed certain ranges, such as in rainbow trout [54], European sea bass [55], grass carp [56], and southern catfish [57]. Other studies have found that in isocaloric diets, rainbow trout feeding rates are not significantly affected by dietary lipid levels [58]. This indicates that fish mainly adjust feed intake according to dietary energy levels, and the effect of fat on fish feeding rates may depend more on its energy-supplying role. Lipids such as phospholipids and cholesterol have certain feeding stimulant effects on some aquatic animals [59-60]. Dietary supplementation with appropriate essential fatty acids can improve feed intake and feed efficiency in aquatic animals [61].

2.3 Effects of Carbohydrates on Appetite

Carbohydrates are the most widely distributed organic compounds in nature, typically accounting for 40%-80% of dry weight in plants, and are the most important energy source for humans and animals. Carbohydrates supply 50%-55% of total energy in human diets and over 50% in livestock. Although aquatic animals can also use carbohydrates as an energy source, their limited insulin secretion and glucose metabolism capacity restrict carbohydrate application, which is influenced by fish species, carbohydrate type, and digestibility. Generally, carbohydrates supply no more than 50% of total energy for aquatic animals [44]. Since plant protein sources contain much higher carbohydrate levels than fish meal, understanding carbohydrate effects on appetite is necessary.

The specific effects of carbohydrate ingestion on animals are shown in Figure 2 [Figure 2: see original paper] [62]. Various starches are defined as: rapidly digestible starch (RDS), referring to starch rapidly digested and absorbed in the small intestine; slowly digestible starch (SDS), referring to starch completely digested and absorbed in the small intestine but at slower rates; and resistant starch (RS), referring to starch that resists digestion in the small intestine and functions like cellulose. In higher animals, starches are currently classified according to glycemic index (GI) and glycemic load (GL) [63-64]. In vitro simulated enzymatic hydrolysis can also be used to evaluate different starch digestibility [59]. Generally, glucose and RDS can increase animal appetite, while SDS and RS suppress appetite. Excessive fructose intake may cause adverse effects [65]. Most scholars believe that carbohydrate effects on appetite are mainly regulated through blood glucose and insulin [66-69], with no significant effects on appetite-related neuropeptides such as CCK, PYY, and ghrelin [20].

Current research on carbohydrate effects on carnivorous fish feeding has some reports. High-carbohydrate diets are generally believed to reduce feeding rates in carnivorous fish because fish spontaneously regulate feed energy intake within certain ranges, i.e., isocaloric feeding mechanism [70]. However, other studies show that when appropriate starch is added as an energy source in diets, carnivorous fish adopt strategies to increase feed intake to maintain normal growth, such as in southern catfish [71], longsnout catfish [72], largemouth bass [73], and culter [74]. However, excessive carbohydrate addition in carnivorous fish diets causes damage, mainly manifested as increased visceral ratio, increased liver glycogen, and increased visceral fat content [67]. Current research on carbohydrate effects on fish feeding mechanisms is limited to blood glucose content and carbohydrate metabolism-related enzyme activities. Studies have found that carnivorous fish have high carbohydrate digestibility but cannot quickly metabolize and convert it to energy, causing prolonged postprandial hyperglycemia, which confirms their limited capacity to utilize and metabolize glucose [75].

2.4 Effects of Nucleotides on Appetite

Nucleotides are low-molecular-weight compounds with important physiological and biochemical functions including encoding genetic information, regulating energy metabolism, transmitting cellular signals, and acting as coenzymes. Since animal bodies can synthesize various nucleotides and no specific deficiency symptoms exist, nucleotides have long been considered non-essential nutrients. Recent studies have found that nucleotides, as feeding stimulants, can significantly improve animal appetite, promote intestinal growth and development and post-injury repair, and benefit the growth of intestinal beneficial microorganisms

[76]. In aquatic animals, dietary nucleotide supplementation can increase feeding rates in Atlantic salmon [77] and striped bass [78], but inhibit feeding in red sea bream, striped bass, and tiger puffer [26], with mechanisms requiring further research.

2.5 Effects of Vitamins on Appetite

Due to small animal requirements for vitamins and the ability to meet needs through exogenous supplementation, few reports exist on vitamin effects on animal appetite. In fishes, deficiencies in vitamin C, pantothenic acid, folic acid, niacin, and inositol cause anorexia [44]. In higher animals, vitamins A and D have more obvious effects on appetite [79-81]. Vitamin D deficiency in diets significantly impairs insulin secretion in mice, ultimately reducing feed intake [81]. Excessive vitamin D intake causes appetite suppression in young children [80]. High vitamin A levels can downregulate leptin mRNA expression in mice without causing increased feed intake [82].

2.6 Effects of Mineral Elements on Appetite

Mineral elements related to aquatic animal appetite mainly include magnesium, iron, and zinc [47]. In higher animals, zinc has the most obvious regulatory effect on appetite. Zinc is a component of gustin in saliva, and zinc deficiency reduces taste stimulation, thereby affecting appetite. Zinc deficiency also reduces activities of various zinc-containing enzymes required for metabolism, affecting nucleic acid and protein synthesis and decomposition. Additionally, zinc can directly alter activities of norepinephrine receptors, dopamine receptors, serotonin receptors, and opioid peptide receptors in the central nervous system to regulate appetite and affect the nervous system, manifested as altered amino acid metabolism and neurotransmitter content (mainly catecholamines), leading to abnormal feeding [83-84]. Both zinc deficiency and high zinc can regulate gene expression in rat pituitary. Zinc deficiency downregulates NPY mRNA expression and upregulates CCK and calcitonin gene-related peptide (CGRP) mRNA expression levels, while high zinc upregulates melanin-concentrating hormone and ghrelin mRNA expression levels [85]. No systematic reports currently exist on other mineral element effects on appetite.

In mammals, high-protein diets easily induce satiety and stimulate secretion of appetite-suppressing regulatory peptides, while carbohydrates and fats differ, particularly due to low taste sensitivity to fat. Since protein and carbohydrates produce similar total energy, future fish feed formulation should reasonably reduce dietary protein levels, with protein only meeting minimum requirements, allowing more fat and carbohydrates to supply energy. This becomes particularly urgent when feed protein source shortages become a bottleneck for sustainable aquaculture development.

Reducing the energy-supplying role of dietary protein allows more protein to be used for growth, thereby reducing dietary protein levels, improving protein utilization efficiency, alleviating feed protein source shortages, and reducing nitrogen pollution of water environments from massive metabolic nitrogen excretion.

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