Peptide transport and animal growth: the fish paradigm

Protein digestion products are transported from the intestinal lumen into the enterocyte both in the form of free amino acids (AAs), by a large variety of brush border membrane AA transporters, and in the form of di/tripeptides, by a single brush border membrane transporter known as PEPTide Transporter 1 (PEPT1). Recent data indicate that, at least in teleost fish, PEPT1 plays a significant role in animal growth by operating, at the gastrointestinal level, as part of an integrated response network to food availability that directly supports body weight. Notably, PEPT1 responds to both fasting and refeeding and is involved in a phenomenon known as compensatory growth (a phase of accelerated growth when food levels are restored after a period of growth depression). In particular, PEPT1 expression decreases during fasting and increases during refeeding, which is the opposite of what observed so far in mammals and birds. These findings in teleost fish document, to our knowledge, for the first time in a vertebrate model, a direct correlation between the expression of an intestinal transporter, such as PEPT1, primarily involved in the uptake of dietary protein degradation products and animal growth.

Keywords: di/tripeptides; PEPTide Transporter 1; teleost fish; growth; fasting/refeeding

1. INTRODUCTION

The modern mode of thinking that digested protein is transported from the intestinal lumen into enterocytes and then into the circulation both as amino acids (AAs) and di/tripeptides dates back to the mid-1970s. Today, we know that di/tripeptides are taken up by a single transporter known as PEPTide Transporter 1 (PEPT1). However, some questions remain unanswered. For instance, although PEPT1 knock-out models have been generated [1,2], it is not clear whether the intestinal peptide transporter plays a role in the up- or downregulation of animal growth. Indeed, by deleting the intestinal peptide transporter pept1 (previously known as pep-2) body size is reduced in an invertebrate animal model, such as the nematode Caenorhabditis elegans [1,3], whereas Pept1 null mice grow to normal size, body weight and organ weight [2].

In recent years, interest in piscine PEPT1 has grown rapidly [4,5]. This is owing to the recurring observation that fish can efficiently use dietary di/tripeptides to sustain development, growth and metabolism [6–14].

2. MAJOR, SPECIFIC ASPECTS OF FISH GROWTH

In most fish, growth is indeterminate and the majority of absorbed nutrients are invested in accreting muscle tissue [15]. Muscle growth in juvenile fish increases both the size (hypertrophia) and number of muscle fibres (hyperplasia). By contrast, the increase in the number of fibres in mammals and birds is arrested shortly after embryonic development has been completed [16], and further muscle growth is mainly caused by hypertrophy of existing fibres. Skeletal muscle forms 40–60% of the body mass in most adult fish. In muscle, all of the synthesized protein accumulates as growth, unlike in other tissues, such as liver or gills, in which high fractional rates of protein synthesis are matched by similarly high rates of protein degradation, with the effect of an inherently low rate of growth efficiency. As a result, the contribution of these tissues to overall growth of the fish is minute [17]. Since muscle may account for more than half of the fish’s body mass, and muscle is characterized by low fractional rates of protein synthesis, yet the highest growth rate efficiency of any tissue [17], it is not surprising that muscle protein synthesis per se is an excellent overall measure of fish growth.

Furthermore, the natural life cycle of many fish species includes a fasting period as a consequence of temporal and spatial food availability in the aquatic environment. Fish are well adapted to survive for long periods without food, and metabolic depression seems to be an important strategy in response to periods of food scarcity [18,19]. When food levels are restored, growth can increase over and above normal rates in these fish. This phenomenon is known as compensatory growth [20,21].

The fasting/refeeding paradigm has been widely used to investigate the molecular mechanisms underlying the transition from a catabolic to an anabolic state in fish [22–25]. For instance, in juvenile rainbow trout (Oncorhynchus mykiss) fasted for 10 weeks, refeeding resulted in a 15-fold increase in insulin-like growth factor I (IGF-I) mRNA 12 days following refeeding, and in a much smaller increase in the less abundant insulin-like growth factor II (IGF-II) mRNA [22].

3. PEPTIDE TRANSPORT(ERS) AND GROWTH: THE FISH PARADIGM

Recently, sea bass (Dicentrarchus labrax) has emerged as an excellent fish model for muscle growth studies as it exhibits extensive juvenile (post-metamorphosis) muscle hyperplasia, which contributes to its large adult size. We have demonstrated in this species that nutritional status influences the expression of several genes that encode for physiologically relevant proteins which participate in both an endocrine and autocrine/paracrine fashion in promoting compensatory growth induced by refeeding [25,26]. In our experiments (for details see the electronic supplementary material), sea bass nutritional status (figure 1c) influenced the expression of key growth-related genes, such as myostatin in muscle (electronic supplementary material, figure S1), IGF-I and IGF-II in liver and muscle (electronic supplementary material, figure S2a–d), and these regulatory responses correlated highly with...
changes in fish body weight and condition factor (a morphological indicator of body shape) (figure 1a,b). At the gastrointestinal level, the stomach responded to fasting by upregulating ghrelin (electronic supplementary material, figure S3a) and downregulating gastricsin (electronic supplementary material, figure S3b) expression as part of an integrated response to food availability. Under the same experimental conditions, PEPT1 expression in the proximal intestine (figure 1d) decreased during fasting and increased during refeeding [27], which is the opposite of what is observed in mammals and birds [28–33], suggesting that PEPT1 operates in direct support of fish (muscle) growth.

These data document a correlation between the expression of an intestinal transporter, such as PEPT1, which is primarily involved in the uptake of dietary protein degradation products, and animal growth for the first time, to our knowledge, in a vertebrate model. In fish, PEPT1 provides the necessary amount of AA to sustain net muscle protein synthesis, and thus body growth. Further evidence indicating that (synthetic) dietary di/tripeptide containing indispensable AA is responsible for enhanced weight gain of fish is supported by the significantly increased PEPT1 expression in the enterocytes of salmonid fish [34].

4. PERSPECTIVES

In our opinion, fish represent an excellent model for studying the effects of protein administration on animal growth because of the direct correlation that exists between dietary protein availability and accretion of body mass. In this respect, PEPT1 function is perfectly integrated into the physiological response scheme, representing a route for absorbing the bulk of protein that is needed to sustain body growth. Of course, this is a simplified model that cannot be applied to higher vertebrates (humans included), which are determinate growers. In fact, PEPT1 expression...
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...increases during fasting and decreases during refeeding in mammals and birds, which suggests a different, and most probably more sophisticated and complex control of the transporter activity. However, this does not exclude the possibility that PEPT1 may play a significant role in developmental stages in which linear accretion prevails even in higher vertebrates. No data are available on this point so far. Finally, an increasing number of researchers in the fish biological sciences are currently focusing on and discussing the potential role of peptide transport for the uptake of dietary AA in fish. This attention mainly derives from the observation that teleosts can efficiently use dietary dipeptide-based diets. Recent studies have demonstrated that dietary dipeptides can enter the fish intestinal cell via PEPT1 transporter. This transporter is highly expressed in the intestinal epithelium of fish, and its activity has been shown to be crucial for the absorption of dietary dipeptides.

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