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Somatostatin signaling and the regulation of growth and metabolism in fish

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Abstract

The study of the somatostatins (SS) signaling system in fish has provided important information about the structure, function, and evolution of SSs and their receptors. The SS signaling system elicits widespread biological actions via multiple hormone variants, numerous receptor subtypes, and a variety of signal transduction pathways. SSs alter growth via both direct and indirect actions, including inhibiting growth hormone release at the pituitary, decreasing hepatic GH sensitivity, and lowering plasma IGF-I levels. Metabolism also is significantly influenced by SSs. SSs stimulate the breakdown of energy stores and influences digestion, food intake, nutrient absorption, and food conversion both directly and through the modulation of other hormonal systems. The study of fish, which display a diversity of habitat types and life history forms, reveals that the SS signaling system helps regulate energy partitioning and integrate metabolism with growth and other biological processes.

Keywords: Preprosomatostatin; Somatostatin receptors; Feeding; Lipolysis; Glycogenolysis

1. Introduction

Since its initial discovery and isolation from sheep hypothalamus in 1973 (Brazeau et al., 1973), our understanding of the physiological actions of somatostatin (SS) has increased considerably. Originally noted for its inhibition of growth hormone (GH) release, SS is now known to have a broad spectrum of effects on energy allocation, digestion, and metabolism (Patel, 1999; Nelson and Sheridan, 2006a). Somatostatins occur in representatives of every major group of vertebrate, and the 14-amino acid form (SS-14-I) characterized by Brazeau et al. (1973) is highly conserved (Lin and Peter, 2001; Nelson and Sheridan, 2005). Several species possess additional SS forms that vary in amino acid length and/or composition (Lin and Peter, 2001; Nelson and Sheridan, 2005; Youson et al., 2006). Interestingly, many instances of differential function of the SS variants have been reported (Sheridan et al., 2000). The distribution of SS production also appears important to its function because peptides appear to operate in a paracrine/autocrine manner as well as in a systemic fashion.

Somatostatins are synthesized by numerous cell types, including neural and epithelial cells, and display a brain-gut distribution (Barnett, 2003). They occur in several tissues, including the gastrointestinal tract, thyroid, pancreatic islets, the nervous system and other sites (Patel, 1999; Nelson and Sheridan, 2005). In parallel with the ubiquitous distribution of SS peptides, numerous SS receptor (SSTR) subtypes exist in many different tissues (Møller et al., 2003; Nelson and Sheridan, 2005), resulting in a complex SS signaling system consisting of multiple hormone variants that interact with numerous SSTRs.

Fish are the most numerous and diverse group of vertebrate. They inhabit a wide-range of aquatic habitats and have evolved a variety of life history patterns, including indeterminant growth and natural periods of extended food deprivation. The study of fish has provided considerable insight into the structure, function, and evolution of SSs and their receptors. This review will provide an update on our understanding of the SS signaling system and the role of this system on regulating growth and metabolism.

2. Overview of the somatostatin signaling system

The SS signaling system consists of an elaborate network of signal molecules, G-protein coupled SSTRs, and cellular effec-

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tor pathways. The elaborate nature of the system extends from extensive diversity at every level; there is molecular heterogeneity of the signal itself as well as of the receptors. In addition, the receptors can link to several different effector pathways through numerous types of G-proteins. Differential interaction among the components of the system underlies the vast multi-functional nature of the SS family of peptide hormones.

The molecular heterogeneity of the SS peptide family arises from the tissue-specific differential processing of precursor protein (preprosomatostatin, PPSS) as well as from the existence of multiple SS genes that encode different PPSSs (Patel, 1999; Sheridan et al., 2000). Somatostatin-14, conserved in most fish and other vertebrates studied, is a product of PPSS I (Nelson and Sheridan, 2005; Ye et al., 2005). N-terminally extended forms of SS also can arise from PPSS I based on processing. For example, a SS-24 could result in some species of basal teleosts and a SS-26 in the white sucker and rainbow trout (Sheridan et al., 2000; Youson et al., 2006). Most teleost fish also express PPSS II and some, such as goldfish, possess PPSS III (Lin and Peter, 2001; Nelson and Sheridan, 2005; Canosa et al., 2007). PPSS II, which contains [Tyr^7, Gly^{10}]-SS-14 at its C-terminus (denoted SS-14-II), could be processed into SS-25-II or SS-28-II in many species of fish, and possibly to SS-27-II in four osteoglossomorph species (Lin and Peter, 2001; Nelson and Sheridan, 2005; Youson et al., 2006). PPSS II products have been characterized in anglerfish, eel, flounder, goldfish, salmon, sculpin, tilapia, trout, white sucker, and four osteoglossomorphs (Nelson and Sheridan, 2005; Youson et al., 2006). Rainbow trout possess two different variants of PPSS II: PPSS II′ which could yield SS-14-II and SS-28-II, and PPSS II″ which could yield SS-14-II and SS-25-II (Sheridan et al., 2000). PPSS III is characterized by [Pro^2]-SS-14 at its C-terminus and probably gave rise to cortistatin (Nelson and Sheridan, 2005; Canosa et al., 2007). As a result of the existence of multiple SS genes and differential processing, a single species of fish may produce numerous forms of SS (Fig. 1). The evolution of the SS family is complex, and its multigenic nature appears to result from a series of gene duplication events, including the tetraploidization of many species such as goldfish and rainbow trout (Nelson and Sheridan, 2005). Increasing evidence indicates that PPSSs are differentially expressed in fish and that their expression is regulated by nutritional state and numerous hormones, including cholecystokinin (CCK), 17β-estradiol, dopamine, insulin, insulin-like growth factor-I (IGF-I), GH, glucagon, and testosterone (Nelson and Sheridan, 2005).

The physiological actions of SSs are mediated by G-protein coupled transmembrane somatostatin receptors (SSTR). Four receptor subtypes have been described in fish: SSTR 1–3 and 5 (Gracey et al., 2001; Lin and Peter, 2001; Nelson and Sheridan, 2005). In addition, several isoforms exist (e.g., SSTR1A/SSTR1B); unlike the case in mammals, these isoforms appear to arise from distinct mRNAs (Lin and Peter, 2001; Nelson and Sheridan, 2005). SSTRs are found in many tissues, including kidney, thyroid, immune cells, adrenal glands, pancreas, gastrointestinal tract, and brain, and the distribution is often both differential and overlapping (Sheridan et al., 2000; Lin and Peter, 2001). The expression of SSTR mRNAs is regulated by nutritional state and numerous hormones, including 17β-estradiol, INS, IGF-I, GH, and testosterone (Nelson and Sheridan, 2005). It also appears that SS ligands are selective for specific receptor subtypes (Gong et al., 2004), and that they are coupled in a particular manner to cellular effector pathways (Yunker et al., 2003).

SSTRs are known to link to a number of second messenger systems, including Ca^{2+} and K^+ ion channels, adenylyl cyclase, MAP kinase (MAPK), phospholipase C, and phospholipase A2 (Reisine and Bell, 1995; Patel, 1999). In goldfish pituitary, Ca^{2+} appears necessary for cAMP-dependent stimulated GH secretion, and while SS-14 inhibits this GH release, it does not totally abolish Ca^{2+} signals (Yunker and Chang, 2004). In rainbow trout liver cells, MAPK mediated SS-14 inhibition of GH-stimulated IGF-I expression (Hagemeister and Sheridan, 2007).

Research reveals significant structure–function relationships among the SS family of peptides. For example, in rainbow trout, INS levels are unaffected by SS-14-I, but are reduced after injection of SS-25-II (Eilertson and Sheridan, 1993). Differential efficacy of SS ligands to reduce GH secretion also has been demonstrated. SS-14-I and SS-14-III are more potent than goldfish brain SS-28-II at reducing PACAP-stimulated GH release in goldfish pituitary cells, but all three ligands exhibited simi-

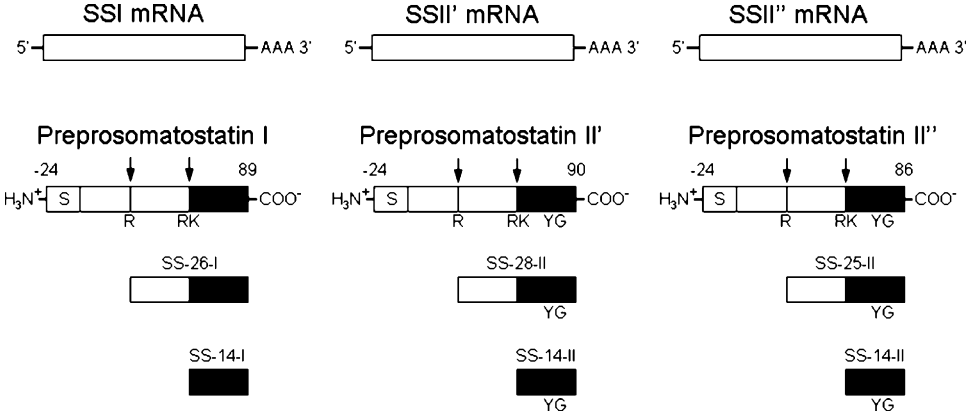

Fig. 1. Biosynthesis of somatostatins in rainbow trout. Arrows indicate putative cleavage sites; SS, somatosatatins; other letters are single-letter amino acid abbreviations.