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Minireview

Spexin as a neuroendocrine signal with emerging functions

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ABSTRACT

Spexin (SPX), a novel peptide coevolved with the galanin/kisspeptin family, was first identified by bioinformatics prior to its protein purification/functional studies. Its mature peptide is highly conserved among different vertebrate classes. Based on the studies in mammals and fish models, SPX was found to be widely distributed at tissue level, secreted into systemic circulation, identified at notable levels in central nervous system and peripheral tissues, and has been confirmed/implicated in multiple functions in different tissues/organs, suggesting that SPX may serve as a neuroendocrine signal with pleotropic functions. In this article, different isoforms of SPX and their binding with their cognate receptors GalR2 and GalR3, the biological functions of SPX reported in mammals including GI tract movement, energy balance and weight loss, fatty acid uptake, glucose homeostasis, nociception and cardiovascular/renal functions, as well as the recent findings in fish models regarding the role of SPX in reproduction and feeding control will be reviewed with interesting questions for future investigations.

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1. Introduction

Spexin (SPX), also referred to as neuropeptide Q, is a polypeptide encoded by the C12orf29 gene located in chromosome 12 of the human genome (Wan et al., 2010). It was first identified in 2007 by data mining of human proteome with hidden Markov method (Mirabeau et al., 2007) and the finding was later confirmed by another group using evolutionary probabilistic models based on the genome database reported in different vertebrates (Sonmez et al., 2009). It is one of the recent examples for identification of novel peptides by bioinformatics prior to their protein purification/functional studies. Using sequence analysis and comparative synteny, SPX has been recently proposed to be coevolved with galanin (Gal) and kisspeptin (Kiss) and classified as a member of the Gal/Kiss peptide family (Kim et al., 2014). Based on the studies in fish (e.g., goldfish) and mammals (e.g., rodents & human), SPX are known to be widely expressed in different tissues/organs, including the brain, heart, lung, liver, thyroid, adrenal, muscle, body fat, ovary, testis, pancreas, stomach and different parts of the GI tract (Mirabeau et al., 2007; Porzionato et al., 2010; Wong et al., 2013). In representative species, e.g., human (Walewski et al., 2014) and goldfish (Ma et al., 2017), SPX immunoreactivity can be detected in systemic circulation and modified by physiological status (e.g., obesity) or hormonal signals (e.g., insulin). Meanwhile, notable levels of SPX, both transcript and protein signals, can also be located in different brain areas as well as in neurons/cell bodies within the hypothalamus and other brain nuclei, e.g., in the rat (Porzionato et al., 2010) and goldfish (Liu et al., 2013). Consistent with its wide range of tissue distribution, increasing functions of SPX start to emerge in recent years together with the new information for SPX isoforms and their receptors, suggesting that the newly discovered peptide may serve as a neuroendocrine signal with pleotropic functions. In this article, the structural aspects of SPX and its binding to different SPX receptors, the biological functions of SPX reported in mammals related to smooth muscle contraction in GI tract, energy balance and weight loss, fatty acid uptake, glucose homeostasis, nociception and cardiovascular/renal functions, as well as the recent findings in fish models regarding the role of SPX in reproduction and appetite control will be reviewed with stress on the unexplored areas still await for future investigations.

2. Spexin and its binding with GalR2 and GalR3

The structural organization of the coding sequence of SPX is well conserved from fish to mammals with a hydrophobic signal peptide followed by a linker region and the 14 a.a. mature peptide of SPX flanked by RR/KR and GRR dibasic cleavage sites (Liu et al., 2013; Mirabeau et al., 2007; Sonmez et al., 2009; Wong et al., 2013)

Abbreviations: SPX, spexin; Gal, galanin; Kiss, kisspeptin; LH, luteinizing hormone; GalR1, type I galanin receptor; GalR2, type II galanin receptor; GalR3, type III galanin receptor; hs-CRP, high-sensitivity C-reactive protein test index; HbAlc, haemoglobin A1C.

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(Fig. 1A). Based on the expression study of SPX in pancreatic βTC3 cells, protein signals of SPX could be located in the secretory vesicles with insulin as well as in the culture medium, suggesting that SPX can be processed properly and released by exocytosis at the cellular level (Mirabeau et al., 2007). In mammals, except for panda, dog and cat with a Ala^{6} to Ser^{6} substitution, the a.a. sequence of SPX mature peptide is identical among different species with the consensus sequence of NWTPQAMLYLKGAQ (Fig. 1B). The same sequence can also be found in representative species of bird, reptile and amphibian as well as in coelacanth, suggesting that the mature peptide of SPX is well preserved during the evolution of tetrapod lineage. In ray-finned fishes, a Ala^{13} to Thr^{13} substitution is observed in SPX mature peptide and the consensus sequence NWTP QAMLYLKGTQ can be found in all the species examined to date (referred to as "fish SPX"). As revealed by NMR spectroscopies, the solution structure of fish SPX is composed of an N-terminal random coil from Asn^{1} to Pro^{4} followed by an extended α helix from Gln^{5} to Gln^{14} in the C-terminal and the molecular surface of fish SPX is largely hydrophobic with Lys^{11} as the only charged residue, which is believed to play a key role in receptor binding/activation. At present, the solution structure of mammalian SPX is not available but knowledge-based modelling has predicted that the mammalian SPX with a Thr^{13} to Ala^{13} substitution also exists in the form of a helical peptide highly comparable if not identical to the 3D structure of fish SPX (Lin et al., 2015).

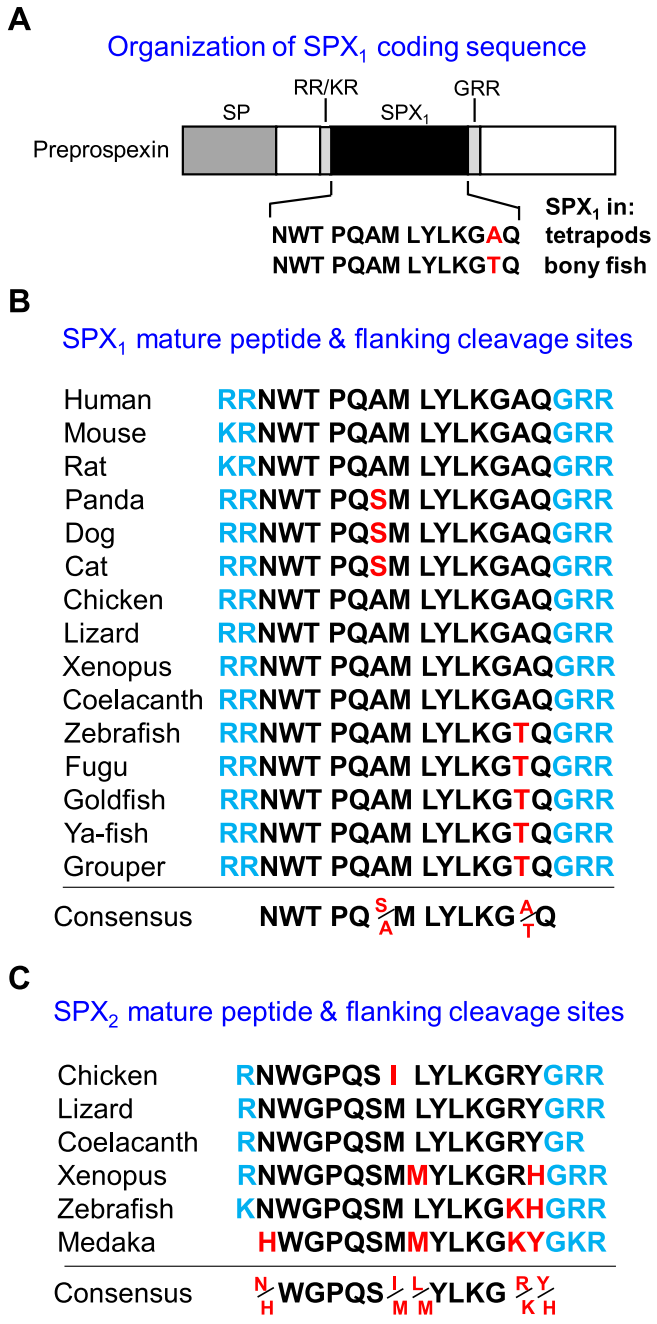

Fig. 1. Protein sequences of SPX reported in vertebrate species. (A) Structural organization of the protein coding sequence of SPX_1 reported in tetrapods and fish models. The coding sequence of SPX_1 is composed of a signal peptide (SP) followed by a linker region, SPX_1 mature peptide flanked by dibasic protein cleavage sites (RR/KR & GRR) and a C-terminal tail region. The consensus sequence of tetrapod and fish SPX_1 mature peptide has only one a.a. substitution at position 13. The structural organization of the protein coding sequence of SPX_2 (e.g., in zebrafish) is highly comparable with that of SPX_1. Alignment of (B) SPX_1 and (C) SPX_2 mature peptide and its flanking monobasic/dibasic cleavage sites reported in different species. The sequence alignment was conducted using Clustal-W algorithm with residues labelled in red for a.a. substitution(s) found in the consensus sequence of SPX_1/SPX_2 mature peptide and in blue for the flanking monobasic/dibasic cleavage sites. (Figures modified from Wong et al., 2013; Kim et al., 2014.) (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Based on recent data mining and comparative synteny, a second form of SPX, namely SPX_2, has been identified in species ranging from fish to bird but not in mammals (the first form of SPX reported previously is now renamed as "SPX_1") (Kim et al., 2014). In respective species, SPX_2 is encoded by a separate gene and the structural organization of its coding sequence is comparable to SPX_1, except that its mature peptide is flanked by R and GRR/GKR cutting sites, and depending on the species, up to 4 a.a. substitutions could be found among position 1, 3, 6, 7, 13 and 14 compared to the corresponding sequence of SPX_1 (Fig. 1C). Despite the sequence variations found in the signal peptide, linker region and C-terminal tail, the mature peptides of the two SPX are highly conserved, suggesting that SPX has been evolved under strong selection pressure and may be involved in important functions essential for survival. Since GRR/GKR is the target site for peptidylglycine α-amidating monooxygenase (Merkler, 1994) and the motif is well-conserved in the two forms of SPX, the C-terminal of SPX mature peptide is believed to be α-amidated and the modification may have an effect on its peptide stability/receptor binding.

Recently, type II (GalR2) and type III Gal receptors (GalR3) have been confirmed to be the cognate receptors for SPX (Kim et al., 2014), which is consistent with the idea that SPX is a member of the Gal/Kiss peptide family. Apparently, SPX_1 from mammals and SPX_1 and SPX_2 from *Xenopus* and zebrafish could not exhibit binding affinity nor the ability to activate type I Gal receptor (GalR1). In the same study, human GalR2 was shown to be promiscuous for $SPX_{1/2}$ and Gal binding/activation with a higher affinity for Gal but human GalR3 was found to be more selective for SPX_1 and SPX_2 and the preference for SPX over Gal was also observed in GalR3 from *Xenopus* (Kim et al., 2014). Of note, two forms of GalR2, GalR2a and GalR2b, could be identified in lower vertebrates including fish and amphibians (Fig. 2), which might be the result of whole genome duplication occurred during the early phase of vertebrate evolution (Yant and Bomblies, 2015). However, the corresponding sequence for GalR3 was not found in the genome databases of fish models. As revealed by functional expression in cell line (e.g., HEK293 cells), GalR2a from *Xenopus* and zebrafish could still retain the promiscuity/preference for Gal binding but the corresponding receptors for GalR2b were found to be highly selective for SPX_1 and SPX_2, despite a cross-activity with Gal at high doses (Kim et al., 2014). These findings, as a whole, raise the possibility that the GalR2b in lower vertebrates may be the functional equivalence of GalR3, which was evolved prior to the appearance

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