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Minireview

Bv8/Prokineticin proteins and their receptors

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Abstract

The Bv8/Prokineticins (PKs) are a new family of peptides identified in frog, fish, reptiles and mammals that signal through two highly homologous G-protein coupled receptors, PKR1 and PKR2. Bv8/PK proteins possess a unique structural motif comprising five disulfide bonds and a completely conserved N-terminal hexapeptide sequence that is essential for the peptide's biological activities. Over the past few years, several biological functions of Bv8/PK proteins have been elucidated. This review considers all the published data on the action and physiological role of this new biological system implicated in angiogenesis and neurogenesis, in reproduction and cancer and in regulating physiological functions that underly circadian rhythms, such as the sleep/wake cycle, hormone secretion and ingestive behaviors. The high expression level of human Bv8/PK2 in bone marrow, lymphoid organs and leukocytes suggested an involvement of these peptides in hematopoiesis and in inflammatory and immunomodulatory processes. Our review highlights the role of the Bv8/PK and their receptor system in setting the pain threshold under normal and pathological conditions.

Keywords: Bv8; Prokineticins; Prokineticin receptors; Angiogenesis; Reproductive organs; Cancer; Neurogenesis; Circadian rhythm; Intestinal motility; Pain; Inflammation

Contents

Introduction

In 1999 a small protein rich in cystein residues was isolated from the skin secretion of the frog *Bombina variegata* and named Bv8, to indicate its origin (*B. variegata*) and its molecular weight (8 kDa) (Mollay et al., 1999). Bv8 contracted

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guinea pig, rat and mouse ileum, relaxed rat colon, and induced hyperalgesia in rats. Homologus of Bv8 were identified in skin secretions of other amphibians, in lizards, in fishes of *Takifugu* species (Table 1) and in the venom of the black mamba, mamba intestinal toxin, MIT-1 or VRPA (Schweitz et al., 1999a; Joubert and Strydom, 1980). Because many bioactive sequences of peptides secreted by the olocryne glands of amphibian skin are conserved throughout evolution to subserve basic cellular or developmental processes (Erspamer, 1994), the high degree of identity between amphibian, fish and reptile Bv8-like peptides suggested that similar peptides could also be present in mammals. Within a few years after the discovery of Bv8, cDNA cloning confirmed the presence of Bv8 hortologues in the mouse, rat, cattle, monkey and man (Table 2). The mammalian proteins are named prokineticin1 (PK1 or EG-VEGF, endocrine gland-derived vascular endothelial growth factor) and prokineticin2 (PK2 or mBv8) because of their ability to contract guinea pig ileum. They are codified by two different genes, PROK1 and PROK2. A second form of PK2 has been identified and named PK2b on account of an insert of 21 basic amino acids in its sequence.

Three independent groups subsequently identified two closely related G-protein-coupled receptors for Bv8/PKs, prokineticin receptor 1 (PKR1) and prokineticin receptor 2 (PKR2) (Lin et al., 2002; Masuda et al., 2002; Soga et al., 2002).

Intensive research over the past few years has shown that the biological activities of Bv8/Prokineticin proteins range from angiogenesis and involvement in reproduction and cancer, to

Table 1
Bv8-related peptides of frogs, fishes, lizards and snakes

Peptides	Primary structure	Species
		Amphibians
	1————————————————————————————————38	
Bv8	AVITGACDKDVQCGSGTCCAASAWSRNIRFCIPLGNSG	*Bombina variegate*
Bm8a	AVITGVCDRDAQCGSGTCCAASAFSRNIRFCVPLGNNG	*Bombina maxima*
Bm8b	AVITGVRDRDAQCGSGTCCAASAFSRNIRFCVPLGNNG	*Bombina maxima*
Bm8c	AVITGVCDRDAQCGSGTCCAASAFSRNVRFCVPLGNNG	*Bombina maxima*
Bm8d	AVITGVCDRDAQCGSGTCCAASAFSRNIRFCVPLGNNG	*Bombina maxima*
Bm8e	AVITGV**C**DRDAQ**C**GSGT**CC**AASAFSRNIRF**C**VPLGNNG	*Bombina maxima*
Bm8f	AVITGV**C**DRDAQ**C**GSGT**CC**AASAFSRNIRF**C**VPLGNNG	*Bombina maxima*
Bo8	AVITGA**C**DRDVQ**C**GSGT**CC**AASAWSRNIRF**C**VPLGNSG	*Bombina orientalis*
	39————————————————————————————————77	
Bv8	ED**C**HPASHKVPYDGKRLSSL**C**P**C**KSGLT**C**SKSGEKFK**C**S	*Bombina variegate*
Bm8a	EE**C**HPASHKVPYNGKRLSSL**C**P**C**NTGLT**C**SKSGEKFQ**C**S	*Bombina maxima*
Bm8b	EE**C**HPASHKVPYNGKRLSSL**C**P**C**NTGLT**C**SKSGEKYQ**C**S	*Bombina maxima*
Bm8c	EE**C**HPASHKVPYNGKRLSSL**C**P**C**NTGLT**C**SKSGEKFQ**C**S	*Bombina maxima*
Bm8d	EE**C**HPASHKVPYNGKRLSSL**C**P**C**NTGLT**C**SKSGEKSQ**C**S	*Bombina maxima*
Bm8e	EE**C**HPASHKVPYNGKRLSSL**C**P**C**NTGLT**C**PKSGEKFQ**C**S	*Bombina maxima*
Bm8f	EE**C**HPASHKVPSDGKRLSSL**C**P**C**NTGLT**C**SKSGEKYQ**C**S	*Bombina maxima*
Bo8	EE**C**HPASHKVPYDGKRLSSL**C**P**C**KSGLT**C**SKSGAKFK**C**S	*Bombina orientalis*
		Fishes
	1————————————————————————————————38	
Fugu-1	AVITGACERDVQCGLGLCCAVSLWLRGLRMCAPRGLEG	*Takifugu bimaculatus*
Fugu-2	AVITGACEKDSQCGGGMCCAVSLWIRSLRMCTPMGREG	*Takifugu chinensis*
	39————————————————————————————————77	
Fugu-1	DECHPFSHKVPYPGKRQHHTCPCLPHLVCTRDRDSKYRC	*Takifugu bimaculatus*
Fugu-2	DDCHPMSHTVPFFGKRLHHTCPCLPNLSCIPMDEGRAKC	*Takifugu chinensis*
	78————————————94	
Fugu-1	TDDFKNVDLYEVGQTLR	*Takifugu bimaculatus*
Fugu-2	LSTYKYPDYYL	*Takifugu chinensis*
		Snakes
	1————————————————————————————————38	
MIT-1	AVITGA**C**ERDLQ**C**GKGT**CC**AVSLWIKSVRV**C**TPVGTSGE	*Dendroaspis polylepsis*
	39————————————————————————————————77	
MIT-1	D**C**HPASHKIPFSGQRKMHHT**C**P**C**APNLA**C**VQTSPKKFK**C**	*Dendroaspis polylepsis*
	−80	
MIT-1	LSK	*Dendroaspis polylepsis*
		Lizards
	1————————————————————————————————38	
VAR-1	AVITGA**C**DKDLQ**C**GEGM**CC**AVSLWIRSIRI**C**TPLGSSGE	*Varanus varius*
VAR-2	AVITGA**C**DKDLQ**C**GEGM**CC**AVSLWIRSIRICTPLGSSGE	*Varanus varius*
	39————————————————————————————————77	
VAR-1	DCHPLSHKVPFDGQRKHHTCPCLPNLVCGQTSPGKYKCL	*Varanus varius*
VAR-2	DCHPLSHKVPFDGQRKHHTCPCLPNLVCGQTSPGKHKCL	*Varanus varius*
	78—84	
VAR-1	PEFKNVF	*Varanus varius*
VAR-2	PEFKNVF	*Varanus varius*