



Snake venom dipeptidyl peptidase IV: Taxonomic distribution and quantitative variation

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ABSTRACT

The present study examined the taxonomic distribution of dipeptidyl peptidase IV (DPP IV) activity in venoms of 59 ophidian taxa, representing seven subfamilies of the Families Elapidae and Viperidae. DPP IV activity is extremely variable at all taxonomic levels. It ranged from essentially none in laticaudine, hydrophiine, and some bungarine and elapine venoms, to 10.72 μmol 4-methoxy- β -naphthylamine liberated per min per 200 μg venom, for *Ophiophagus hannah*. Intra- and interpopulational variation were examined among eight populations of prairie rattlesnakes (*Crotalus viridis viridis*), Great Basin rattlesnakes (*Crotalus viridis lutosus*) and southern Pacific rattlesnakes (*Crotalus viridis helleri*). Among these populations, the mean weighted range of variation was 4.9-fold, and even among litter mates of *C. v. lutosus*, DPP IV activity varied as much as 5.6-fold. The two most salient findings, the near ubiquity of DPP IV in snake venoms and its great quantitative variability, even among full siblings, are paradoxical. The widespread distribution of the enzyme suggests an important role in envenomation, while the variable activity levels suggest that DPP IV and by extension, other individual enzymatic constituents, may not be under much individual selective pressure.

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1. Introduction

Mammalian dipeptidyl peptidase IV (DPP IV) is a highly glycosylated serine protease (Bauvois, 1988; Slimane et al., 2000) that cleaves N-terminal dipeptides from substrates having proline, alanine, or hydroxyproline in the penultimate position. It occurs in both soluble and membrane-bound forms, the human form being known as CD26 (Ulmer et al., 1990). Mammalian DPP IV is believed to play three pivotal roles: 1. Activation or inactivation of biologically active peptides via removal of an N-terminal dipeptide. This process is involved in regulation of the immune and endocrine systems (Vanhoof et al., 1995; Morimoto et al., 1994; Hildebrandt et al., 2000), pathogenesis of diabetes mellitus and obesity (Holst and Deacon, 1998; Ahren et al., 2000; Deacon et al., 2001; Conarello et al., 2003; Villhauer et al., 2003), and HIV infection (Morimoto et al., 1994; Vanhoof et al., 1995); 2. Cell-cell, cell-extracellular matrix, and cell-virus contacts. CD26 may play a role in cell attachment to collagen (Bauvois, 1988) and it serves as a co-receptor for viruses and as a homing factor for organ, breast, and prostate tumors (Johnson et al., 1993; Cheng et al., 1998; Abdel-Ghany

et al., 1998); 3. Signal transduction. Membrane-bound DPP IV transduces specific signals through the plasma membrane (Mittrücker et al., 1995; Torimoto et al., 1991; Gaetaniello et al., 1998). It also regulates the responsiveness of T-cells to specific antigens detected in blood plasma (Ansoorge and Schon, 1987; Tanaka et al., 1994).

Perhaps most importantly with regard to the present story, high levels of DPP IV are also found in blood capillaries, suggesting a role in local regulation of blood pressure (Heymann and Mentlein, 1984; Werner et al., 1987; Kato et al., 1996; Koyama et al., 1997, 1998), because of the enzyme's ability to catabolize Substance P (Ahmad et al., 1992), neuropeptide Y and peptide YY (Zukowska-Grojec et al., 1986; Corder et al., 1987; Sheikh, 1991; Pawlik et al., 1992; Allen et al., 1993; Grandt et al., 1993; Mentlein et al., 1993; Mentlein, 1999; Preston et al., 1998).

In a study of coral snake (*Micrurus*) venom toxicities in laboratory mice and natural prey species, Jorge da Silva and Aird (2001) found Gly-Pro-p-nitroanilide hydrolytic activity in 13 of 15 *Micrurus* venoms, and in venoms of *Bungarus multicinctus*, *Naja naja*, and *Bothrops moojeni*. They attributed that activity to DPP IV, although it could conceivably have resulted from the combined actions of various aminopeptidases (Turzynski and Mentlein, 1990; Matsushima et al., 1991; Yaron and Naider, 1993; Gasparello-Clemente and Silveira, 2002). The following year, Aird (2002) offered a hypothetical explanation for the presence of DPP IV in venoms, suggesting that its role was to counteract a

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Table 1

Identities, origins and localities for venom samples examined in this study

Sub-family	Species	Location	Source/ID	# of specimens	
Acanthophiinae	<i>Acanthophis laevis</i>	Iryan Jaya	Zooherp		
	<i>Aspidelaps scutatus</i>		KRZ	20	
	<i>Pseudechis colletti</i>	Australia	KRZ	2	
Bungarinae	<i>Bungarus fasciatus</i>	China	Zooherp		
	<i>Bungarus fasciatus</i>		KRZ	2	
Elapinae	<i>Bungarus multicinctus</i>	Nanning, China	SVRI		
	<i>Dendroaspis angusticeps</i>		KRZ	10	
	<i>Dendroaspis jamesonii</i>		KRZ	10	
	<i>Dendroaspis polylepsis</i>		Biotoxins		
	<i>Dendroaspis viridis</i>	Ghana	Zooherp		
	<i>Micrurus fulvius</i>	Naples, Collier Co., FL	KRZ	5	
	<i>Naja annulifera</i>		KRZ	10	
	<i>Naja atra</i>	Nanning, China	SVRI		
	<i>Naja haje</i>		KRZ	5	
	<i>Naja kaouthia</i>		KRZ	240	
	<i>Naja melanoleuca</i>		KRZ	7	
	<i>Naja nigricollis</i>	Tanzania	Zooherp		
	<i>Naja nigricollis nigricollis</i>				
	<i>Naja nivea</i>		KRZ	6	
	<i>Naja oxiana</i>		KRZ	3	
	<i>Naja pallida</i>		KRZ	12	
	<i>Naja sputatrix</i>	Java	Zooherp		
	<i>Naja tripudians</i>	Thailand	Zooherp		
	<i>Ophiophagus hannah</i>	Thailand	Zooherp		
	<i>Ophiophagus hannah</i>		KRZ	6	
	Laticaudinae	<i>Laticauda semifasciata</i>		JSI	
		<i>Hydrophis cyanocinctus</i>		JSI	
<i>Lapemis hardwickii</i>			JSI		
Crotalinae	<i>Agkistrodon c. contortrix</i>	Unknown	Biotoxins		
	<i>Agkistrodon c. contortrix</i>	Hardeeville, Jasper Co., SC	KRZ	60	
	<i>Agkistrodon p. conanti</i>	Florida	Biotoxins		
	<i>Agkistrodon p. leucostom</i>	Clarksdale, DeKalb Co., MO	KRZ Pool	40	
	<i>Agkistrodon p. piscivorus</i>	Hardeeville, Jasper Co., SC	KRZ Pool	3	
	<i>Bothrops moojeni</i>	Goiânia, Goiás, Brasil	CEPB Pool	>75	
	<i>Calloselasma rhodostoma</i>	Thailand	KRZ Pool	15	
	<i>Crotalus adamanteus</i>	Florida	Biotoxins		
	<i>Crotalus atrox</i>	Bagdad, Yavapai Co., AZ	SDA 2701		
		Bagdad, Yavapai Co., AZ	SDA 2702		
		Phoenix, Maricopa Co., AZ	SDA 2801		
	<i>Crotalus c. cerastes</i>	El Dorado Canyon, Clark Co., NV	SDA 1901 SDA 2502 SDA 3601		
	<i>Crotalus durissus cascade</i>	Fortaleza, Ceará, Brasil	SDA Pool	~10	
	<i>Crotalus d. cumanensis</i>	Unknown	SDA 3801		
	<i>Crotalus d. terrificus</i>	Unknown	SDA 3802 SDA 3703		
	<i>Crotalus h. atricaudatus</i>	Chesapeake, Chesapeake Co., V	CEPB Pool	>25	
	<i>Crotalus lepidus klauberi</i>	Sta. Barbara Ranch, Durango, M	SDA		
		Sta. Barbara Ranch, Durango, M	SDA 1701		
		Sta. Barbara Ranch, Durango, M	SDA 1702		
		Sta. Barbara Ranch, Durango, M	SDA 1703		
	Sta. Barbara Ranch, Durango, M	SDA 1704			

Table 1 (continued)

Sub-family	Species	Location	Source/ID	# of specimens
	<i>Crotalus mitchellii pyrrhus</i>	Bagdad, Yavapai Co., AZ	SDA 2901 SDA 3301 SDA 3302	
	<i>Crotalus m. molossus</i>	Arizona	KRZ	
	<i>Crotalus r. rubber</i>		SDA 3401	
	<i>Crotalus s. scutulatus</i>		SDA 2101 SDA 2301 SDA 2401 SDA Pool	
	<i>Crotalus vegrandis, Juv.</i>	Venezuela	SDA 3001	
	<i>Crotalus viridis cerberus</i>	Rye, Gila Co., AZ	SDA 3101	
	<i>Crotalus viridis helleri</i>	Unknown	SDA 3102	
		Unknown	SDA 3103	
		Unknown	SDA 3104	
		Unknown	SDA 3105	
		Unknown	SDA 3106	
		Unknown	SDA 3107	
		Unknown	SDA 3108	
	<i>Crotalus viridis lutosus</i>	South Eden Ranch, Cache Co., UT	SDA 01	
		South Eden Ranch, Cache Co., UT	SDA 02	
		City Creek Canyon, Salt Lake Co. S of Burley, Cassia Co., ID	SDA 01	
		Bennett's Mtn., Elmore Co., ID	SDA 2501	
		Bennett's Mtn., Elmore Co., ID	SDA 2601	
		Bennett's Mtn., Elmore Co., ID	SDA 2602	
		Bennett's Mtn., Elmore Co., ID	SDA 2603	
		Bennett's Mtn., Elmore Co., ID	SDA 2604	
		Bennett's Mtn., Elmore Co., ID	SDA 2605	
		Bennett's Mtn., Elmore Co., ID	SDA 2606	
		Bennett's Mtn., Elmore Co., ID	SDA 2607	
		Bennett's Mtn., Elmore Co., ID	SDA 2608	
		Bennett's Mtn., Elmore Co., ID	SDA 2609	
		Bennett's Mtn., Elmore Co., ID	SDA 2610	
		Bennett's Mtn., Elmore Co., ID	SDA 2611	
		Bennett's Mtn., Elmore Co., ID	SDA 2612	
		Bennett's Mtn., Elmore Co., ID	SDA 2613	
		Bennett's Mtn., Elmore Co., ID	SDA 2614	
		Bennett's Mtn., Elmore Co., ID	SDA 2615	
		Bennett's Mtn., Elmore Co., ID	SDA 2616	
		Bennett's Mtn., Elmore Co., ID	SDA 2617	
		Bennett's Mtn., Elmore Co., ID	SDA 2618	
		Bennett's Mtn., Elmore Co., ID	SDA 2619	
		Bennett's Mtn., Elmore Co., ID	SDA 2620	
		Bennett's Mtn., Elmore Co., ID	SDA 2621	
	<i>Crotalus viridis viridis</i>	Wray, Yuma Co., CO	SDA 53	
		Wray, Yuma Co., CO	SDA 55	

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