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# Melittin-Like Peptides from the Shark-Repelling Defense Secretion of the Sole *Pardachirus pavoninus*


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**Three ichthyotoxic peptides, pardaxins P-1 to P-3, have been isolated from the defense secretion of the sole *Pardachirus pavoninus*. Pavoninins, the steroid glycosides with shark-repelling ability, had previously been isolated therefrom. Each pardaxin consists of 33 amino acid residues having a distinctly hydrophilic carboxyl terminal region and a predominantly hydrophobic remainder; the pardaxin is thus strongly surfactant. These peptides show marked physical and pharmacological similarities to melittin, the major active constituent of bee venom, yet they lack sequence homology. They are probably also responsible for the predator-repelling property of the sole.**


SOLES OF THE GENUS *PARDACHIRUS* secrete toxic material from the peculiar mucous glands that line their dorsal and anal fins (*1*). In addition to being ichthyotoxic and hemolytic (*2*), the crude secretion of *Pardachirus marmoratus*, Moses sole in the Red Sea, protects the fish from shark attacks (*3, 4*); the secretion of *P. pavoninus*, peacock sole in the western Pacific, presumably does the same (*1*). We have shown that groups of steroid monoglycosides, pavoninins from *P. pavoninus* and mosesins from *P. marmoratus*, are responsible in part for the toxicity and shark-repellent activity of the secretions (*5*).

On the other hand, Primor *et al.* reported isolation of pardaxin, an ichthyotoxic protein from the secretion of *P. marmoratus* (*6*), but its complete amino acid sequence has not been reported. We report here the isolation and primary structures of three toxic peptides from the secretion of *P. pavoninus*. These peptides are nearly identical to pardaxin (*7*), and therefore have been named pardaxins P-1 to P-3, where P refers to the species name.

Five *P. pavoninus*, averaging 20 cm in length, were captured along sandy areas near coral reefs around Ishigaki Island, Ryukyu Archipelago, Japan. We expressed the toxic secretion from the fish once daily over a 4-day period beginning on the first day of capture by placing the live fish in a shallow pan and pressing lightly along the base of their dorsal and anal fins. The collected secretion was stored frozen until lyophilization, which yielded 27 g of crude material including an undetermined amount of sea salt. Typically, 1 g of this material was twice precipitated from 10 ml of 0.1*M* acetic acid or 0.1*M* ammonium hydroxide by slow addition of 100 ml of cold acetone. This procedure produced a precipitate (420 mg) that was free of pavoninins—lipophilic active factors with shark-repellent activity (*5*)—and yet was ichthyotoxic and hemolytic. Incubation of the precipitate with chymotrypsin destroyed the activity, demonstrating the peptidic nature of the active components.

The ichthyotoxic factor in the precipitate


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was first concentrated by gel filtration in a fraction (fractions numbered 62 to 77 in Fig. 1A) that accounted for 15 to 20% by weight of the total recovered material. The toxic fraction was then separated by anion-exchange chromatography into three active fractions—1, 2, and 3—which accounted for 17, 23, and 7% by weight, respectively; the remaining material lay in inactive fraction 4 (Fig. 1B). Though fractions 2 and 3 were often poorly resolved (Fig. 1B), occasionally they were completely separated.

Final purification, accomplished by reversed-phase high-performance liquid chromatography (HPLC) (*8*), gave the major active component in each of the three ion-exchange fractions 1 to 3 with the same retention time, while a minor component was obtained from fractions 2 and 3 with slightly less retention time. Purity of the five components was further demonstrated by sodium dodecyl sulfate (SDS) disc electrophoresis (*9*), which indicated the molecular weights for all the peptides to be approximately 2800.

The amino acid analysis of these peptides indicated that they all consist of 33 amino acids with seven serine residues and a large percentage of hydrophobic residues and that they lack six amino acids (Tyr, Trp, Cys, His, Arg, and Asx) (*10*). The major active peptides from fractions 2 and 3 as separated by HPLC not only had identical amino acid compositions, but were also indistinguishable from each other on the basis of carboxyl terminal analysis with carboxypeptidase A, total enzymatic hydrolysis with carboxypeptidase Y, and peptide maps produced by thermolysin digestion. We therefore concluded that the two are the same compound, pardaxin P-1. In the ion-exchange chromatography medium, the peptide probably takes multiple forms of aggregation with slow equilibration, leading to their irreproducible separation. The minor components from fractions 2 and 3 are also identical and were named pardaxin P-3, and pardaxin P-2 is eluted in fraction 1.

Both pardaxin P-1 and pardaxin P-2 caused death in killifish, *Oryzias latipes*, in 30 minutes at a concentration of 25 μg/ml, the threshold concentration being 10 μg/ml. Pardaxin P-3 has not been isolated in sufficient quantity to allow proper bioassay, but is presumed, on the basis of its nearly identical sequence to pardaxin P-1, to be active.

Amino acid sequencing of the three peptides led to the determination of their primary structures (Fig. 2). Despite the similarity in the carboxyl terminal sequence of pardaxins P-1 and P-2, carboxypeptidase A digestion performed on them to confirm their carboxyl terminal sequences released the carboxyl terminal amino acids from pardaxin P-2 only one tenth as fast as from pardaxin P-1. To eliminate the possibility that the carboxyl-terminus of pardaxin P-2 was blocked or that it had been erroneously sequenced, it was digested with thermolysin and the carboxyl terminal octapeptide fragment was isolated by HPLC. The sequencing result of the fragment agreed with that of the parent peptide, and its secondary-ion mass spectrum with a molecular ion peak at a mass-to-charge ratio (*m/z*) of 764, $(M + H)^+$, accorded with a free carboxyl terminal glutamic acid. The suppressed rate of the carboxyl-terminal hydrolysis of pardaxin P-2 can be attributed to a secondary conformation that decreases the susceptibility of the peptide to the enzymatic attack (*11*). Evaluation of possible secondary structures according to the method of Chou and Fasman (*12*) shows that pardaxin P-2 probably has a reverse turn near its carboxyl terminus; the probability of such a structure is much less for pardaxin P-1.

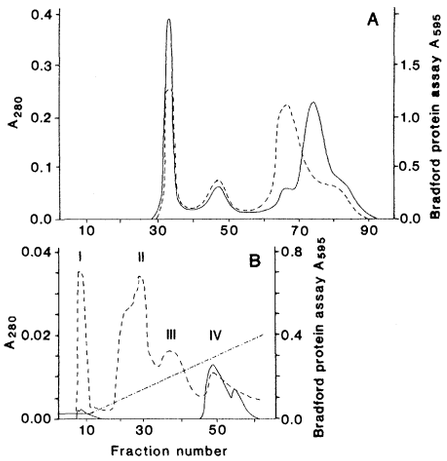


Fig. 1. Chromatographic separation of pardaxins. (A) Crude precipitate was loaded onto a column of Sephadex G-150 (medium, 2.5 by 95 cm) inflated with 0.1*M* ammonium bicarbonate and eluted at 4°C at a rate of 20 ml/hour with a peristaltic pump at the outlet. (B) The active gel filtration fraction was applied to a column of DEAE Toyopearl (1.5 by 30 cm) equilibrated with 10 m*M* ammonium acetate buffer, *p*H 6.7, and eluted at 25 ml/hour with a linear gradient (–·–·–) to the 400 m*M* buffer over 12 hours. The eluents from both columns were monitored by absorption at 280 nm (——) and by the colorimetric protein assay with the method of Bradford (------) (*20*). Collective fractions were assayed for ichthyotoxicity.

In the course of HPLC purification of pardaxins, two somewhat less well retained peptides, which had accompanied pardaxins P-1 and P-2 in the preceding separation, were isolated as minor components. Both differed from the corresponding pardaxins only by the absence of the four amino terminal residues (*13*). Neither of these peptides appears to be ichthyotoxic; the peptide corresponding to pardaxin P-1 showed no effect at a concentration of 78 μg/ml, whereas pardaxin P-1 or P-2 caused death in 15 minutes at this concentration. Apparently the four amino terminal residues play a crucial role in the activity.

The sequences of the pardaxins are similar to that of melittin, the toxic peptide from the bee *Apis mellifera* (*14*, *15*) (Fig. 2). Both have hydrophilic carboxyl terminal regions, hydrophobic amino terminal regions, and central sections capable of forming amphiphilic α helices (*16*). Our preliminary studies have also demonstrated the qualitative similarities of the pardaxins to melittin: they lyse erythrocytes, display strong surfactant activity (*17*), aggregate into tetrameric forms at high buffer concentrations as determined by gel filtration, and require their amino terminal regions for activity (*18*). There are differences: the pardaxins are seven residues longer than melittin, have completely different primary structures, and carry acidic carboxyl terminal regions (the carboxyl terminus of melittin is basic). Nevertheless, their activities may arise by similar mechanisms of action (*19*).

The ichthyotoxic fraction from gel filtration was tested for the repellent activity on

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                    5                   10                  15                  20
P-1   Gly-Phe-Phe-Ala-Leu-Ile-Pro-Lys-Ile-Ile-Ser-Ser-Pro-Leu-Phe-Lys-Thr-Leu-Leu-Ser-
P-2   – – – – – – – – – – – – – Ile – – – – – –
P-3   – – – – Phe – – – – – – – – Leu – – – – – –

Melittin                        Gly-Ile-Gly-Ala-Val-Leu-Lys-Val-Leu-Thr-Thr-Gly- Leu-Pro-

                        25                  30
P-1   Ala-Val-Gly-Ser-Ala-Leu-Ser-Ser-Ser-Gly-Glu-Gln-Glu
P-2   – – – – – – – – – – Gly – –
P-3   – – – – – – – – – (–)(Glu) – –

Melittin  Ala-Leu-Ile-Ser-Trp-Ile-Lys-Arg-Lys-Arg-Gln-Gln-NH2
                                    Hydrophilic domain
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Fig. 2. Amino acid sequences of pardaxins P-1 to P-3, produced by a protein sequencer (Applied Biosystems 470A), and that reported for melittin for comparison (*14*, *15*). Pardaxin P-3 residues 30 and 31 were not successfully determined, but are assumed as shown in parentheses from the amino acid composition and by comparison with pardaxins P-1 and P-2.

two white-tip reef sharks, *Triaenodon obesus*. When 100 mg of this material dissolved in 5 ml of sea water was injected into the mouth of the docile shark through an extension tube attached to a syringe, the shark displayed a clear escape behavior; control experiments elicited no response. This observation suggests that the pardaxins, as well as the previously described pavoninins, are shark-repelling factors of the defense secretion.


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8. Typically with an HPLC column (10 by 250 mm) of Hypersil WP-300-5$C_4$, eluted with 30 minutes linear gradient from 36 to 72% aqueous acetonitrile with 0.1% trifluoroacetic acid at 3 ml/min, monitored by absorption at 220 nm.
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# Isolation of a New Human Retrovirus from West African Patients with AIDS


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**The etiological agent of AIDS, LAV/HTLV-III, is common in Central Africa but is not endemic in other areas of that continent. A novel human retrovirus, distinct from LAV/HTLV-III, has now been isolated from two AIDS patients from West Africa. Partial characterization of this virus revealed that it has biological and morphological properties very similar to LAV but that it differs in some of its antigenic components. Although the core antigens may share some common epitopes, the West African AIDS retrovirus and LAV differ substantially in their envelope glycoproteins. The envelope antigen of the West African virus can be recognized by serum from a macaque with simian AIDS infected by the simian retrovirus termed STLV-III$_{mac}$, suggesting that the West African AIDS virus may be more closely related to this simian virus than to LAV. Hybridization experiments with LAV subgenomic probes further established that this new retrovirus, here referred to as LAV-II, is distantly related to LAV and distinct from STLV-III$_{mac}$.**


THE ACQUIRED IMMUNE DEFICIENCY syndrome (AIDS) has been etiologically linked to infection by the human retrovirus termed lymphadenopathy-AIDS-virus (LAV), which is also known as human T-lymphotropic virus type III (HTLV-III) or AIDS-related virus (ARV) (*1–4*). This virus is closely related by many characteristics to the lentiviruses (*5, 6*). Retrospective clinical and seroepidemiological data indicate a recent emergence of this viral infection in the West, where the AIDS epidemic apparently began in 1981 (*7*), and it is frequently assumed that the virus was imported from other parts of the world.

Several studies have indicated that LAV infection is common and may be endemic in certain Central African countries (*8–10*). Although AIDS patients in these countries do not belong to the classical high-risk groups recognized in the West, transmission of the virus is likely to be the same, that is, by sexual or blood contact. Retrospective studies indicate that the AIDS virus was present in Central Africa in the 1970's, and there is serological evidence that LAV infection appeared earlier in Africa than in the West (*11, 12*). It has therefore been suggested that the AIDS epidemic originated in Central Africa.

Numerous LAV isolates have been obtained from African patients with AIDS or related syndromes, as well as from healthy LAV carriers. These isolates are not distinguishable from the American or European isolates by their biological and serological properties (*8, 10*), indicating that, despite their somewhat higher genetic variability compared to isolates in the West (*13, 14*), their antigenic regions are highly conserved. Some African patients with AIDS, however, show repeatedly negative tests for serum antibodies to LAV/HTLV-III. We have studied two such patients from West Africa, where the number of AIDS cases is low and where LAV infection seems not to be endemic (*15*). We report here the isolation, from these two patients, of a new human retrovirus (*16*) that is related to but distinct from both LAV/HTLV-III and the recently described simian retrovirus termed STLV-III$_{mac}$, the putative etiological agent of simian AIDS in captive macaques (*17–19*).

The first patient is a 29-year-old man from Guinea Bissau (adjoining the southern


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