Discussion. Dopamine is the natural precursor of noradrenaline and it is a potent beta-adrenoceptor agonist. At relatively high doses, it also has alpha-adrenoceptor agonist activity[9]. However, it is unique to dopamine that it is able to selectively reduce renal and mesenteric vascular resistances[4,9]. This 'dopaminergic' effect cannot be blocked by propranolol or phenoxybenzamine[10,11]. Since dopamine exerts both pressor and depressor effects[9], the final effect will depend on the interaction of various factors. One of these factors is the level of sodium in the diet[2], and the present report shows the effect of yet another factor, anesthesia. The results show that in sodium pentobarbital anesthetized rats, the pressor response to i.v. dopamine is abolished. It is known that anesthesia, particularly with barbiturates, affects the regulation of blood pressure[12] as well as the animal's response to exogenous agents[6,7]. In addition, the blood pressure response to dopamine is also species-dependent. Thus, in anesthetized dogs, a large dose of dopamine results in a pressor response,[13] while a purely depressor response is observed in anesthetized rabbits and guinea pigs[4,14].

In constrast to the present study, Grabowska[15] showed that dopamine caused an increase in the blood pressure in the anesthetized Wistar rat. This contradiction may be due to the experimental set up. Grabowska[15] used urethane-anesthetized and bilaterally vagotomized Wistar rats. Furthermore, some test doses of dopamine were given i.p. In the study reported here, the pentobarbital-anesthetized Sprague-Dawley rats were not vagotomized, and all solutions were given i.v. It is unlikely that the type of anesthetic used could have contributed to the difference in response, since it has been shown that inactin and pentobarbital are equipotent in depressing the cardiovascular response to acute hemorrhage in the rat[16].

Except at the highest dose infused, and in the conscious state, dopamine did not significantly affect the heart rate, a result that is similar to the observation in the dog[13,17]. In man, large doses of dopamine cause an increase in arterial blood pressure and induce a reflex bradycardia[4,9].

The pressor action of dopamine has been linked to a direct activation of the alpha-adrenoceptors[1,18]. Since this pressor effect of dopamine is abolished in anesthetized rats, it is reasonable to assume that anesthesia suppresses the activation of the alpha-adrenoceptors. This is supported by the observation in this study that equipressor responses to noradrenaline and phenylephrine are also suppressed in the anesthetized rat. Noradrenaline and phenylephrine are known to increase the blood pressure specifically by a generalized vasconstriction via the activation of alpha-adrenoceptors, with a consequent reflex bradycardia. It is interesting to note that even this reflex bradycardia is also suppressed by anesthetization. Since anesthetization suppressed the increase in blood pressure during noradrenaline and phenylephrine infusions, it is possible that the suppressed reflex bradycardia is due to a reduction of the stimulus (i.e. reduced increase in blood pressure).

The suppression of the pressor effect of dopamine by anesthesia is much greater than in phenylephrine-infused rats. This is possibly due to the reduced activation of the alpha-adrenoceptors since it is known that dopamine causes a reduction in blood pressure in animals pre-treated with alpha-adrenoceptor blocking agents[3,4]. In addition, the release of dilator prostaglandins[6] as well as renal, mensenteric and coeliac bed vasodilation[5] would contribute to the depressor effect of dopamine in the anesthetized rats. But whether these actions of anesthesia are centrally or peripherally mediated cannot be ascertained from the results of this study.

It is concluded that pentobarbital-anesthetized rats are unresponsive to the pressor effect of i.v. dopamine which suggests that anesthetization is a determinant of the blood pressure response to dopamine.

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Histochemical evidence for the presence of dipeptidylpeptidase IV in the Schwann cells of skin unmyelinated axons

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Summary. DPP IV activity was localized in the nerve fascicles of cat glabrous skin at light and electron microscope levels. The observation that the DPP IV end product was restricted to the axon-Schwann cell interface suggests that this enzyme may be involved in the interactions between unmyelinated axons and their Schwann cells.
Key words. Ultrahistochemical localization; dipeptidylpeptidase IV; Schwann cell.

Dipeptidylpeptidase IV (DPP IV) is a serine exopeptidase which removes X-Pro sequences from N-termini of peptides or artificial substrates[1,2]. The histochemical localization of DPP IV has been studied in various tissues[3,4], including peripheral nerve structures[5,6]. The biological role of DPP IV in peripheral nerve structures is obscure. However, the ability of DPP IV to degrade effectively substance P (SP) has been demonstrated biochemically[7,8]. The undecapeptide SP has a widespread distribution in the central and peripheral nervous system[9], including a subpopulation of primary sensory

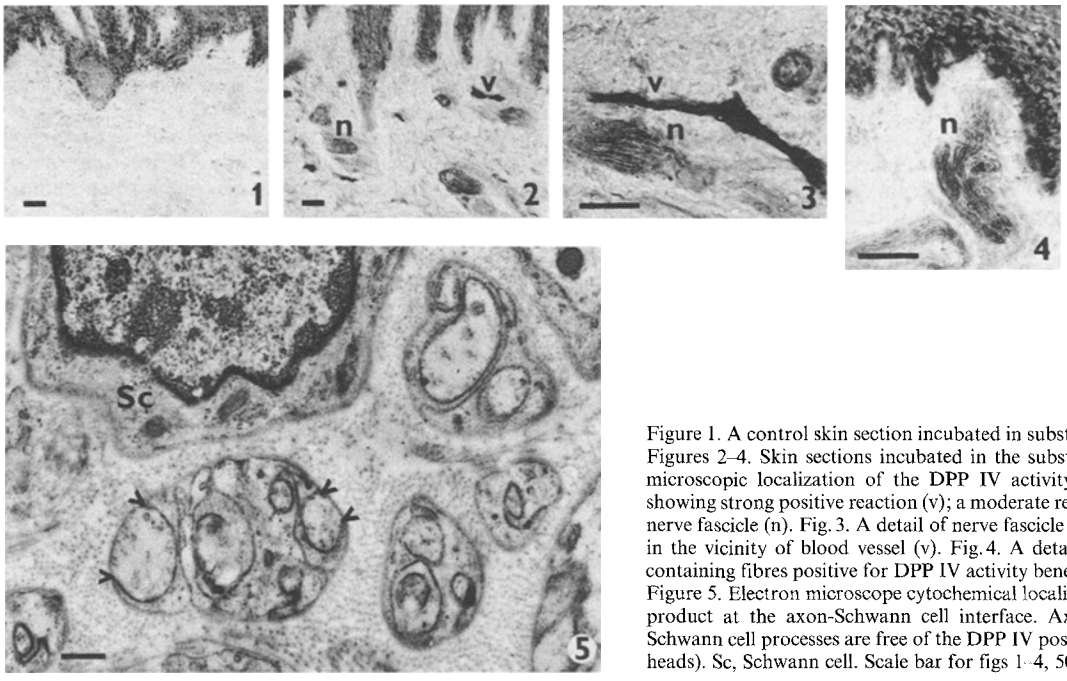

Figure 1. A control skin section incubated in substrate-free medium. Figures 2–4. Skin sections incubated in the substrate medium for light microscopic localization of the DPP IV activity. Fig. 2. Blood vessel showing strong positive reaction (v); a moderate reaction was observed in nerve fascicle (n). Fig. 3. A detail of nerve fascicle (n) with positive fibers in the vicinity of blood vessel (v). Fig. 4. A detail of nerve fascicle (n) containing fibres positive for DPP IV activity beneath epithelium. Figure 5. Electron microscope cytochemical localization of DPP IV end-product at the axon-Schwann cell interface. Axonal patches without Schwann cell processes are free of the DPP IV positivity (between arrowheads). Sc, Schwann cell. Scale bar for figs 1–4, 50 μm; for fig. 5, 50 nm.

neurons[10]. It is considered as a candidate for a neurotransmitter role in these neurons both for the central transmission of afferent information[11] and as a peripheral mediator of neurogenic inflammation[12] or as a trophic substance[13]. Immunohistochemical studies have shown abundant SP-containing nerve fibers in the mammalian skin[10, 14, 15]. Little is known, however, about the presence of DPP IV activity in nerves entering the skin. The present paper describes the light and electron microscope histochemical localization of DPP IV activity in the cat glabrous skin with special reference to the nerve fibers.

Materials and methods. The histochemical localization of DPP IV activity was performed in cat hind paw-pad glabrous skin. Sections of fresh and paraformaldehyde-fixed skin, 15 μm thick, cut perpendicularly to the surface, were incubated as described previously for light and electron microscopic localization of the DPP IV activity[5, 6]. L-glycyl-prolyl-4-methoxy-2-naphthylamide (Bachem, Bubendorf, Switzerland) was used as substrate and either Fast Blue B or hexazotized new fuchsine (Merck, FRG) were added to the medium as coupling agents for light and electron microscopy, respectively. Control sections were incubated in substrate-free medium.

Results and discussion. As described previously, DPP IV activity was present in blood vessels[3, 4], in perineurial sheaths of somatosensory nerves[4, 5], and in the capsule of simple lamellar corpuscles located in dermal papillae[5]. In addition, the present study revealed that the red-brownish azo-dye produced staining of weaker intensity in the nerve fibers found in the vicinity of blood vessels and sweat glands as well as beneath the epithelium (figs 2–4). In the electron microscope, the fine electron-dense reaction product formed dark lines which sharply marked the axon Schwann cell interface of unmyelinated fiber bundles. However, the reaction product was absent in the patches where the Schwann cell processes were deficient and the axon directly abutted on to the basal lamina (fig. 5). These unreactive patches suggest that DPP IV is confined to the plasma membrane adjacent to the Schwann cell rather than to the axolemma. On the other hand, the plasma membrane of the free Schwann cell surface was also devoid of the DPP IV reactivity.

The location of SP-like immunoreactive unmyelinated nerve fibers in the mammalian skin described previously[10, 14, 15], and the DPP IV reactivity revealed in the present study in the same loci suggest the association of the SP-positivity of nerve fibers with the DPP IV activity of their Schwann cells. The restriction of DPP IV activity to direct axon-Schwann cell junctions implies that this enzyme activity may be involved in the interactions between unmyelinated axons and their Schwann cells. It is well known that DPP IV has the ability to cleave successively the SP_{1-2}, SP_{3-4} and SP_{5-11} fragments from the N-terminus of SP, as revealed biochemically[7]. There is evidence that synthetic analogs of the SP fragments influence the morphology of peripheral nerve system cultures. For example, the dipeptide Lys-Pro (SP_{3-4}) has a mitogenic effect on the glial cells and stimulates a prolongation of the neurites in the chick ganglion trigeminale cultured in vitro[16, 17]. The effect of SP on target cells through effective fragments has been confirmed by pharmacological studies[18–20]. However, further studies will be required to investigate this concept in peripheral nerve structures.

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