Innervation of the cavernous body of the human efferent tear ducts and function in tear outflow mechanism

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ABSTRACT

The lacrimal sac and nasolacrimal duct are surrounded by a wide cavernous system of veins and arteries comparable to a cavernous body. The present study aimed to demonstrate the ultrastructure of the nervous tissue and the localisation of neuropeptides involved in the innervation of the cavernous body, a topic not previously investigated. Different S-100 protein antisera, neuronal markers (neuron-specific enolase, anti-200 kDa neurofilament), neuropeptides (substance P, neuropeptide Y, calcitonin gene-related peptide, vasoactive intestinal polypeptide) and the neuronal enzyme tyrosine hydroxylase were used to demonstrate the distribution pattern of the nervous tissue. The ultrastructure of the innervating nerve fibres was also examined by means of standard transmission electron microscopy.

The cavernous body contained specialised arteries and veins known as barrier arteries, capacitance veins, and throttle veins. Perivascularly, the tissue was rich in myelinated and unmyelinated nerve fibres in a plexus-like network. Small seromucous glands found in the region of the fundus of the lacrimal sac were contacted by nerve fibres forming a plexus around their alveoli. Many nerve fibres were positive for S-100 protein (S 100), neuron-specific enolase (NSE), anti-200 kDa neurofilament (RT 97), calcitonin gene-related peptide (CGRP), substance P (SP), tyrosine hydroxylase (TH), and neuropeptide Y (NPY). Vasoactive intestinal polypeptide (VIP) immunoreactivity was only demonstrated adjacent to the seromucous glands.

Both the density of nerve fibres as well as the presence of various neuropeptides emphasises the neural control of the cavernous body of the human efferent tear ducts. By means of this innervation, the specialised blood vessels permit regulation of blood flow by opening and closing the lumen of the lacrimal passage as effected by the engorgement and subsidence of the cavernous body, at the same time regulating tear outflow. Related functions such as a role in the occurrence of epiphora related to emotional responses are relevant. Moreover, malfunction in the innervation of the cavernous body may lead to disturbances in the tear outflow cycle, ocular congestion or total occlusion of the lacrimal passages.

Key words: Lacrimal sac; nasolacrimal duct; tears; epiphora; neuropeptides.

INTRODUCTION

The lacrimal sac and nasolacrimal duct as parts of the efferent tear duct system are surrounded by a network of large capacitance vessels connected caudally with the cavernous body of the nasal inferior turbinate (Duke-Elder, 1961; Thale et al. 1997; Paulsen et al. 1998). Although more than two-thirds of the bony canal between the orbit and inferior turbinate are filled by this wide luminal vascular plexus (Thale et al. 1998; Fig. 1*a*), most textbooks of anatomy do not mention its existence. Histologically, the whole vascular plexus is embedded in a helical system of collagen bundles as well as elastic and reticular fibres (Thale et al. 1997, 1998). In addition to these structures, subepithelial seromucous glands are found in the region of the nasolacrimal duct and the fundus of the lacrimal sac (Joers, 1899; Serra, 1927; Rivas et al. 1991; Paulsen et al. 1998; Fig. 1*b*). Functionally, the vascular plexus can be compared to a cavernous

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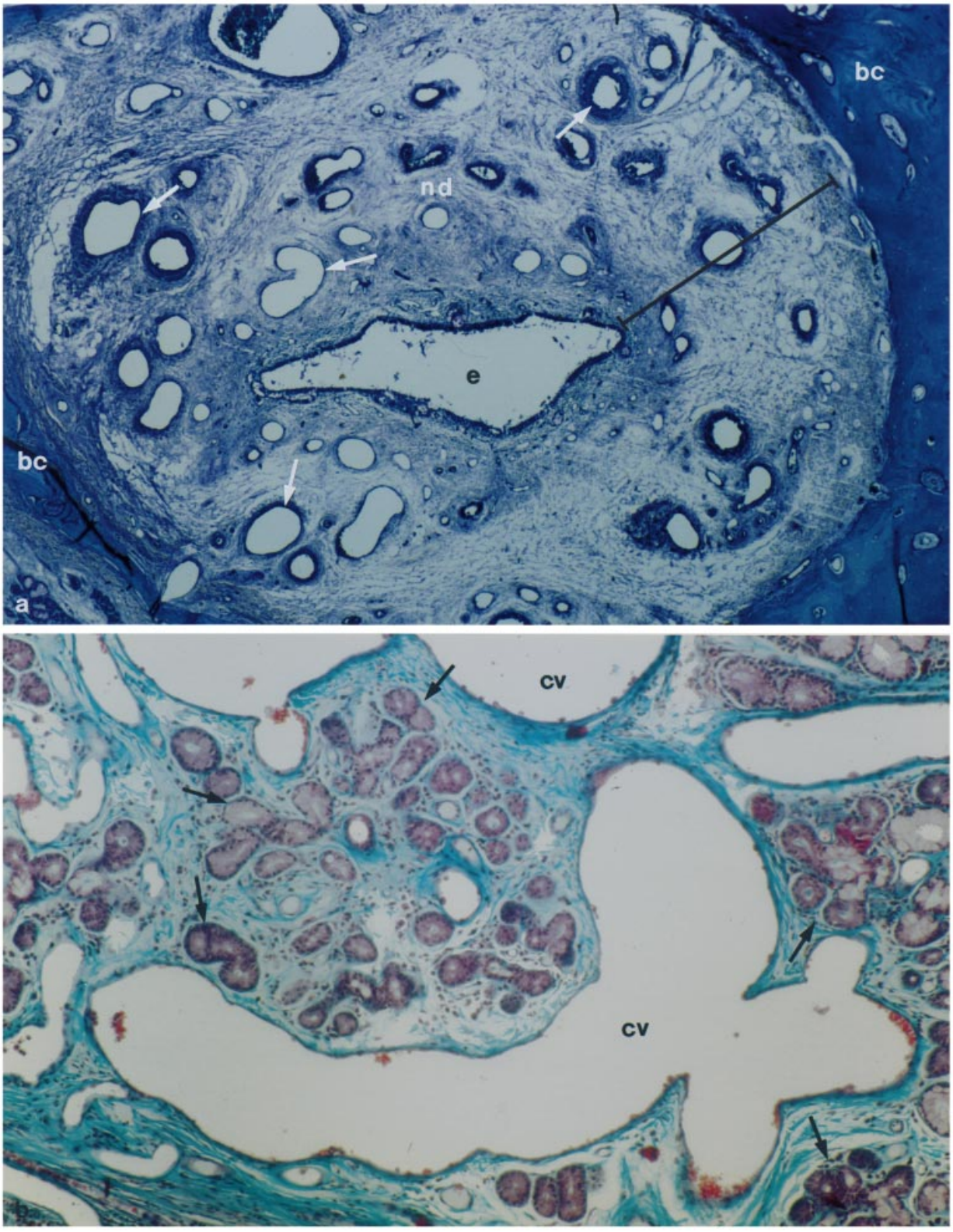

Fig. 1. (*a*) Cross-section of a nasolacrimal duct (nd) (female, 67 y). More than two-thirds of the surrounding bony canal (bc) are filled by a cavernous body (black bar) rich in blood vessels with wide lumina (arrows) (Thale et al. 1998). e, Lumen of the nasolacrimal duct. Toluidine blue, ×28. (*b*) Horizontal section through the cavernous body of the lacrimal sac (male, 83 y). The lamina propria contains seromucous glands (arrows) (Joers, 1899; Serra, 1927; Rivas et al. 1991; Paulsen et al. 1998). cv, Lumen of capacitance veins of the cavernous body, Goldner, ×113.

body containing specialised arteries, venous lacunae and veins (Paulsen et al. 1999). It has been shown that the arteries possess 2 muscle layers. They are called 'barrier arteries' because reduction or interruption of blood supply to downstream blood vessels is characteristic of their function. These arteries split just beneath the epithelium into superficial arcading branches. A dense network of capillaries arises from these branches to supply blood to the seromucous glands of the lamina propria and supply nutrients to the epithelium. The blood from the capillary network is collected by short postcapillary venules that drain into widely convoluted venous lacunae (Fig. 1*b*). These blood vessels are called 'capacitance veins' based on their assumed ability to store large amounts of blood. Segments of the capacitance veins are sometimes narrowed. The tunica media of these segments contains a layer of helically arranged smooth muscle cells that effects closure of the segment. In agreement with the nomenclature of the nose these structures are termed 'throttle veins'. They can reduce or interrupt the venous blood outflow and allow large amounts of blood to accumulate inside the capacitance veins. Finally, blood is collected by large veins that drain the blood out of the lacrimal passage. In addition, arteriovenous anastomoses have been demonstrated to connect branches of the arteries with capacitance veins (Paulsen et al. 2000).

It has been suggested that these specialised blood vessels, while regulating blood flow, also permit opening and closure of the lumen of the lacrimal passage effected by the engorgement and subsidence of the cavernous body, thus at the same time regulating tear outflow. An important role in the absorption and drainage of lacrimal fluid has also been hypothesised (Paulsen et al. 1998, 2000; Thale et al. 1998).

The present study examined the ultrastructure and distribution of nerve fibres immunoreactive with antisera against neurofilaments, neuropeptides and neuronal enzymes in the cavernous body of the human efferent tear ducts, along with its surrounding structures including the seromucous glands, to evaluate the innervation of the tissue and determine its role in the swelling mechanism.

MATERIAL AND METHODS

Lacrimal systems of adults were obtained from 20 body donors (12 male, 8 female, aged 39–85 y) prepared in the Department of Anatomy, Christian Albrecht University of Kiel, Germany, within 48 h of death, or during endonasal surgery. Material from surgical procedures was obtained with the permission of the medical ethics commission. The specimens were taken from individuals free of recent trauma, eye or nasal infections and diseases potentially involving or affecting lacrimal function.

Light microscopy

For light microscopy, lacrimal systems (4 male, 2 female, aged 63–81 y) were fixed in 4% formalin, decalcified in 20% EDTA as required, dehydrated in graded concentrations of ethanol and embedded in paraffin. Sections (7 μm) in 3 planes were stained with toluidine blue (pH 8.5), resorcin-fuchsin-thiacine picric acid, and according to Goldner's method (Romeis, 1989). The slides were examined with a Zeiss Axiophot microscope.

Immunohistochemistry

For immunohistochemical analysis, 9 samples (6 male, 3 female, aged 39–85 y) were fixed in Zamboni's solution (Zamboni & de Martino, 1967) overnight at 4 °C, then rinsed several times in 0.1 M phosphate-buffered saline (PBS) and saturated overnight at 4 °C with 10% and 30% sucrose in 0.1 M phosphate buffer (PB). This was followed by freezing and sectioning (7 μm) in a cryostat. After preincubation with 10% standard goat serum in PBS, the sections were incubated with various primary antisera to human neuropeptides and neuronal markers in a humidity chamber at room temperature (Table 1). The following antibodies were used: mouse anti-RT 97 monoclonal antibody (Boehringer, Mannheim, Germany, diluted 1:200); mouse anti-S-100 monoclonal antibody (Boehringer, Mannheim, Germany, concentrated); rabbit anti-VIP polyclonal antibody (Biotrend, Köln, Germany, diluted 1:800); rabbit anti-CGRP polyclonal antibody (Boehringer, Mannheim, Germany, diluted 1:100); rabbit anti-NPY polyclonal antibody (Cambridge Research Chemicals, Cambridge, UK, 1:2500); rabbit anti-TH monoclonal antibody (Chemicon International, Temecula, CA, USA, diluted 1:800); mouse anti-NSE polyclonal antibody IgG (DAKO, Glostrup, Denmark, diluted 1:100); rabbit anti-SP polyclonal antibody (Biotrend, Köln, Germany, diluted 1: 2000). Following careful rinsing in PBS, the secondary antibody was incubated (30 min with biotin-labelled species-specific secondary antibodies (DAKO, Glostrup, Denmark, diluted 1:200) in inactivated human serum, diluted 1:20 with PBS). Sections were then incubated for 30 min with ABC-complex (DAKO, Glostrup, Denmark, diluted 1:100). Fol-

Table 1. *Details of antisera*

Antigen	Code	Donor species	Dilution	Source
RT 97	1178709	Mouse	1:200	Boehringer, Mannheim, Germany
S-100	1471767	Mouse	Conc.	Boehringer, Mannheim, Germany
VIP	VA 1285	Rabbit	1:800	Biotrend, Köln, Germany
CGRP	1295241	Rabbit	1:100	Boehringer, Mannheim, Germany
NPY	CA-09295	Rabbit	1:2500	Cambridge Research Chemicals, Cambridge, UK
TH	AB 152	Rabbit	1:800	Chemicon International, Temecula, CA, USA
NSE	M 873	Mouse	1:100	DAKO, Glostrup, Denmark
SP	SA 1270	Rabbit	1:2000	Biotrend, Köln, Germany

RT 97, anti-200 kDa neurofilament; S-100, S-100 protein; VIP, vasoactive intestinal polypeptide; CGRP, calcitonin gene-related peptide; NPY, neuropeptide Y; TH, tyrosine hydroxylase; NSE, neuron-specific enolase; SP, substance P.

lowing the peroxidase-substrate solution reaction (Sigma, Deisenhofen, Germany) sections were rinsed with cold tap water, counterstained with hemalaun and, finally, mounted with DePeX. For immunohistochemistry of S-100, a fluorescein isothiocyanate (FITC)-conjugated goat antimouse IgG was used for 45 min as secondary antibody: 2 negative control sections were used in each case. One was incubated with the second antibody only, the other with the primary antibody only. Sections of human peripheral nerve and muscle were used as positive controls. All slides were examined under a Zeiss Axiophot microscope also equipped for epifluorescence.

Transmission electron microscopy

For transmission electron microscopy 5 additional samples (2 male, 3 female, aged 61–68 y), obtained during endonasal surgery, were fixed in 3.5% glutaraldehyde (in 0.1 M Sørensen phosphate buffer solution at pH 7.4) at 4 °C for 1 wk. After dehydration in graded concentrations of ethanol they were embedded in Araldite. Semithin sections were prepared for light microscopy, ultrathin sections for electron microscopy. Ultrathin sections were contrasted with uranyl acetate and lead citrate. Examination was carried out with a Zeiss TEM 902 electron microscope.

RESULTS

General anatomy

The lacrimal sac and nasolacrimal duct were surrounded by a vascular plexus (Fig. 1*a*) which was connected to the cavernous body of the inferior turbinate. The duct was embedded in a bony canal formed by the maxilla and the lacrimal bone. More than two-thirds of the bony canal between the orbit and inferior turbinate were filled by the vascular plexus. Histologically, a subepithelial layer containing a wide capillary network was distinguishable from a surrounding layer of connective tissue including blood vessels of differing diameter. The connective tissue was made up of collagen bundles as well as elastic and reticular fibres arranged in a helical pattern. In addition to the vascular system, small seromucous glands were detected lying inside the connective tissue (Fig. 1*b*). The secretory tubular epithelia of the seromucous glands formed numerous lobules separated by connective tissue septa. In most cases they were situated in the region of the fundus of the lacrimal sac. Their excretory ducts penetrated the epithelium into the lumen of the sac.

Immunohistochemistry (*Table 2*)

200 kDa neurofilament. RT 97-immunoreactive myelinated nerve fibre bundles were found loosely distributed throughout the bulk of connective tissue of the subepithelial layer and between the blood vessels of the cavernous body (Fig. 2*a*).

S-100 protein (*the antiserum reacting with both S-100α and S-100β subunits*). S-100-immunoreactivity occurred in about the same density as the RT 97-immunoreactive nerve fibres (Fig. 2*c*). Apart from these coarse nerve fibre bundles, immunofluorescence of S-100 was visible in the area of the mixed glands, the subepithelial layer and in the mucosa (Fig. 2*d*). S-100-immunoreactive nerve fibres were also seen to enter the walls of interlobular blood vessels. In addition, within the parenchyma of mixed glands, scattered groups of epithelial cells were S-100-immunoreactive, while the majority of the cells remained unstained.

Neuron-specific enolase (*NSE*). NSE-immunoreactive structures were identified in the subepithelial region, around the blood vessels of the cavernous body (Fig. 3*a*, *b*) and also abundantly in the area of the seromucous glands. Moreover, some fine nerve

Table 2. *Antigen profile*

Cellular elements in association with neuronal structures	Immunoreactive polypeptides/proteins (antigens)							
	RT 97	S-100	NSE	VIP	CGRP	NPY	TH	SP
Connective tissue of the cavernous body	+++	+++	+++	—	—	+	+++	—
Serous glands in the cavernous body	—	+	++	++	+	+	+++	++
Blood vessels of the cavernous body	—	—	++	—	+	+	+++	++

RT 97, anti-200 kDa neurofilament; S-100, S-100 protein; VIP, vasoactive intestinal polypeptide; CGRP, calcitonin gene-related peptide; NPY, neuropeptide Y; TH, tyrosine hydroxylase; NSE, neuron-specific enolase; SP, substance P.

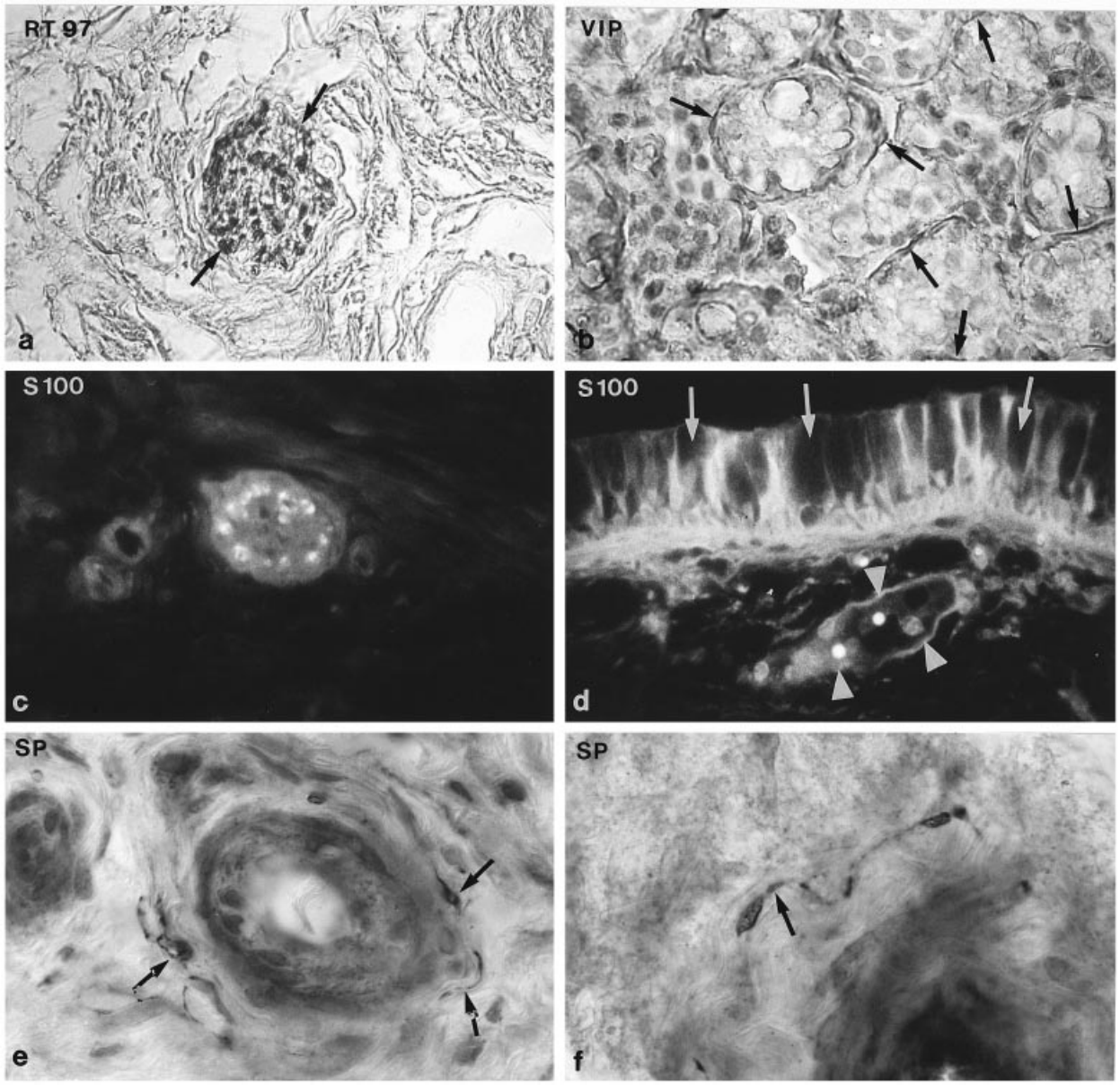

Fig. 2. (*a*) Visualisation of a myelinated nerve (arrows) showing immunoreaction with RT 97 in the connective tissue of the cavernous body, ×242. (*b*) VIP-immunoreactive nerve fibres (arrows) in association with secretory tubules of seromucous glands, ×380. (*c*) Distribution of S-100 protein in a myelinated nerve of the cavernous body, ×380. (*d*) S-100 immunoreactivity inside epithelial cells of the nasolacrimal duct. Reactivity is restricted to epithelial cells, whereas goblet cells inside the epithelium (arrows) are not stained. Arrowheads, subepithelial blood vessel, ×380. (*e*) SP-immunoreactive nerve fibres (arrows) in association with a blood vessel inside the connective tissue of a lobule of a seromucous gland, ×242. (*f*) SP-immunoreactive nerve fibres (arrow) in association with a blood vessel of the cavernous body, ×380.

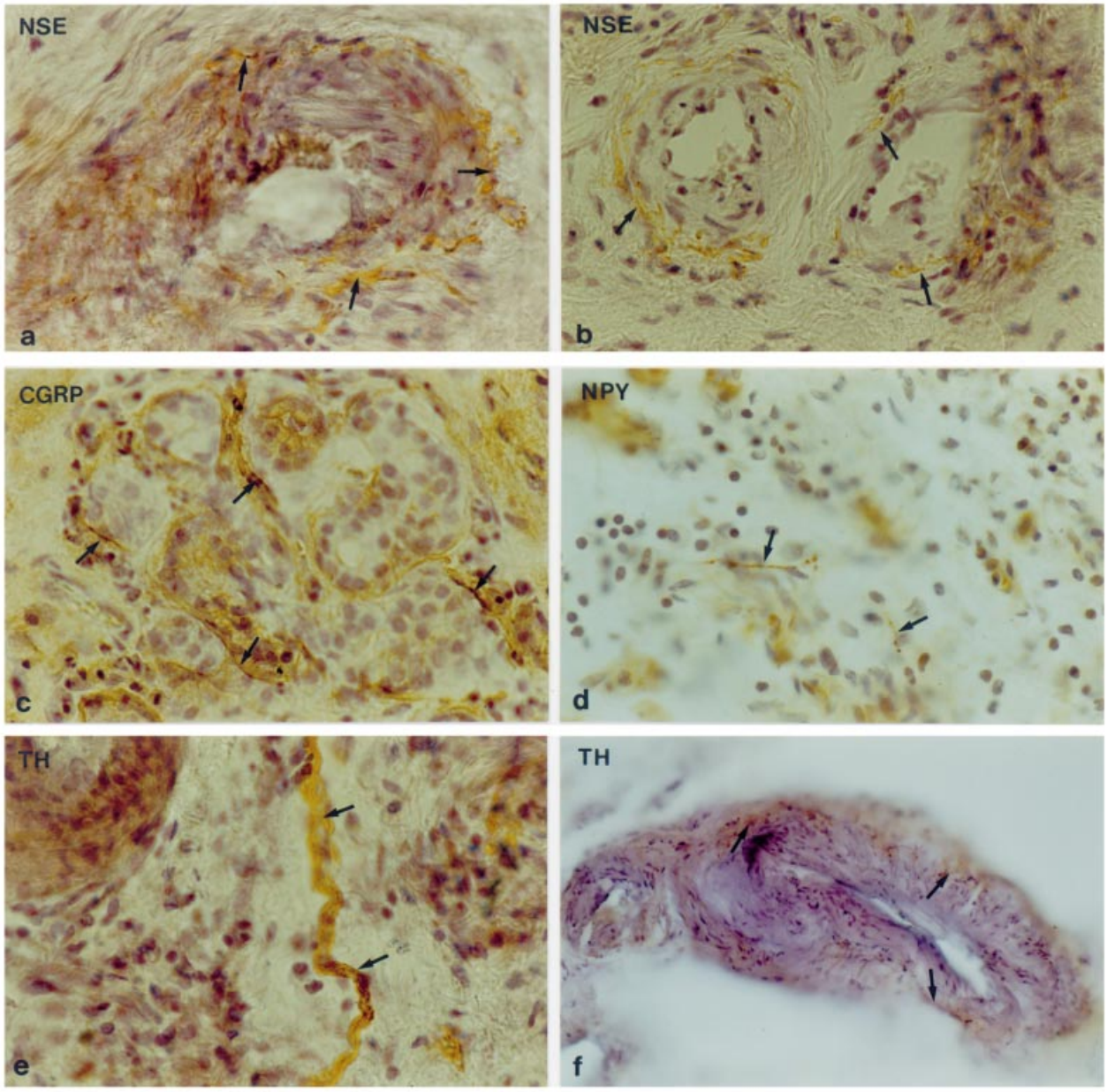

Fig. 3. (*a*) NSE-immunoreactive nerve fibres (arrows) in the wall of a barrier artery, ×376. (*b*) NSE-immunoreactive nerve fibres (arrows) in the walls of 2 small throttle veins, ×376. (*c*) CGRP-immunoreactive nerve fibres (arrows) in association with acinus cells of seromucous glands. ×376. (*d*) NPY-immunoreactive nerve fibres (arrows) in the connective tissue of the cavernous body, ×376. (*e*) Visualisation of a TH-immunoreactive nerve fibre (arrows) in the connective tissue of the cavernous body, ×376. (*f*) Distribution of TH-immunoreactive nerve fibres (arrows) in the wall of a barrier artery, ×120.

fibres formed a network around secretory cells of the seromucous glands.

Vasoactive intestinal polypeptide (*VIP*). VIP-immunoreactive structures were only stained within the body of seromucous glands of the efferent tear ducts. Between the secretory tubules, scattered portions of fine and also thicker nerve fibres were stained (Fig. 2*b*). Fibres around blood vessels in the intralobular and interlobular connective tissue septa also appeared to show a positive reaction to the antibody.

Calcitonin gene-related peptide (*CGRP*). Few CGRP-immunoreactive nerve fibres were identified in the intertubular stroma. The stained fibres were associated with secretory tubules, intralobular ducts, and blood vessels. Around the acinar cells of the glands thicker nerve fibre bundles were stained (Fig. 3*c*).

Neuropeptide Y (*NPY*). NPY-immunoreactivity was associated with blood vessels of the cavernous body (Fig. 3*d*), the subepithelial capillary bed and the

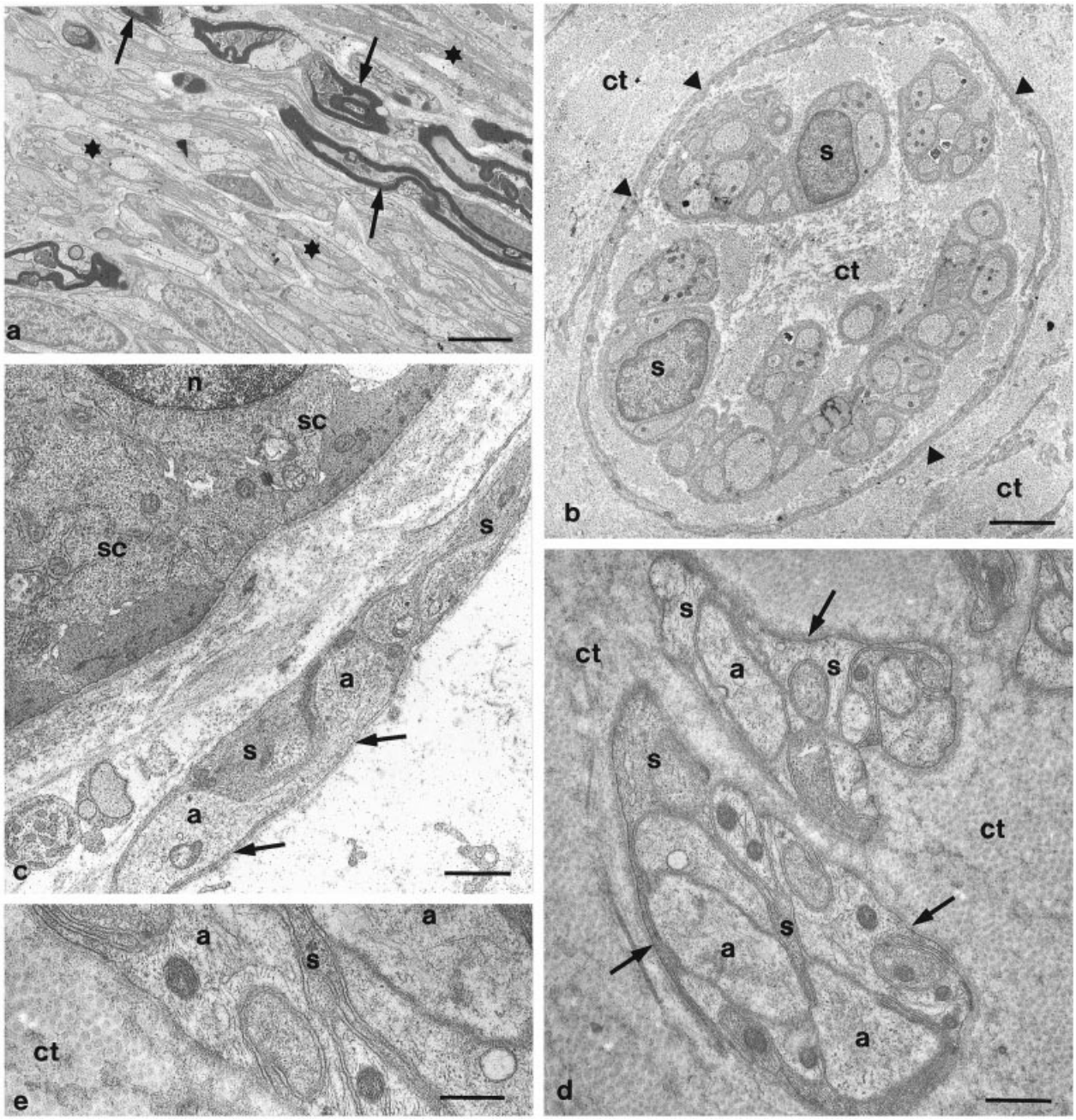

Fig. 4. (*a*) Longitudinal section through a thick nerve bundle inside the connective tissue of the cavernous body. In addition to myelinated nerve fibres (arrows) many unmyelinated nerve fibres (stars) are visible. Bar, 9 μm. (*b*) Cross section of a small unmyelinated nerve surrounded by perineurium in the connective tissue of the cavernous body. The perineurium (arrowheads) completely surrounds the endoneurium which contains numerous unmyelinated axons and associated Schwann cells (s). The latter are separated from the endoneurial connective tissue (ct) by basement membranes. Bar, 2.5 μm. (*c*) Part of an unmyelinated nerve fibre (arrows) in close association with serous acinar cells (sc). n, Nucleus of an acinar cell; a, axon; s, cytoplasm of a Schwann cell. Bar, 1.6 μm. (*d*) Unmyelinated nerve fibres (arrows) in the connective tissue (ct) of a capacitance vein. a, Axons; s, Schwann cells. Bar 7.5 μm. (*e*) Higher magnification of *d*. ct, Connective tissue; s, Schwann cell cytoplasm; a, axons. Bar, 5 μm.

blood vessels of the seromucous glands. The main localisation of NPY-immunoreactive nerve fibres was around and in the walls of arterioles, where fine positive fibres were identified intermingled with smooth muscle cells of the tunica media.

Tyrosine hydroxylase (*TH*). TH-immunoreactive nerve fibres were identified loosely scattered throughout the connective tissue of the efferent lacrimal tear ducts (Fig. 3*e*). They were also detected in abundance between the lobules of seromucous glands and in association with blood vessels of the cavernous body (Fig. 3*f*).

Substance P (*SP*). SP-immunoreactive nerve fibres were seen in a distinct association with glandular

epithelium of seromucous glands as well as with blood vessels inside the lobules of the seromucous glands (Fig. 2*e*) and the vascular system of the cavernous body (Fig. 2*f*). Thicker nerve fibre bundles were stained around the seromucous glands and blood vessels.

Ultrastructure of the nervous tissue

Nerve bundles composed of myelinated and unmyelinated fibres (Fig. 4*a–e*) were visible in the connective tissue of the subepithelial layer and the cavernous body. Profiles of nervous tissue were also numerous in seromucous glands. The nerve fibres were surrounded by a perineurial sheath (Fig. 4*b*). This enclosed either single Remak fibres with multiple axons or a combination of myelinated and unmyelinated fibres. The endoneurial spaces contained collagen fibrils (Fig. 4*b*). Numerous profiles of nerve fibres showed variable numbers of axons free of the surrounding Schwann cell cytoplasm within a defined area. Such nerve fibres were located immediately adjacent to the basal cell layers of the alveoli in narrow connective tissue septa between alveolar buds (Fig. 4*c*) and in the neighbourhood of capillaries. The axons formed so-called 'synapses a distance' with basally located glandular cells and with blood vessels. The axons contained small, clear vesicles and larger, dense core vesicles.

The blood vessels of the cavernous body of the efferent lacrimal tear ducts were also supplied by a dense innervation. Unmyelinated, longitudinally cut nerve bundles and smaller axon conglomerates were detected in the arterial adventitia (Fig. 4*d*, *e*). Generally, in contrast to arteries, veins showed few nerve structures which, again in contrast to the arteries, were also located between the smooth muscle cells. However, some of the veins displayed a more pronounced innervation pattern, particularly in their muscular component. In contrast to smaller arterioles, no axons were demonstrated adjacent to capillary walls.

DISCUSSION

In this study, we employed both immunohistochemistry and electron microscopy to examine the innervation of the vascular system as well as integrated seromucous glands surrounding the lacrimal sac and nasolacrimal duct. Specifically, we studied the distribution of different nerve fibres, neurofilaments, neuropeptides and neuronal enzymes in this system. We found a dense innervation of the specialised blood vessels of the cavernous body as well as of the seromucous glands.

In the past, no attention had been paid to the nerve supply of the cavernous body and the seromucous glands located subepithelially in the lacrimal sac. Only Tsuda (1952) described some nerve endings forming a plexus-like network in the subepithelial tissue of human efferent tear ducts.

By contrast, the distribution and function of nervous tissues and neuropeptides in the lacrimal gland (Seifert et al. 1996; Tsukahara & Tanishima, 1974), in the accessory lacrimal glands (Seifert et al. 1993, 1997; Seifert & Spitznas, 1994), in the meibomian glands (Seifert & Spitznas, 1996), and in the nasal vascular bed (Cauna, 1970*a*, *b*; Cauna & Cauna, 1975; Knipping et al. 1995; Riederer et al. 1997) have been investigated extensively. In human efferent tear ducts, electron microscopy shows the structure and subtle distribution of nerve fibres around subepithelially located seromucous glands and blood vessels of the cavernous body as well as the delicate neuronal profiles in nervous stromal septa between the alveolar buds of seromucous glands and in the connective tissue between blood vessels of the cavernous body. The observation of few axons within the glandular stroma of seromucous glands and around blood vessels of the cavernous body, and especially the presence of nerve fibres with unmyelinated axons, indicate that the seromucous glands and the musculature of the blood vessels of the cavernous body are in fact among the target tissues of these nerve fibres.

The ultrastructural findings are completed by demonstration of the distributional pattern of different neuronal markers and neuropeptides. RT 97 has been shown to mark an epitope located on the human 200 kDa neurofilament which is found in myelinated axons not only of the central nervous system but also the peripheral nervous system (Wood & Anderton, 1981; Anderton et al. 1982; Kahn et al. 1987). S-100 protein, consisting of 2 subunits, S-100α and S-100β (Haimoto et al. 1987), is a calcium-binding protein first described by Moore (1975) in Schwann cells and other glial cells. In addition to its occurrence in the nervous system, S-100α is also expressed in the exocrine cells of salivary, mammary and sweat glands. Its function in nonnervous tissue is still unknown. It is believed to be involved in the metabolism of cardiac and slow-switch muscles, metabolism of free fatty acids and lipolysis in adipocytes (Haimoto et al. 1987). These assumptions are supported by the present finding of S-100 protein in the mucosa of the lacrimal sac and nasolacrimal

duct as well as earlier findings of lipid droplets localised in the apical part of the duct epithelial cells (Paulsen et al. 1998). Based on its wide distribution it is supposed that the peptide belongs to the diffuse endocrine cells, the paraneurons (Fujita, 1977), which may play a role in the interaction between the endocrine, nervous and immune system in the main lacrimal gland (Kelleher et al. 1991). Using an antibody recognising both subunits, S-100α and S-100β, the protein is identified in the same myelinated nerve fibre bundles marked by RT 97 as well as in finer unmyelinated nerve fibres in the mucosa, the subepithelial region, the blood vessels of the cavernous body, and in the area of the seromucous glands in the efferent tear ducts. Compared with the S-100 protein, immunohistochemistry of neuron-specific enolase permits representation of the whole innervation of the efferent tear ducts. NSE is shown as a molecular marker for nerves of the peripheral and central nervous system (Schmechel et al. 1978).

Neuropeptides are believed to act as transmitters or modulators of transmitters (Cripps & Patchen-Moor, 1989; Cripps & Bennett, 1992; Fahrenkrug, 1993). Lundberg and coworkers (Lundberg et al. 1980; Johansson & Lundberg, 1981) demonstrated VIP to be colocalised with acetylcholine in many species (Lundberg et al. 1980; Dartt, 1989; Matsumoto et al. 1992). VIP is reported to have a direct influence on the stimulation of protein secretion in glandular cells (Dartt et al. 1984). In the human efferent tear ducts, VIP only occurs between the secretory tubules and around blood vessels of the intra and interlobular connective tissue septa of the seromucous glands, a finding known from other loci in humans and other mammals (Buthler et al. 1984; Sibony et al. 1988; Matsumoto et al. 1992; Seifert et al. 1996; Riederer et al. 1997). SP and CGRP are mainly found in sensory fibres (Robinson et al. 1980; Tervo et al. 1982; Seifert et al. 1996). In some secretory tissues CGRP has been shown to have a vasodilatory effect with increasing vascular permeability (Lundberg et al. 1988). SP promotes secretomotor and vasodilatory effects (Rudich & Butcher, 1976) and protein secretion (Singh et al. 1994). Demonstration of both neuropeptides was found to play a role both in the glandular tissue and the blood vessels of the cavernous body in the efferent tear ducts. NPY is an important peptide in a multitude of physiological processes (Lehmann, 1990). Abundantly found in sympathetic neurons, it is used as indicator for this tissue (Lundberg et al. 1982). A similar function can be discussed for TH. TH catalyses the reaction from tyrosine via dopamine to noradrenaline (Lindvall et al. 1981) and thus reveals a sympathetic function. Both neuropeptides could be demonstrated in the efferent tear ducts in a similar manner. They are localised in close association with blood vessels of the cavernous body and seromucous glands.

The demonstrated neuronal structures and neuropeptides identified in the seromucous glands and the cavernous body are indicative of the complexity of regulation and modulation of the human efferent tear duct system by a variety of biological signals.

The function of the autonomic innervation in the seromucous glands of the efferent tear ducts as well as that of the sensory innervation may thus be in the control of the secretion output. The possibility cannot be ruled out that there is a close structural relationship between the sensory and autonomic fibres in secretory regulation.

The demonstrably dense innervation of the specialised blood vessels of the cavernous body may play an important role in tear outflow. In this context, drainage of tears certainly involves a number of different mechanisms. A decisive role is played by capillary attraction (Hill et al. 1974; Wilson & Merril, 1976), aided by contraction of the lacrimal part of the orbicularis muscle with blinking (Jones, 1961; Nagashima & Araki, 1963; Becker, 1992; Thale et al. 1998) and distension of the sac, as well as a passive 'wringing out' of the sac because of its medial attachment and helically arranged fibrillar structures (Thale et al. 1998). It has been shown that the cavernous body of the lacrimal passage is the morphological correlate of a further mechanism effecting tear outflow (Paulsen et al. 2000). When the net outflow of blood from the cavernous body is less than the inflow, the mucosa expands and functionally decreases tear outflow through the efferent tear duct system. This mechanism acts, for instance, to provide protection against foreign bodies that have entered the cornea or conjunctiva: not only is tear fluid production increased by the lacrimal gland, tear outflow is also interrupted by the swelling of the cavernous body to flush out the foreign body and protect the efferent tear ducts themselves. This protection system can only function on the basis of a complex neuronal reflex feedback mechanism starting with the dense innervation of the cornea and ending with the innervation of the cavernous body inside the lacrimal tear ducts. The pathophysiology of functional lacrimal drainage insufficiency, i.e. patients with epiphora despite patent lacrimal passages on syringing, can thus be explained as follows. Malfunction in the innervation of the different blood vessels of the vascular bed may lead to disturbances in

the tear outflow cycle, ocular congestion or total occlusion of the lacrimal passages. Such malfunctions may be caused by acute diseases such as dacryocystitis or, for example, disorders of the autonomic nervous system.

Besides increased tear secretion from the lacrimal gland and accessory lacrimal glands, epiphora related to emotions such as sorrow or happiness can be explained hypothetically by the same mechanism: cholinergic innervation of specialised blood vessels in the cavernous body can lead to obstruction of the lumen of these blood vessels with a reduction of blood outflow. Consequent swelling of the submucosal cavernous tissue can cause closure of the lacrimal passage. By contrast, adrenergic innervation of the blood vessels of the cavernous tissue may affect a mechanism—albeit controversial—involving relaxation of the submucosal swelling and improvement of lacrimal tear passage. Since the regulation of the cavernous body is subject to autonomic control, a pharmacological influence is a possibility here.

In conclusion, the innervation of the cavernous body of the lacrimal passage plays an important role in tear outflow. Further investigations will be necessary to evaluate its function in different pathological conditions of the efferent tear ducts, especially in xerophthalmia (dry eye syndrome).

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