Cell and Tissue Research (2019) 375:217–225
https://doi.org/10.1007/s00441-018-2946-3

MINI REVIEW

# Neuropeptides in sensory signal processing

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Received: 9 July 2018 / Accepted: 9 October 2018 / Published online: 30 October 2018


**Abstract**
Peptides released from trigeminal fibers fulfill well-understood functions in neuroinflammatory processes and in the modulation of nociceptive signal processing. In particular, calcitonin gene-related peptide (CGRP) and substance P (SP), released from afferent nerve terminals, exert paracrine effects on the surrounding tissue and this has been recently highlighted by the prominent parcrine role of CGRP in the development of headache and migraine. Some recent communications suggest that these sensory neuropeptides may also modulate the workings of sensory organs and influence afferent signals from nose, tongue, eyes and ears. Here, we briefly review the evidence for modulatory effects of CGRP and SP in the sensory periphery.

**Keywords** Neuropeptide · Sensory · Trigeminal · Chemesthesis · CGRP

## Chemesthesis and olfaction

The detection of external chemicals is mediated mainly by olfactory sensory neurons (Mainland et al. 2014), taste receptor cells (Roper and Chaudhari 2017), pheromone receptor cells (Silva and Antunes 2017), solitary chemosensory cells (Tizzano and Finger 2013; Lee et al. 2014) and nociceptors (Viana 2011). In addition to their specific machinery for chemo-electrical transduction, some of these cells may also respond to paracrine modulation by neuropeptides. Evidence for a modulatory role of neuropeptides released from trigeminal nociceptive terminals is available for several chemosensory modalities. CGRP is present in fibers innervating chemosensitive structures within the nasal and oral cavities (Fig. 1). Peptidergic innervation may thus provide a platform for tuning the responsiveness of the chemical senses.

In the mammalian nose, peptidergic trigeminal fibers innervate areas covered with respiratory epithelium but they are also present in the sensory epithelia (Table 1; Silverman and Kruger 1989; Lee et al. 1995). A network of trigeminal fibers grows within the *lamina propria* and free sensory terminals reach into epithelial tissues. They innervate arterioles, venules, the acini of mucus glands and subpopulations of epithelial cells. This network detects mechanical stimuli, noxious temperatures and a great diversity of irritants, which elicit a stinging or pungent sensation through activation of transduction channels such as TRPV1 and TRPA1 (Roper 2014). Peptidergic fibers are present throughout the nasal cavity and the paranasal sinuses (Sato et al. 2017) and CGRP and SP are released upon activation of Aδ fibers and C fibers. Moreover, inflammatory conditions elevate neuropeptide levels in nasal epithelia (Lim et al. 2011). The peptides mediate vasodilation, plasma protein exudation and mucus secretion and they attract immune cells to regions of inflammation (Stead et al. 1987; Barnes et al. 1991; Lacroix 2003). When stimulated, trigeminal fibers can elicit sneezing, a protective reflex that may clear the nasal cavity of harmful substances (Songu and Cingi 2009). The detection of chemical irritants is termed chemesthesis (Viana 2011) and links exist between chemesthesis, olfaction, taste and other chemical senses, probably mediated by CGRP and SP.

Within the respiratory epithelium, some trigeminal terminals are associated with solitary chemosensory cells, a microvillar cell type that can be stimulated by bitter (and therefore potentially toxic) substances, by high concentrations of odorants, as well as by bacterial signaling compounds (Finger et al. 2003; Gulbransen et al. 2008; Lin et al. 2008b; Tizzano et al. 2010; Tizzano and Finger 2013). These cells detect signs of a chemical hazard and generate afferent alarm signals in

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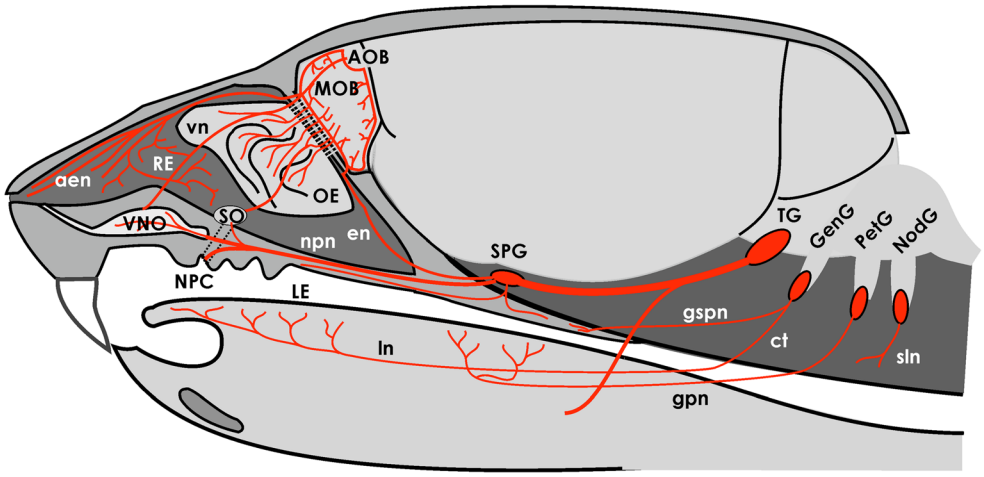


**Fig. 1** Schematic overview of chemosensory regions in a rodent head innervated by fibers immunoreactive to CGRP antisera (red). aen, anterior ethmoid nerve; AOB, accessory olfactory bulb; ct, chorda tympani; en, ethmoid nerve; GenG, geniculate ganglion (VII); gpn, glossopharyngeal nerve; gspn, greater superficial petrosal nerve; LE, lingual epithelium; ln, lingual nerve; MOB, main olfactory bulb; NodG, nodose ganglion (X); NPC, nasopalatine canal; npn, nasopalatine nerve; OE, olfactory epithelium; PetG, petrosal ganglion (IX); RE, respiratory epithelium; sln, superior lanryngeal nerve; SO, septal organ; SPG, sphenopalatine ganglion; TG, trigeminal ganglion (V); vn, vomeronasal nerve; VNO, vomeronasal organ. Based on data from Genovese et al. (2017), Schaefer et al. (2002) and Silverman and Kruger (1989)

peptidergic polymodal nociceptors, which can trigger a sharp drop in respiration rate through a brainstem reflex (Saunders et al. 2013). CGRP release from nociceptive fibers may also result in neurogenic inflammation, a first response to bacterial insult (Saunders et al. 2014). Thus, peptidergic trigeminal innervation of nasal epithelia provides a protective function based on chemoreception, a system for which the term "chemofensor complex" was coined (Green 2012).

In the olfactory neuroepithelium, the trigeminal network is not as dense as in the respiratory area. Trigeminal fibers with varicosities containing CGRP and SP enter the neuroepithelium (Finger et al. 1990; Daiber et al. 2013) and the neuropeptides may be released near any of the cell types within the tissue, including olfactory sensory neurons, microvillous chemosensory cells supporting epithelial cells and secretory cells in mucous glands. The olfactory epithelium does not contain solitary chemosensory cells and the resident TRPM5-expressing microvillous cells are not closely associated with trigeminal fibers (Lin et al. 2008a). Subepithelial acini of Bowman glands are encapsulated by CGRP-expressing fibers, suggesting trigeminal control of mucus production (Silverman and Kruger 1989). Most odorants co-stimulate trigeminal terminals if inhaled at sufficiently high concentrations (Cain 1977; Doty et al. 1978; Silver and Moulton 1982; Hummel and Livermore 2002; Brand 2006). Psychophysical studies have shown that trigeminal activity attenuates olfactory perception (Cain and Murphy 1980; Frasnelli et al. 2007; Daiber et al. 2013), an effect that may, in part, be mediated by neuropeptides. Mammalian olfactory sensory neurons express the CGRP receptor-associated proteins CRCP (CGRP-receptor component protein), CRLR (calcitonin receptor-like receptor) and RAMP1 (receptor activity-modifying protein 1) and the ex vivo odor response of rat olfactory sensory neurons, the electroolfactogram, is reduced by CGRP (Daiber et al. 2013). Thus, epithelial CGRP release can suppress olfactory processing in favor of chemesthetic processing. Cross-talk may also occur in the olfactory bulb where CGRP was reported to exert an inhibitory input on network activity (Genovese et al. 2017). In the vomeronasal organ, the main pheromone-sensing structure of mammals, peptidergic trigeminal innervation is dense at the opening of the tube-like organ into the nasal cavity, around blood vessels and in the medial wall of the central venuos sinus of the organ (Canto Soler and Suburo 1998; Uddman et al. 2007). CGRP- and SP-positive fibers enter the sensory neuroepithelium that comprises mainly pheromone-sensitive neurons. These peptidergic fibers may be part of a reflex system that regulates the access to the lumen of the vomeronasal organ.

## Taste perception

The mammalian taste system probes food material for appetitive qualities (salty, sweet and umami) and aversive qualities (bitter and sour). The lingual epithelium, as well as the various taste buds embedded in this tissue, is innervated by peptidergic fibers containing CGRP and/or SP (Table 1; Silverman and Kruger 1989; Silverman and Kruger 1990; Astback et al. 1997; Ishida et al. 2002; Ogura et al. 2007; Kawashima et al. 2012). Similarly innervated are the soft palate and the pharyngeal epithelium, which also contribute to taste perception (Hayakawa et al. 2010), as is the nucleus of the solitary tract, the first level of gustatory signal processing in the brainstem (Stratford et al. 2017). Upon

**Table 1** Distribution of cells expressing the neuropeptide CGRP (left) and its receptor components (right) in the cochlear, vestibular end organs, eyes, nose and tongue (left). CR-IR- CGRP receptor immunoreactivity; CLR—calcitonin like receptor; RCP—CGRP-receptor component protein; RAMP1—receptor activity-modifying protein 1 CGRP receptor distribution

| Tissue | Structure | References | CL-IR or receptor component (RCP, CLR, RAMP1) |
|---|---|---|---|
| Cochlea | | | |
| Sensory epithelium | Medial Olivocochlear efferents (MOC) | Mouse (Dickerson et al. 2016; Maison et al. 2003a, 2003b); g.pig (Cabanillas and Luebke 2002); human (Schrott-Fischer et al. 2007) | CLR cochlea lysate (Western) mouse (Dickerson et al. 2016) |
| | Lateral Olivocochlear efferents (LOC) | Mouse (Dickerson et al. 2016; Maison et al. 2003a, 2003b) human (Kong et al. 2002; Schrott-Fischer et al. 2007) | RCP cochlea lysate (Western) - mouse (Dickerson et al. 2016) |
| Spiral modiolar artery (SMA) | Trigeminal afferents | Gerbil (Herzog et al. 2002); g.pig (Carlisle et al. 1990); rat (Lyon and Payman 2000) | CR-IR SMA blood free (mRNA) - gerbil (Herzog et al. 2002) |
| Middle ear | Trigeminal, C1-C2 DRG | Rat (Uddman et al. 1999) | |
| Tympanic membrane | Afferent axons | Rat (Uddman et al. 1999); human (Yamazaki and Sato 2014) | |
| Vestibule | | | |
| Crista—sensory epithelium | Vestibular efferents | Mouse (Luebke et al. 2014); chinchilla (Ishiyama et al. 1994); g.pig (Hara et al. 2005; Scarfone et al. 1996) rat (Ohno et al. 1993, Tanaka et al. 1989a, 1989b, Wackym 1993, Wackym et al. 1993); human (Kong et al. 2002; Popper et al. 2002) | |
| Macula—sensory epithelium | Vestibular efferents | Mouse (Luebke et al. 2014); chinchilla (Ishiyama et al. 1994); g.pig (Hara et al. 2005; Scarfone et al. 1996) rat (Ohno et al. 1993, Tanaka et al. 1989a, 1989b, Wackym 1993, Wackym et al. 1993); human (Kong et al. 2002; Popper et al. 2002) | |
| Eye | | | |
| Retina | Müller glia | Rat (Blixt et al. 2017) | CR-IR retina (Western) - chicken (119) ciliary body, iris - rabbit (79) |
| | Amacrine cells | Chicken (Kiyama et al. 1985) | CR-IR retina - pig, cat, g-pig, monkey (Heppt et al. 2002) |
| | Vascular smooth muscle | Rat (Blixt et al. 2017) | CR-IR ciliary body - pig, cat, g.pig, monke (Heppt et al. 2002) CLR & RAMP1 retina - rat (Blixt et al. 2017) |
| Choroid | Intrinsic choroidal neurons | Duck (Schrodl et al. 2001); human (De Hoz et al. 2008); mouse (Toriyama et al. 2015) | CLR choroid (mRNA) - mouse (Toriyama et al. 2015) RAMP1 choroid (mRNA) - mouse (105) |
| Optic nerve | Schwann cell glia | Rat (Blixt et al. 2017) | |
| | Central retinal artery | Rat (Bergua et al. 2003); rhesus monkey (Ye et al. 1990) | |
| Cornea | Trigeminal afferents | G.pig (Alamri et al. 2015; Bron et al. 2014; Stone et al. 1986; Uusitalo et al. 1989); sheep (Bortolami et al. 1991); mouse (De Felipe et al. 1999, He and Bazan 2016); dog (Marfurt et al. 2001); rat (Beckers et al. 1992; Hiura and Nakagawa 2012; Jones and Marfurt 1991, 1998; Murata and Masuko 2006; Nakamura et al. 2007; Silverman and Kruger 1989); human (Ueda et al. 1989) | |
| Nose | | | |
| Olfactory epithelium | Trigeminal afferents | Rat (Daiber et al. 2013; Frasnelli et al. 2007) | CR-IR / in-situ olfactory sensory neurons - rat (Daiber et al. 2013) |
| Respiratory epithelium | Trigeminal afferents | Rat (Schaefer et al. 2002; Silver and Moulton 1982; Silverman and Kruger 1989) | |

**Table 1** (continued)

| Tissue | Structure | References | CL-IR or receptor component (RCP, CLR, RAMP1) |
|---|---|---|---|
| Nasal mucosa | Trigeminal afferents | Rat (Amores et al. 1991; Grunditz et al. 1994; Lee et al. 1995); human (Heppt et al. 2002; Uddman et al. 1999) | |
| Olfactory bulb | | Rat (Genovese et al. 2017; Schaefer et al. 2002) | |
| Tongue | | | |
| Gustatory epithelium | Fungiform papillae | Dog (Hino et al. 1993); rat (Astback et al. 1997; Ishida et al. 2002; Kawashima et al. 2012; Montavon et al. 1991; Silverman and Kruger 1989, 1990; Watanabe et al. 2013); mouse (Kawashima et al. 2012; Ogura et al. 2007; Wakisaka et al. 1996) | |
| | Superior Glossophary. Ganglion | Rat (Hayakawa et al. 2010) | |

(Kiyama et al. 1985; Stone et al. 1986; Tanaka et al. 1989a, 1989b; Ueda et al. 1989; Uusitalo et al. 1989; Amores et al. 1991; Bortolami et al. 1991; Jones and Marfurt 1991; Montavon et al. 1991; Usami et al. 1991; Beckers et al. 1992; Hino et al. 1993; Ohno et al. 1993; Wackym et al. 1993; Grunditz et al. 1994; Ishiyama et al. 1994; Heino et al. 1995; Scarfone et al. 1996; Wakisaka et al. 1996; Jones and Marfurt 1998; De Felipe et al. 1999; Uddman et al. 1999; Lyon and Payman 2000; Rosenblatt et al. 2000; Marfurt et al. 2001; Cabanillas and Luebke 2002; Heppt et al. 2002; Herzog et al. 2002; Kong et al. 2002; Popper et al. 2002; Maison et al. 2003a; Hara et al. 2005; Murata and Masuko 2006; Nakamura et al. 2007; Schrott-Fischer et al. 2007; De Hoz et al. 2008; Hiura and Nakagawa 2012; Watanabe et al. 2013; Bron et al. 2014; Smith and Keil 2015; Toriyama et al. 2015; Dickerson et al. 2016; He and Bazan 2016; Wang et al. 2016)

detection of salty or sour stimuli, afferent signals traveling to the brainstem via the *Chorda tympani* (Fig. 1) were reduced when CGRP was injected into the lingual artery (Simon et al. 2003). It thus appears that CGRP has the potential to modulate gustatory signals and to co-determine taste perception. Peptidergic fibers grow around taste buds (perigemmal fibers) and inside taste buds (intragemmal fibers). CGRP released from intragemmal, peptidergic nerve terminals can exert specific effects on the resident taste cells. Type-III sour taste cells, which form serotonergic synapses with afferent fibers (Roper and Chaudhari 2017), respond to CGRP with increased calcium signaling and release of serotonin (Huang and Wu 2015). Serotonin also has a paracrine effect: it inhibits type-II taste cells, the sensors for sweet, bitter and umami taste. Type-II cells use ATP as a transmitter to activate purinergic receptors on afferent neurons (Kinnamon and Finger 2013) but they do not form afferent synapses. The currently available data indicate that intragemmal CGRP-release during chemesthetic stimulation alters the output of a taste bud but it is still unclear how this modulation affects taste perception. Moreover, the function of perigemmal peptidergic fibers has not been examined yet.

## Inner ear—hearing and balance

CGRP is present in the endolymphatic compartment of the vestibular (otolith and semicircular organs) and cochlear sensory organs but it is restricted to efferent axons (Table 1). The vestibular crista and macula end organs receive cholinergic efferent projections from a cluster of 300–400 neurons located dorsolateral to the genu of the facial nerve. Vestibular efferents are myelinated axons bi-laterally with individual axons branching divergently to form axo-somatic contact with type-II hair cells and axo-axonic connections with calyceal endings of vestibular afferent neurons (see Mathews et al. 2017). Similarly, the efferent innervation of the cochlea comprises lateral (LOC) and medial olivocochlear (MOC) projections, the former ipsilateral and the latter projecting 75% of axons to the contralateral cochlear. LOC efferent axons are unmyelinated and form predominantly axo-axonic synapses with IHC afferents but they may also terminate axo-somatically on IHCs (Fig. 2). MOC axons are myelinated and form axo-somatic contacts with outer hair cells (Ciuman 2010) (Fig. 2). This architecture allows olivocochlear efferents and thereby CGRP to exert both pre-(hair cell) and post-(afferent) synaptic influence on vestibular and cochlear signals.

The physiological role of MOC efferent projections is to reduce the gain of the cochlear amplifier through inhibition of OHC motility to serve protective and selective filtering functions (Smith and Keil 2015). In contrast, the role of LOC efferents, in which the incidence of CGRP co-expression is

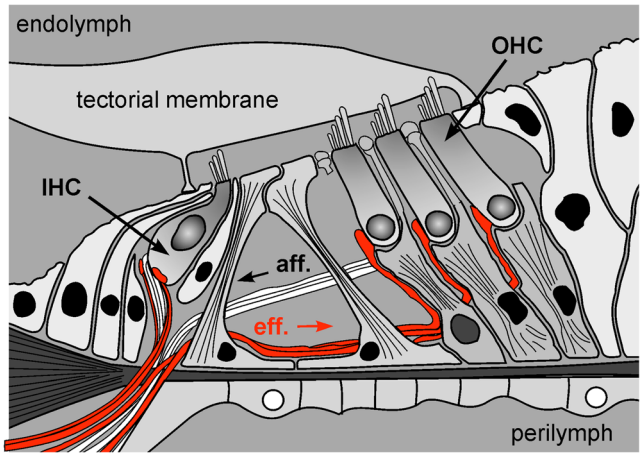


**Fig. 2** Topography of the mammalian Corti-organ with efferent, CGRP-positive innervation (red) and afferent innervation (gray) of inner hair cells (IHC) and outer hair cells (OHC). Based on data from Ciuman (2010)

higher, is less well understood. However some recent insight has been provided by mice constitutively lacking alphaCGRP (Lu et al. 1999). Inner hair cell signaling is compromised in CGRP−/− mice as evidenced by a ca. 20% reduction in the amplitude of auditory brainstem responses (ABR), while distortion product emission recordings (DPOAE) indicative of OHC function were not altered (Maison et al. 2003b). This has prompted the suggestion that CGRP via axo-axonic synapses may set the dynamic range of cochlear afferents by determining the slope of their frequency encoding glutamate signaling from IHCs (Maison et al. 2003b). In the same CGRP null line, tests of vestibular function showed an approximate 50% reduction in the dynamic range (gain) of the vestibulo-ocular reflex (VOR) without any effect on response delay (phase) (Luebke et al. 2014). After controlling for potential changes in CGRP content in motoneurons supplying extraocular muscles, Luebke et al. (2014) suggested that akin to CGRPs influence in the cochlear, efferent release of CGRP extends the range of vestibular afferent encoding.

The blood supply to the inner ear is also innervated by peptidergic axons of trigeminal and autonomic origin. Trigeminal axons expressing CGRP and SP course along the inferior cerebellar artery to terminate amongst vestibular dark cells (Vass et al. 1998) and along the spiral modiolar artery (SMA) to innervate arterioles supplying the stria vascularis of the cochlear (Carlisle et al. 1990). The potent vasodilator properties of CGRP, suggest that this peptidergic perivascular innervation of the SMA contributes to the tight regulation of cochlear blood flow that in turn affects hair cell function through maintenance of the endolymphatic potential (Shi 2011). Peptidergic axons of somatosensory origin also innervate structures in the middle ear (Uddman et al. 1988) and the tympanic membrane (Yamazaki and Sato 2014) where they subserve a classical protective role in the detection and response to potentially and overtly damaging stimuli (Saunders and Weider 1985).

## Vision

Most studies of CGRP and SP in the visual system were conducted in the context of migraine research because of the vasoactive effects these neuropeptides may have in the retina and the optic nerve. Light can intensify migraine headache through retinal ganglion cells, which converge on dura-sensitive thalamic neurons projecting to the somatosensory cortex (Noseda et al. 2010; Goadsby et al. 2017). The severity of photophobia, a condition that can be triggered by migraine

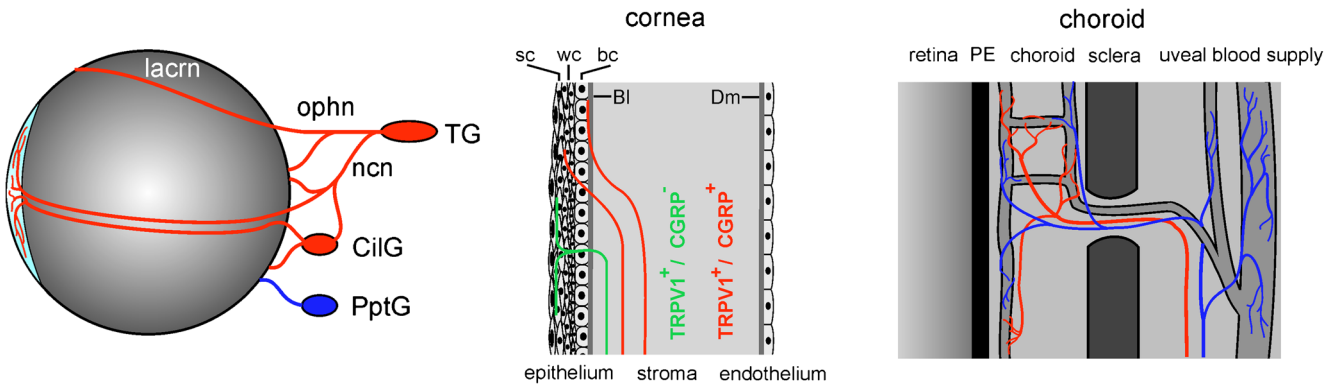


**Fig. 3** Peptidergic innervation of the anterior and posterior regions of the eye. The cornea receives peptidergic sensory fibers from the trigeminal ganglion (TG) through the nasociliary nerve (ncn) and the ciliary ganglion (CilG). These fibers terminate in distinct layers of the corneal epithelium (center: sc, squamous cells; wc, wing cells; bc, basal cells; Bl, Bowman's layer; Dm, Descemet's membrane). Lacrimal glands are reached by peptidergic fibers of the lacrimal nerve (lacrn). In the posterior wall of the eye, peptidergic innervation is provided by the ophthalmic nerve (ophn), the nasociliary nerve (nsn), the ciliary ganglion (CilG) and the parasympathic pterygopalatine ganglion (PptG). CGRP/SP-positive terminals target choroidal blood vessels (right: red), while parasympathic, VIP-positive terminals reach both choroidal blood vessels and larger arterioles of the uveal blood supply (right: blue). Based on data from Alamri et al. (2015) and Reiner et al. (2018)

and other forms of headache, depends on RAMP1, a component of the CGRP receptor (Recober et al. 2009), suggesting a link between CGRP and light-induced headache. The eye receives dense trigeminal innervation in the cornea and in the conjunctiva, which detect thermal, mechanical and chemical stimuli and that can also release CGRP and SP to promote neurogenic inflammation and wound healing (Belmonte et al. 2004) (Fig. 3). Moreover, peptidergic trigeminal fibers innervate the eye choroid and contribute to vascular smooth muscle control and, hence, regulate the uveal (non-retinal) blood supply to the eye (Schrodl et al. 2001; Nickla and Wallman 2010) (Fig. 3). The retina, in contrast, appears to be almost free of sensory fibers. Perivascular peptidergic fibers accompany the central retinal artery, a branch of the posterior ciliary artery in the optic nerve, right to the optic disc where they end at the level of the retinal pigment epithelium without entering the retina itself (Ye et al. 1990; Bergua et al. 2003). CGRP released from these fibers appears to exert a regulatory effect on cells in the pigmented epithelium (Troger et al. 2003), with possible involvement in retina development and maintenance.

Immunohistochemical studies demonstrated CGRP, as well as its receptors CRL and RAMP1, to be present within the inner nuclear layer, the ganglion cell layer as well as in Müller glia cells (Caruso et al. 1990; Blixt et al. 2017). Functional evidence also supports the hypothesis of CGRP effects in retinal signal processing. Interocular injection of CGRP increased light-induced electroretinograms in rabbits (Cao et al. 1993) and studies with the CGRP-receptor antagonist BIBN4096 suggested that CGRP is involved in the generation of spreading depression in chick retina preparations (Wang et al. 2016). Furthermore, electrical stimulation of trigeminal ganglia caused increased levels of CGRP and SP in the pigment epithelium, the photoreceptor outer segments, the outer and inner nuclear layers and in the ganglion cell layer (Bronzetti et al. 2007). Finally, experiments with rat models for stroke and nerve injury provided evidence that a release of CGRP or SP from retinal cells during hyperexcitation or ischemia has a neuroprotective function in the retina, which may be related to their ability to increase blood flow (Yang et al. 2011; Sakamoto et al. 2014). Taken together, these data suggest that CGRP and SP can be released in the inner and outer retina and may target neurons in the retinal network. The significance of local neuropeptide release on retinal signal processing still has to be established.

In conclusion, CGRP and SP in the trigeminal system are primarily associated with primary afferent nociceptive neurons and release of the neuropeptides exerts prominent effects on some neurons and on the vasculature. Indeed, blockade of the potent vasodilator action of CGRP is the mechanism implicated in the preliminary success and prospective clinical use of small molecule and antibody therapies targeting the CGRP-receptor and CGRP for migraine (Tso and Goadsby 2017; Messlinger 2018). In addition and by virtue of their location in both afferent somatosensory and efferent neurons, sensory neuropeptides are able to exert cross-modal effects on vision, taste, balance, hearing and smell. Cross-modal neuropeptide effects may be exerted on the specialized sensory end organs through regulation of their vasculature, in development and possibly as integral regulators of the functioning sensory apparatus itself.

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