



Review

Roles of calcitonin gene-related peptide in the skin, and other physiological and pathophysiological functions



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ABSTRACT

Skin immunity is regulated by many mediator molecules. One is the neuropeptide calcitonin gene-related peptide (CGRP). CGRP has roles in regulating the function of components of the immune system including T cells, B cells, dendritic cells (DCs), endothelial cells (ECs), and mast cells (MCs).

Herein we discuss actions of CGRP in mediating inflammatory and vascular effects in various cutaneous models and disorders.

1. Introduction

CGRP was identified in 1982 by Amara et al. (Amara et al., 1982). CGRP consists of 37 amino acids, created from alternative RNA processing of the calcitonin gene. CGRP exists in two forms, α -CGRP (CGRP I) and β -CGRP (CGRP II). In humans, they are from two different genes (Brain et al., 1986), differ by three amino acids and share >90% homology, exerting biological effects, including vasodilation through similar mechanisms (Morris et al., 1984; Amara et al., 1985; Steenbergh et al., 1986). The calcitonin (CALC) I gene gives rise to either calcitonin or α -CGRP via alternative splicing, while a separate CALC II gene yields β -CGRP (Alevizaki et al., 1986; Steenbergh et al., 1986). α -CGRP is more abundant, located in specific regions in the central and peripheral nervous system. β -CGRP is found primarily in the gut, enteric nerves and pituitary gland (Mulder et al., 1985; Brain et al., 1986; Brain and Grant, 2004).

CGRP acts on calcitonin receptor-like receptors (CLRs) associated with receptor activity modifying proteins (RAMPs), needed for full functionality. The CGRP receptor consists of a CLR and a single transmembrane protein, RAMP1. CGRP is produced primarily in sensory nerves together with neuropeptides such as substance P (SP), as well as in the central nervous system. CGRP expression is also abundant in trigeminal ganglion neurons (Iyengar et al., 2019). CGRP expression by other cells is also known, including Langerhans cells (LCs), ECs, keratinocytes, fibroblasts, T lymphocytes, B lymphocytes, and monocytes (Hosoi et al., 1993; Bracci-Laudiero et al., 2002; Linscheid et al., 2004;

Ding et al., 2008; Roggenkamp et al., 2013; Granstein et al., 2015). Its production is regulated by nerve growth factor (NGF) and can be secreted together with SP (Park et al., 2010). CGRP is an important vasodilator; it can trigger a signaling cascade that can lead to mast cells (MCs) releasing vasoactive amines such as histamine and serotonin (Voss et al., 2021) that recruit neutrophils and T cells, or it can more directly vasodilate through ATP-dependent potassium channels in arterial smooth muscle (Nelson et al., 1990). CGRP is found in the peripheral and central sensory nervous systems (Rosenfeld et al., 1983; Terenghi et al., 1985). In the periphery, CGRP is synthesized primarily in dorsal root ganglia (DRG) (Gangula et al., 2000), where the pro-peptide is cleaved to the active form and packaged in dense-core vesicles at sensory nerve terminals where it is stored and co-released with SP (Brain and Grant, 2004; Schlereth et al., 2016). Upon depolarization, calcium-dependent pathways trigger the exocytosis and release of CGRP (Matteoli et al., 1988; Russell et al., 2014).

CGRP synthesis is upregulated in damaged nerves (such as peripheral axotomy) and tissues (Russell et al., 2014). Increased levels of CGRP observed with methods such as the enzyme-linked immunosorbent assay (ELISA) show that CGRP is released following transient receptor potential vanilloid 1 (TRPV1) or transient receptor potential ankyrin 1 (TRPA1) activation (Achanta et al., 2018; Pinho-Ribeiro et al., 2018; Zhang et al., 2020). TRPV1 is activated by capsaicin (which stimulates nociceptive afferents), heat, and acid, and acts as a transducer of temperature-sensitive pain (Venkatchalam and Montell 2007). TRPA1 is a chemosensory cation channel in sensory nerves and is activated by cold, endogenous reactive oxygen species, and cellular stress mediators, as

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Abbreviations	
CGRP	calcitonin gene-related peptide;
DC	dendritic cell
EC	endothelial cell
MC	mast cell
CALC	Calcitonin I gene
CLR	calcitonin receptor-like receptor
RAMP	receptor activity modifying protein
SP	substance P
LCs	Langerhans cells
NGF	nerve growth factor
DRG	dorsal root ganglia
TRP	transient receptor potential
ELISA	enzyme-linked immunosorbent assay
TRPV1	transient receptor potential vanilloid 1
TRPA1	transient receptor potential ankyrin 1
CEES	2-chloroethyl ethyl sulfide;
ICAM	intercellular adhesion molecule
VCAM	vascular cell adhesion molecule
AM	adrenomedullin
TIA	transient ischemic attack
RAAS	renin-angiotensin-aldosterone system
NPY	neuropeptide Y
VIP	vasoactive intestinal peptide,
MAPK	mitogen activated protein kinase
NFκB	nuclear factor κB
ERK1/2	extracellular signal related kinase1/2
FPD	fibroproliferation disease
EMT	epithelial-mesenchymal transition
FMT	fibroblast-to-myofibroblast transdifferentiation
APC	antigen presenting cell
DTH	delayed-type hypersensitivity
AHR	airway inflammation and hyperresponsiveness
pDMEC	primary murine dermal microvascular EC
(ROR)-γt	retinoic acid receptor-related orphan receptor gamma
UVB	ultraviolet B
UCA	cis-urocanic acid
DNFB	2,4-dinitro-1-fluorobenzene
CHS	contact hypersensitivity
BoNT-A	botulinum neurotoxin A
RvD3	resolvin D3
BTX-B	botulinum toxin B
ETR	erythematotelangiectatic subtype of rosacea
TP	telangiectatic photoaging

well as pungent extracts like sulfur mustard and 2-chloroethyl ethyl sulfide (CEES), a sulfur mustard analog, promoting vesicant injury manifested as blistering (Bandell et al., 2004; Viana 2016). Both TRPV1 and TRPA1 channels trigger exocytosis of CGRP via a pathway that leads to increased intracellular calcium levels as shown in vitro by using ELISA and enzyme immunoassay techniques (Quallo et al., 2015; Shang et al., 2016; Eberhardt et al., 2017), and in vivo, leading to neurogenic vasodilation (Pozsgai et al., 2012). Thus, CGRP is essential for neurogenic inflammatory responses and other microvascular effects from neuropeptide release. CGRP and SP are two of the main proinflammatory neuropeptides released from nerve terminals-SP acts on NK1 receptors to mediate increased microvascular permeability (Cao et al., 2000), and CGRP is a potent vasodilator, contributing to the formation of edema, increased blood flow, and infiltration of inflammatory cells locally. Interestingly, although rodent MCs respond to CGRP, there is a report that human MCs do not (Kulka et al., 2008) and human mast cells may not express functional CGRP receptors (Eftekhari et al., 2013).

Endothelial cells (ECs) synthesize and store CGRP in Weibel-Palade bodies, likely involved in autoregulation of hemodynamics (Ozaka et al., 1997). CGRP receptors are expressed on monocytes, macrophages, and neutrophils, along with epidermal cells such as keratinocytes, melanocytes and LCs. Human dermal microvascular ECs were also found to express mRNA for CLR and RAMP1-3 (Nikitenko et al., 2003).

In skin, CGRP-immunoreactive nerve fibers are just under, and occasionally penetrating into the epidermis, sometimes forming fiber bundles deep to the epidermis (Schotzinger and Landis 1990), although single fibers run either near blood vessels or sweat glands (Wallengren 1997). In human skin, CGRP evokes slowly developing erythema within several hours (Wallengren et al., 1987; Wallengren and Hakanson 1987); this is not due to MC histamine or C-fiber tachykinins, as the effects were not suppressed by pre-treatment with mepyramine (histamine H1 receptor inverse agonist) or compound 48/80 (promoter of MC degranulation and histamine release) (Wallengren and Hakanson 1992; Wallengren et al., 1992). The longer-lasting and more widespread vascular effects of CGRP infer a gradual diffusion of CGRP, with direct vasodilation.

Nitric oxide (NO) generated from glyceryl trinitrate (GTN) acts downstream to CGRP to evoke vasodilatation and probably headache (Geppetti et al., 2012). It is also reported that CGRP signaling inhibits NO

production through pannexin-1 channel activation in endothelial cells. (Gaete et al., 2019). What is known is that periarterial nerve stimulation leads to vasodilation resistant to propranolol and atropine in the isolated mesenteric vascular bed (Kawasaki et al., 1988). Concurrent CGRP release during the vasodilation response (Fujimori et al., 1989), and the ability to block vasodilatation with CGRP antiserum (Han et al., 1990) demonstrates that this nonadrenergic, noncholinergic vasodilation is regulated by endogenous CGRP (Han et al., 1990). Thus, CGRP-containing nerves tonically mediate vascular tone in mesenteric resistance vessels.

Inflammatory skin conditions including atopic dermatitis, psoriasis and rosacea may be regulated by nerve-derived immunomodulators including SP and CGRP. SP and CGRP act on vascular ECs and smooth muscle cells. SP increases vascular permeability by increasing intercellular adhesion molecules (ICAMs) and vascular cell adhesion molecules (VCAMs) on vascular epithelial cells and enhancing VEGF release from MCs (Lindsey et al., 2000; Castellani et al., 2010; Mishima et al., 2011), which both significantly enhance vascular permeability and induce proliferation of vascular ECs in vivo (Boesiger et al., 1998; Grutzkau et al., 1998), ultimately causing plasma extravasation and edema through hypervascularization and infiltration of inflammatory cells (Brain and Williams 1989). CGRP is also an important vasodilator of the microvasculature and helps to recruit inflammatory cells (Saria 1984; Zhou et al., 2010), mechanisms of which will be discussed further later in this review.

2. CGRP and vascular effects

2.1. CGRP in migraine

CGRP is key in the pathogenesis of migraines (Sacco and Kurth 2014), perhaps due to its role in vasodilation. CGRP release from trigeminal neurons regulates cerebral vascular tone (O'Connor and van der Kooy 1988; Edvinsson et al., 2012). Whereas plasma levels of CGRP are increased in certain pathological states such as sepsis (Joyce et al., 1990), only cerebral vessel and ipsilateral jugular vein levels of CGRP are elevated in migraine (Edvinsson and Goadsby 1995; Ashina et al., 2000; Messlinger 2018).

CGRP is present in trigeminal ganglia and cerebral arteries and blood

levels in the jugular vein are elevated during headache, particularly migraine and cluster headaches. Some effective CGRP inhibitors appear not to cross the blood brain barrier suggesting a peripheral rather than a direct central action (Edvinsson et al., 2007; Edvinsson and Tfelt-Hansen, 2008). A comprehensive review of mechanisms by which CGRP blockade therapeutically benefits migraine is beyond the scope of this review. However, as stated by Edvinsson and colleagues “given that the trigeminal ganglion is central to the trigeminal vascular pain pathway, speculations that blocking CGRP transmission within the trigeminal ganglion is sufficient to abort or prevent the debilitating symptoms of migraine seems reasonable” (Edvinsson et al., 2018).

CGRP antagonists alleviate migraines, as they can be explicitly designed to act on the trigeminal pain system (Edvinsson et al., 2018). The first non-peptide CGRP antagonist, BIBN 4096 BS, is effective in both animals and humans (Doods et al., 2000; Olesen et al., 2004). There are ongoing clinical trials with CGRP receptor antagonists for migraine treatment and some are approved for human use (Goadsby et al., 2017; Pellesi et al., 2017; Edvinsson et al., 2018). Galcanezumab (LY2951742), fremanezumab (TEV-48125), eptinezumab (ALD403), are monoclonal antibodies against CGRP, and indicated for use in migraine prevention in episodic migraine and chronic migraine (Bigal et al., 2013; Cernuda-Morollon et al., 2013; Giani et al., 2019), as well as for reduction of frequency of attacks in patients with episodic cluster headaches (Pellesi et al., 2020). Ubrogepant is an oral CGRP receptor antagonist, used for relief from acute migraine attacks (Curto et al., 2020). Rimegepant is another oral CGRP antagonist used for acute migraines (Peters 2019). However, telcagepant, another oral compound, was not approved due to liver toxicity (Holland and Goadsby 2018).

Migraines can also be treated by triptan drugs like sumatriptan and rizatriptan, which are 5-HT_{1B/1D} receptor agonists. 5-HT_{1B/1D} receptors are serotonergic receptor subtypes located in the CNS, with one of their roles being vasoconstriction of vessels. As vasodilation in the dura mater could be a contributing factor to the pathogenesis of migraine headache (Humphrey and Feniuk 1991), one way that triptans can alleviate the migraine by constricting the dural blood vessels (Jansen et al., 1992), although vasoconstriction is not always necessary (Do et al., 2019). Neuropeptides such as CGRP are released from dural sensory nerve terminals during migraine attacks, a process mediated by 5-HT_{1B/1D} receptors (Buzzi et al., 1991; Goadsby and Edvinsson 1993). More recently, it was shown that the voltage-gated P/Q-type calcium channel plays an important role in modulating neurotransmitter and neuropeptide release, such as that of CGRP (Xiao et al., 2008). Furthermore, CGRP levels are increased in the cranial circulation specifically in the outflow of the external jugular vein during migraine attacks, and intravenously injecting CGRP into patients can lead to migraine-like headaches (Lassen et al., 2002).

Interestingly, a case report of a migraine patient who developed a possible CGRP receptor antibody (erenumab)-associated skin wound healing disturbance twice during the course of her therapy also suggests that impaired wound healing may be a potential side effect of CGRP antibody treatment as it is clear that CGRP plays significant roles in migration of keratinocytes, vascularization and immune responses (Wurthmann et al., 2020).

2.2. CGRP and cardiovascular effects

CGRP mediates cardioprotective effects in different cardiovascular models and disorders (Li et al., 1996; Depre et al., 2018). Perivascular nerve fibers throughout the body also display CGRP immunoreactivity. Perivascular CGRP fibers are in all vascular beds, generally more abundant around arteries than veins (Uddman et al., 1986). They are potent regulators of local blood flow and carry sensory information (Uddman et al., 1986). Respiratory, gastrointestinal, and genitourinary tracts contain many small arteries with CGRP fibers, particularly the gastroepiploic arteries (Uddman et al., 1986). CGRP fibers are in coronary blood vessels, especially close to myocardial fibers (Uddman et al., 1986;

Sekiguchi et al., 1994). Thus, CGRP may have protective effects in various cardiovascular diseases (Gao et al., 2015). CGRP immunoreactivity is also in nerve cell bodies and nerve fibers in sensory ganglia (Lawson et al., 2002). It has also been shown that CGRP antagonists can worsen cerebral ischemic outcomes in a murine ischemic stroke model (Mulder et al., 2020).

In some models of hypertension, CGRP protected against the onset and advancing of hypertensive conditions by possibly counteracting the pro-hypertensive mechanisms such as the renin-angiotensin-aldosterone system (RAAS) and the sympathetic system (Li et al., 2004). CGRP could also alleviate some of the pathophysiology of heart failure and ischemia, by mediating cardiac hypertrophy, protecting against reperfusion injury, inflammation, and apoptosis (Kee et al., 2018). In myocardial ischemia, CGRP can play a protective role, as IV administration of CGRP led to an increased heart rate and decrease in both systolic and diastolic arterial pressure (Gennari and Fischer 1985). However, there are mixed results with regards to plasma CGRP levels in hypertensive patients; plasma CGRP was higher (Masuda et al., 1992), unchanged (Schifter et al., 1991), and decreased (Edvinsson et al., 1989; Portaluppi et al., 1992). These discrepancies could be due to differences in sampling, radioimmunoassays used, heterogeneity in duration, severity, and treatment of different hypertensive populations (Bell and McDermott 1996). However, plasma CGRP levels were decreased in patients after adrenalectomy to treat another underlying condition, suggesting that CGRP is a compensatory response to hypertension and can become reduced or even inhibited with disease progression (Russell et al., 2014; Smillie et al., 2014). NO plays a role in maintaining low blood pressure and healthy heart function. It was also shown that when vascular NO production is not fully functional, alpha-CGRP can act via the canonical CGRP receptor to protect against cardiovascular dysfunction by promoting mesenteric regulation of blood flow (Argunhan et al., 2021).

Although CGRP is a potent mediator in cardiovascular protection, it is also involved in migraine pathogenesis as mentioned earlier in the review. Therefore, it is important to consider the safety and tolerability profile of anti-CGRP monoclonal antibodies, with regards to both systems. So far, clinical trials have shown that CGRP monoclonal antibodies used for treatment of both episodic and chronic migraine did not demonstrate any safety problems concerning the cardiovascular system (Tso and Goadsby 2017; Khan et al., 2019), although it should be noted that the patients in these trials were young and typically without significant cardiovascular disease. Olcegepant did not have any effect on myocardial vascular conductance in rat and pig, nor did it affect their baseline hemodynamics (Kapoor et al., 2003; Arulmani et al., 2004). These studies suggest that in healthy subjects without cardiovascular conditions, CGRP inhibitors do not pose a threat. However, in patients with cardiovascular conditions, CGRP receptor antagonists could lessen the cardioprotective effect of CGRP (Lu et al., 1999; Chai et al., 2006), as demonstrated by studies showing that CGRP has a protective effect during coronary and cranial ischemia (Li and Peng 2002; Rehni et al., 2008; Cai et al., 2010) and olcegepant, a CGRP receptor antagonist, could block the protective effect of CGRP in a rat heart model (Chai et al., 2006). It is important that more studies on the safety of CGRP receptor antagonists and the downstream effects of CGRP receptor blockade under ischemic conditions be done, in order to confirm both the acute and chronic effects of these drugs when used in patients with increased cardiovascular risk.

2.3. CGRP pharmacology

The more recently discovered adrenomedullin (AM) and amylin are considered to be members of the CGRP/calcitonin family of peptides. AM (52 amino acids) is longer than CGRP (37 amino acids), they exhibit crossreactivity at each other's receptors because biological activity is conserved by the C-terminal 38 amino acids (Alexander et al., 2019). AM is a potent vasodilator in rat skin and amylin is a pancreatic islet amyloid polypeptide which also shares 16 amino acids with both AM and CGRP

(Tso and Goadsby 2017). In vivo experiments that measured changes in local blood flow in rat skin, injection of either AM (3–300 pmol) or CGRP (0.1–30 pmol) led to dose-dependent increases in local blood flow. As of now, CGRP₈₋₃₇ is the best available peptide antagonist for the CGRP receptor and AM₂₂₋₅₂ is the best known antagonist at the AM receptor (Hay et al., 2003; Hay et al., 2004). CGRP₈₋₃₇ also antagonized sustained high blood flow mediated by IL-1 β ; AM mRNA is upregulated by local administration of IL-1 β and sufficient AM is produced to contribute to vasodilatation (Chu et al., 2001). CGRP antagonists such as rimegepant are capable of antagonizing alpha-CGRP mediated signaling through both the AMY₁ receptor and CGRP receptor (Pan et al., 2020), showing that CGRP and amylin share receptors and can have several similar pharmacological and biological actions. Another agent effective against migraine, erenumab, blocks the CGRP signaling by binding both the CGRP and AMY₁ receptors, with an essential requirement for RAMP1, the common subunit in both (Bhakta et al., 2021).

3. Role of CGRP in neurogenic inflammation

Neurogenic inflammation is the process by which sensory nerves induce inflammation by release of inflammatory neuropeptides (Kilo et al., 1997; Cao et al., 2000). Mechanical stress can induce vasoactive neuropeptide release which stimulate skin sensory fibers to release neuropeptides responsible for vessel modifications and fibroblast activation (Akaishi et al., 2008). Most cutaneous cells express functional receptors for neuropeptides such as CGRP, through which they transmit signals from the nervous system; after stimulation with CGRP, these cells, in turn, release other neuropeptides such as neuropeptide Y (NPY), galanin, CGRP, or vasoactive intestinal peptide (VIP), as well as neurotrophins that can further stimulate nerve fibers by recruiting inflammatory cells-hence the term “neurogenic” inflammation (Roosterman et al., 2006; Chiu et al., 2012). NGF can augment CGRP release through signal transduction pathways mediated by signaling proteins Ras and MEK (mitogen-activated protein kinase), through both acute sensitization and long-term upregulation of CGRP expression (Park et al., 2010). Human skin fibroblasts also express mRNA for RAMP1, demonstrating that they also have a low-expression of CGRP receptors (Albertin et al., 2003; Ferreira et al., 2009), and they contribute to the pathogenesis of neurogenic inflammation with induction of extracellular matrix synthesis (Akaishi et al., 2008; Hochman et al., 2008). MCs also release histamine, an important factor in inducing itch. SP, CGRP, and histamine, also directly contribute to vasodilation and permeabilization of vessels, completing the malignant cycle of neurogenic inflammation (Akaishi et al., 2008). In particular, SP recruits inflammatory cells directly. While this has been attributed to action at NK1 receptors, recent data suggests that engagement of MrgprB2/X2 receptors is more relevant to inflammation (Navratilova and Porreca 2019). Also, capsaicin-induced vasodilation in both the rhesus monkeys (Hershey et al., 2005) and humans (Sinclair et al., 2010) is inhibited by a CGRP-receptor antagonist. CGRP plays an important role in dermal blood flow due to capsaicin; MK-0974, a powerful oral antagonist of CGRP, can inhibit vasodilation in the dermis after skin application of capsaicin (Sinclair et al., 2010).

4. CGRP and the skin

4.1. Keratinocytes

Keratinocytes are derived from ectoderm, similar to neurons, and exhibit neurochemical properties (Roosterman et al., 2006). The skin is innervated by sensory neurons that release neuropeptides. CGRP, produced by peptidergic sensory endings in the epidermis, can promote keratinocyte proliferation and cytokine expression (Toyoda et al., 1999). A keratinocyte cell line was used to identify receptors for SP and CGRP on keratinocytes, and their role in keratinocyte neuropeptide signaling, cell proliferation and IL-1 β , IL-6, TNF α , and NGF expression (Shi et al., 2013). Stimulation with SP or CGRP upregulated neuropeptide receptor

expression in keratinocytes and increased keratinocyte secretion of SP and CGRP, implying autocrine or paracrine stimulatory effects. SP activated all 3 families of mitogen activated protein kinase (MAPK) and nuclear factor κ B (NF κ B) in keratinocytes, and CGRP activated p38 and extracellular signal related kinase1/2 (ERK1/2) MAPKs. Accordingly, ERK1/2 and JNK inhibitors reversed neuropeptide-stimulated inflammatory mediatory production in keratinocytes (Lei et al., 2012). In another study, competitive receptor antagonists of CGRP and SP were applied to the epidermis in an in vitro skin model to test whether they affect the neuron-derived effect on epidermal morphogenesis (Roggenkamp et al., 2013). The CGRP antagonist CGRP₈₋₃₇ significantly reduced epidermal thickness compared to the control preparation. Furthermore, CGRP-treated skin models exhibited a thickened epidermis and an increase in proliferating, Ki-67-positive keratinocytes, compared to a lesser degree of thickening of the epidermis when treated with SP (Roggenkamp et al., 2013). These observations could help in designing novel treatments for inflammatory skin diseases and pain disorders, as CGRP antagonists or agonists could be used to disrupt ERK1/2 and JNK signaling pathways involved with exaggerated sensory neuron-keratinocyte signaling.

4.2. Melanocytes

Epidermal melanocytes are anatomically associated with axons in human skin including formation of synapse-like contacts (Hara et al., 1996; Hirobe 2005), and CGRP stimulates melanocyte proliferation. CGRP also increases intracellular cAMP, suggesting an effect on cAMP pathway mediated proliferation. Through immunohistochemistry and electron microscopy, a close physical connection between axon terminals in the epidermis and melanocytes was shown via thickening of either pre- or postsynaptic plasma membranes and submembrane aggregation of vesicles, similar to nervous system synapses (Hara et al., 1996). CGRP could also exert its effects through secretion from intraepidermal free nerve endings (Hara et al., 1996). Melanogenic activity, defined by tyrosinase activity and melanin content, was compared between a pure culture system of melanocytes treated with either CGRP-KCM (medium conditioned by CGRP-stimulated keratinocytes) or CGRP alone. Although CGRP alone had no effect on melanogenic activity, CGRP-KCM upregulated melanogenesis, showing that CGRP stimulated melanogenesis via keratinocyte-derived factors (Toyoda et al., 1999) but does not do so directly. No significant difference in the quantity of melanocytes between cultured melanocytes treated with CGRP alone or with CGRP-KCM (Toyoda et al., 1999) was seen, demonstrating that CGRP directly stimulated melanocyte mitosis without keratinocyte-derived factors. CGRP can enhance the number of dendrites and the average dendrite length per cell (Toyoda et al., 1999). Melanocytes in control medium had short, unipolar/bipolar dendrites, compared to melanocytes stimulated with NGF, an inducer of melanocyte dendricity, or CGRP, which induced multiple, long dendrites. CGRP-KCM further induced elongation of dendrites of melanocytes in different directions (Yaar et al., 1991). Thus, keratinocytes are an important source of exogenous signals that induce melanocyte dendricity. CGRP also influences keratinocytes to release endothelin-1, β FGF, α -melanocyte stimulating hormone, and prostaglandin E₂, which all affect melanocyte dendricity (Snell 1964; Abdel-Malek 1988; Halaban et al., 1988; Hara et al., 1995). Under CGRP's influence, keratinocytes regulate melanocyte morphology and increase melanocyte number, total epidermal melanin content, melanosome maturation, and dendrite formation (Toyoda et al., 1999).

4.3. Fibroblasts

Neuropeptides can directly modulate fibroblasts with implications for wound healing and are associated with hyperproliferative skin and mesenchymal conditions (Peters et al., 2006; Yu et al., 2009). SP can stimulate chemotaxis in human fibroblasts (O'Connor, O'Connell et al., 2004), and in vitro, it is also a powerful chemoattractant for human

fibroblasts as it stimulates a concentration-dependent migratory response (Kahler et al., 1993). Human dermal fibroblasts move after adding SP to the culture medium (Kahler et al., 1993), and SP upregulates the proliferation of skin fibroblasts (Morbidelli et al., 1993). SP, CGRP, and melanocyte-stimulating hormone (alpha-MSH) can also upregulate the IL-8/IL-8RA system of keratinocytes and fibroblasts (Kiss et al., 1999), important for cutaneous inflammation. CGRP may have a role in fibroproliferation disease (FPD) of the skin (Akaishi et al., 2008). Mechanical stress, such as skin stretching, stimulates mechanosensitive nociceptors on sensory fibers in the skin, leading to SP and CGRP release with binding to SP-NK1R and CLR-RAMP-1 receptors on skin cells (Muschter et al., 2019), along with upregulation of MC histamine release (Durham 2016). This suggests innovative therapeutic targets for FPDs of the skin, such as keloids and hypertrophic scars.

Fibroblasts are critical elements of inflamed tissues and are often near neural cells. CGRP promotes IL-1 β - or TNF- α - induced biosynthesis of IL-6 by a non-transformed fibroblast cell line, through post-transcriptional stabilization of IL-6 specific mRNA (Sakuta et al., 1995). Also, CGRP and SP act through their receptors to promote epithelial-mesenchymal transition (EMT), fibroblast-to-myofibroblast transdifferentiation (FMT), and convert stromal cells into smooth muscle cells in endometriotic lesions, increasing migration and invasion, cell contractility, and collagen synthesis, leading to fibrosis (Yan et al., 2019). Interactions between CGRP and fibroblasts also occur in the heart. There is abundant expression of CGRP in rat, mouse, and human myocardium, and cardiac CGRP is mainly derived from cardiac fibroblasts (Li et al., 2020). NF- κ B signaling plays an integral part in cardiac fibroblast activation, seen in aortic coarctation and angiotensin II induced cardiac fibrosis (Higashikuni et al., 2013; Thakur et al., 2014). Autocrine CGRP can inhibit TGF β 1-induced activation of the NF- κ B signal pathway, and activation of TRPA1 alleviated cardiac fibrosis by stimulating synthesis and production of CGRP in cardiac tissues (Li et al., 2020).

4.4. Effects on antigen presenting cells (APCs)

4.4.1. LCs

LCs are dendritic APCs in the epidermis. They are the sole APC in the epidermis in steady-state conditions (Merad et al., 2002). It has been believed that LCs are potent APCs for induction of effector immune responses. However, most experiments in this regard were performed *ex vivo* where LCs underwent maturation. Now it appears that, depending on the circumstances, LCs can also serve to limit immunity (Kaplan 2010; Seneschal et al., 2012; Strandt et al., 2017; Kitashima et al., 2018).

LCs are found in the basal and supra-basal layer of the epidermis, and they can migrate from the skin to the draining lymph nodes during steady-state, without any inflammatory changes (Merad et al., 2002). With inflammation, the migration rate of LCs is increased (Rajesh et al., 2019). LCs play a pivotal role in immune surveillance, as they have a functional relationship with macrophages and DCs, and influence differentiation of Th17 and CD4⁺ follicular helper T cells, and responses of regulatory T cells, CD8⁺ T cells, and Th2 cells (Fujita et al., 2009).

CGRP plays an essential role in immunomodulation (Wang et al., 1992; Hosoi et al., 1993; Asahina et al., 1995; Fox et al., 1997; Torii et al., 1997) by regulating APCs and their capacity to express costimulatory molecules and inhibiting antigen presentation for generation of Th1 immunity while enhancing Th2-type immunity. CGRP upregulates production of IL-10 by LCs, PBMCs and macrophages (Fox et al., 1997; Ding et al., 2008; Mikami et al., 2011). CGRP exposure of LCs *in vitro* prior to use for presenting antigen to responsive T cells led to an increased IL-4 production and a decreased interferon- γ release, consistent with inhibition of a Th1 response and enhancement of Th2-type immunity (Ding et al., 2008). CGRP also decreased production of the Th1 chemokines CXCL9 and CXCL10 stimulated by exposure of LCs to interferon- γ and induces release of the Th2 chemokines CCL17 and CCL22. Thus, CGRP favors Th2-type immunity in skin by at least 2 mechanisms.

4.4.2. Other types of DCs

CGRP inhibits lipopolysaccharide induction of CD80 and CD86 on macrophages and DCs (Bracci-Laudiero et al., 2002). These molecules are ligands for CD28, found on T cells and regulate their ability to develop a competent immune response (Fox et al., 1997; Assas et al., 2014). CGRP also physiologically regulates cytokine production from DCs *in vivo*; DCs from the draining lymph nodes of RAMP1-deficient mice (lacking intact CGRP receptor) showed a tendency to express a high level of IL-12, favoring a Th1 response. To prove the direct effect of CGRP on DCs in the ovalbumin (OVA)- induced delayed-type hypersensitivity (DTH) model, authors showed that footpad swelling, as well as the OVA-specific total IgG and Th-1 mediated IgG2a production, was significantly increased in OVA-immune mice who received RAMP1-deficient OVA-pulsed BMDCs compared to mice who received wild-type OVA-pulsed BMDCs (Mikami et al., 2014). CGRP also inhibits DC maturation and allergen-specific T cell responses, regulating allergic airway inflammation *in vivo* (Rochlitzer et al., 2011). Providing CGRP to sensitized and challenged mice resulted in the normalization of airway responsiveness to inhaled methacholine, used to induce airway inflammation and hyper-responsiveness (AHR) in the mouse model (Dakhama et al., 2002). This discovery suggests using CGRP for treating AHR. Also, CGRP participates in NF- κ B activation and induction of cAMP-responsive suppressor genes in immune cells, especially DCs (Assas et al., 2014), although in the presence of more potent inducers of NF- κ B, it inhibits NF- κ B activation in LCs and ECs (Holzmann 2013). CGRP can also down-regulate the expression of HLA-DR and CD86 by both mature and immature human DCs (Carucci et al., 2000).

4.5. Endothelial cells

CGRP can regulate the outcome of antigen presentation by LCs to T cells by acting on microvascular ECs (Ding et al., 2008). Th17-type T helper cells mediate inflammation and defend the host from invasion against many pathogens while inappropriate Th17 responses and IL-17A production have been linked to many chronic inflammatory conditions including psoriasis, and atopic dermatitis (Cesare et al., 2008; Dhingra and Guttman-Yassky 2014; Sugaya 2020). When primary murine dermal microvascular ECs (pDMECs) (Ding et al., 2016) were exposed to CGRP and co-cultured with LCs, responsive CD4⁺ T-cells and antigen, pDMECs treated with CGRP favored the production of IL-6 and IL-17A by responding T cells, while down-regulating production of IFN γ and IL-22. IL-22 used to be perceived as a significant product of Th17 cells, but it is now known to be also produced by activated Th1, natural killer cells, and gamma delta T-cells (Chien et al., 2014); most of it comes from Th22 cells (Fujita 2013). Further experiments proved that this phenomenon was not dependent on contact between pDMECs and LCs or responding T-cells, but, at least partly, is due to pDMEC production of IL-6. CGRP-treated pDMECs induced a higher proportion of CD4⁺ T-cells expressing intracellular IL-17A and increased IL-17A mRNA, whereas it decreased the proportion of CD4⁺ T cells expressing IFN- γ or IL-22 as well as mRNA levels for these cytokines (Ding et al., 2016). There was also an increase in levels of retinoic acid receptor-related orphan receptor gamma (ROR)- γ t mRNA associated with differentiation of Th17 cells, whereas T-bet (transcription factor in Th1 response) and GATA3 (transcription factor in Th2 response) expression was inhibited. BALB/c mice injected intradermally with CGRP or medium alone, followed by immunization at the injected site with the hapten dinitrofluorobenzene resulted in enhanced production of IL-17A with reduced production of IFN γ in cells from mice treated with CGRP compared to the medium control group upon non-specific stimulation of CD4⁺ T cells from skin-draining lymph nodes (Ding et al., 2016). CGRP also inhibits lipopolysaccharide-stimulated production of pro-inflammatory chemokines such as IL-8, chemokine CCL2, and chemokine CXCL1 by ECs (Huang et al., 2011). This may explain, in part, reports that systemic administration of CGRP inhibits non-immune inflammation induced by local or systemic administration of inflammatory agents (Ding et al.,

2007).

4.6. Direct effects on immune cells

CGRP and VIP have an additive inhibitory effect on T cell proliferation (Ottaway and Greenberg 1984; Teresi et al., 1996). α -CGRP and VIP, administered separately (combination studies not performed), significantly reduce murine splenocyte proliferation induced by the combination of phorbol-12-myristate-13-acetate (PMA) and the calcium ionophore A2387 as well as that of splenic purified CD4⁺ and CD8⁺ T cells (Teresi et al., 1996).

CGRP also regulates B cell behavior. Although CGRP gene transcript expression is almost absent in resting B cells, they were strongly expressed in activated B cells (Bracci-Laudiero et al., 2002). CGRP gene expression was induced by nerve growth factor (NGF), produced by B cells in an autocrine process; anti-NGF antibodies significantly reduced CGRP expression in both resting and activated B-cells. Also, physiological concentrations of CGRP inhibited pre-B cell responses to interleukin-7 (IL-7), preventing B cell development and colony formation (Fernandez et al., 2000). In vivo, CGRP induced a reduction of IL-7-responsive B-cell progenitors in the bone marrow (Schlomer et al., 2007). Furthermore, in peripheral blood mononuclear cells (PBMCs), monocyte adhesion and migration in vivo was influenced via chemoattraction and inflammation-mediated NO synthesis (Wiedermann et al., 2002), which is amplified by the expression and secretion of procalcitonin and CGRP that occurs post-adherence to ECs or plastic surfaces (Linscheid et al., 2004).

5. Ultraviolet radiation-induced immune suppression

Ultraviolet B (UVB, 280–320 nm) radiation regulates immune responses in animals and humans. UVB radiation induced CGRP release from nerve fibers in rat skin (Benrath et al., 1995), which subsequently induced MC release of TNF- α (Gillardon et al., 1995; Niizeki et al., 1997). Urocanic acid, derived from filaggrin catabolism, is abundant in skin, primarily as the trans isomer. Cis-urocanic acid (UCA), derived from formed by a trans-cis isomerization of trans-UCA following UVB exposure, also led to CGRP production (Kurimoto and Streilein 1992). CGRP may be involved in UVB-impaired induction of contact hypersensitivity (CHS), through CGRP release from sensory neurons, followed by release of MC TNF- α , which mediates suppressed CHS in some models (Niizeki et al., 1997). Pre-treatment of mice with a CGRP antagonist inhibited the cis-urocanic acid induction of suppression of CHS (Khalil et al., 2001). In addition, intradermal injection of CGRP induced tolerance to 2,4-dinitro-1-fluorobenzene (DNFB) in both normal and mast cell-deficient mice, and injection of a CGRP receptor antagonist, CGRP₈₋₃₇, into mouse skin subsequently exposed to acute, low-dose UVB radiation, partially prevented tolerance induced by pre-exposure to UVB radiation. A CGRP receptor antagonist applied topically to the irradiated site restored the normal induction of CHS if applied after UVB irradiation but before exposure to contact allergens (Kitazawa and Streilein 2000). A CGRP receptor antagonist applied topically to the irradiated site restored the normal induction of CHS, if applied after UVB irradiation but before exposure to contact allergens (Gillardon et al., 1995). Also, CGRP, detected in human Finn chamber skin samples, was significantly increased after UVB exposure, suggesting contribution to UVB-mediated immunosuppression in humans. In mice, UVB failed to inhibit CHS in sensory-nerve-depleted mice, demonstrating that neuropeptides are involved in this process (Garssen et al., 1998; Sleijffers et al., 2003). Also in mice, CGRP contributed to UVB-induced immune suppression by inducing hapten-specific tolerance via the release of immune suppressive cytokines such as IL-10 (Kitazawa and Streilein 2000). However, it is not clear whether CGRP uses this same mechanism in immunosuppression in

humans.

6. Relevance for inflammatory skin disorders

6.1. Psoriasis

Psoriasis is a chronic, multisystem inflammatory skin disease with a strong genetic predisposition and autoimmune pathogenic traits, characterized by hyperproliferation of keratinocytes (Saraceno et al., 2006), erythema, and pruritus, with cutaneous discomfort and pain. Interestingly, it is known that denervation improves or clears psoriasis and also plays a role in psoriatic arthritis (Dewing 1971; Omland and Gniadecki 2015; Zhu et al., 2016). Additionally, administration of lidocaine hydrochloride into psoriatic plaques was reported to induce significant improvement (Ostrowski et al., 2011). Accordingly, chemical denervation with injection of botulinum neurotoxin A (BoNT-A) into psoriatic lesions results in improvement or resolution of the lesions, including in inverse psoriasis (Mafong et al., 2002). BoNT-A acts by inhibiting neurotransmitter release by cleaving the SPAP25 protein, thus blocking acetylcholine release. It also inhibits CGRP and SP release (Rapp et al., 2006; Meng et al., 2007; Ward et al., 2012). Botox could also decrease plaque severity by decreasing SP- and CGRP-immunoreactive nerve expression and increasing epidermal nerve fiber (ENF) density (Aschenbeck et al., 2018).

Other data supports a role for neuropeptides in psoriasis. SP- and CGRP- containing neuropeptide nerve fibers are more dense in the psoriatic epidermis (Jiang et al., 1998). Blocking common sensory neurogenic mechanisms for TRPV1, TRPA1, and neuropeptides such as SP and CGRP, can inhibit certain spontaneous behaviors indicative of cutaneous discomfort in mice (Kodji et al., 2019). Imiquimod cream is a TLR 7/8 agonist used clinically to strengthen innate immunity to treat viral neoplasms of the skin, such as warts and other skin malignancies and pre-malignancies (Hemmi et al., 2002; Van Belle, de Heusch et al., 2012). Consistent, repeated application of 5% imiquimod skin to the dorsal skin of mice resulted in a psoriasis-like phenotype (Sakai et al., 2016). Mice with C57BL/6J background also exhibit a scratching phenotype, suggesting itch similar to human psoriasis (Swindell et al., 2017). Nociceptors also play a role in IL-23 -mediated imiquimod-induced skin inflammation. In the imiquimod-based mouse model of psoriasis, chemical denervation of TRPV1⁺ nociceptors or genetic deletion of Nav1.8⁺ neurons resulted in decreased skin pathology (Riol-Blanco et al., 2014). Dermal DCs were in proximity with sensory nerves in the dermis, and eliminating nociceptive response in mice led to reduced production of IL-23, IL-17, and the imiquimod-induced inflammation (Riol-Blanco et al., 2014).

There is further evidence from another murine model that the cutaneous nervous system and nerve-derived SP and CGRP play a role in psoriasis. Transecting the thoracic-level of cutaneous nerves at their entry site into dorsal skin of mice prevents a psoriatic phenotype (Ostrowski et al., 2011) in the KC-Tie2 murine model of psoriasiform skin disease, a phenotype based on engineered keratinocyte-specific expression of the angiopoietin receptor Tie2 (Wolfram et al., 2009). Most interestingly, in this model intradermal administration of an SP agonist to denervated skin corrected the loss of CD4⁺ cells and CD11c⁺ cells seen with denervation but did not correct the loss of acanthosis while intradermal administration of CGRP reversed the loss of acanthosis (sub-totally) and corrected CD4⁺ cell loss but did not affect the number of CD11c⁺ cells (Ostrowski et al., 2011).

Another study demonstrated that resolvin D3 (RvD3), a family member of the resolvins with anti-inflammatory and anti-pruritic effects through neuroimmune mechanisms, can reduce skin inflammation in the imiquimod murine model, perhaps by blocking TRPV1 activity via G protein-coupled receptor signaling and CGRP release from DRG neurons

(Sawada et al., 2018; Serhan and Levy 2018; Xu et al., 2018). Botulinum toxin B (BTX-B), when injected into mice with imiquimod-induced psoriasis-like dermatitis, also inhibited SP and CGRP release in the skin, potentially inhibiting nerve elongation, infiltration of immune cells, and IL-17 production, leading to improvement of psoriasis (Amalia et al., 2021).

Nociceptor-immune interactions also have significant contributions to inflammation. In psoriasis-like conditions, skin allergen-sensitized dendritic cells come in direct contact with afferent sensory neurons and activate them. In a study, *C. albicans* induced CGRP by stimulation of Nav1.8-positive nociceptors via the B-glucan receptor Dectin-1. This induction of CGRP is associated with TRPV1 and TRPA1 ion channels, as hindpaw B-glucan injection after Nav1.8-positive nociceptor deletion or in TRPV1/TRPA1 deficiency led to increased skeletal inflammation and impaired CGRP production (Maruyama et al., 2017). These findings show that nociceptors interact with DCs and regulate the IL-23-IL-17 pathway via TRPV1 and TRPA1 ion channels in the psoriasis like dermatitis model, particularly in the context of fungal osteoinflammation.

As discussed above, cutaneous neuropeptides can induce TRP activation and TRP channel activation leads to neurogenic inflammation in skin and pain in conditions involving arthritis.

(Fernandes et al., 2011; Kodji et al., 2019). In addition to psoriasis, cutaneous sensory nerves are involved in other skin conditions such as allergic contact dermatitis (mouse model) and pruritus (Prignano et al., 2009; Wilson et al., 2011; Liu et al., 2013; Therene et al., 2018). Topical capsaicin led to depletion of sensory neuropeptides with repeated application-efficient in minimizing both psoriasis-associated skin lesions as well as cutaneous discomfort, albeit with initial burning as a side-effect (Bernstein et al., 1986). Although psoriasis treatments generally improve pruritus, this does not always correlate with lesion regression (Prignano et al., 2009; Therene et al., 2018).

Through a study that involved stimulation of spinal cord synapses and activating spinal TRPA1 by pungent foods and products of lipid peroxidation, it was shown that TRPA1 receptors were a potential trigger for the release of CGRP in tissues that include mouse skin (Quallo et al., 2015). It was also recently shown that activating neuronal and nonneuronal TRPA1 receptors has a protective role in imiquimod-induced psoriasiform dermatitis in mice. The variation in outcome of the imiquimod-induced reaction in TRPA1 knockout mice, TRPV1 knockout mice, and TRPV1/TRPA1 double-knockout mice were observed, and it was proposed that imiquimod has TRPA1 agonist activity that exerts anti-inflammatory activity in the skin although pro-inflammatory TRPV1 activity was dominant (Kemeny et al., 2018). Another study showed further contribution of the TRPA1-sensory nerve pathway in cutaneous discomfort of psoriasis involving neuropeptide (CGRP, SP) dependent mechanisms through the imiquimod model (Kodji et al., 2019).

These findings demonstrate that the activation of TRP channels and the release of CGRP could play a significant role in the phenotypic expression of psoriasis. Most importantly, they suggest the possibility of a new locus for therapeutic manipulation.

6.2. Atopic dermatitis

Atopic dermatitis is a chronic inflammatory skin disorder manifested as eczematous skin eruptions with intense pruritus with persistent flares and remissions. The exact mechanisms and etiology of atopic dermatitis are not unclear, but there are multifactorial genetic and environmental components. Chronic inflammatory skin conditions, such as atopic dermatitis and psoriasis, share common features of increased neurotrophin expression and peptidergic nerve fibers, supporting a role for neurogenic inflammation (Peters 2012; Chen and Lyga 2014). CGRP can shift LCs toward Th2 responses by enhancing LC antigen presentation for Th2 responses and inhibiting presentation for the Th1 response. There is some evidence suggesting involvement of CGRP in atopic dermatitis (reviewed in Granstein et al., 2015). SP might also have a role in atopic

dermatitis; the NK1 antagonist aprepitant inhibited itch in atopic dermatitis mouse models and exhibited some efficacy in pruritus in humans (Stander et al., 2010). Hyperinnervation with increased SP- and CGRP-positive nerve fibers in the epidermis and papillary dermis, along with increased MC-nerve fiber contacts in lesional skin compared to non-lesional skin was found in AD (Ostlere et al., 1995; Jarvikallio et al., 2003). NGF levels were also increased in the plasma of patients with atopic dermatitis, which could be correlated with clinical severity and eosinophil counts (Yamaguchi et al., 2009). Phototherapy reduces the level of epidermal NGF and decreases epidermal hyperinnervation in patients with AD (Tominaga et al., 2009). In this regard, NGF can induce CGRP in sensory nerve cells (Horiuchi et al., 2005; Park et al., 2010). Although plasma levels of CGRP were not increased in AD patients, they were significantly higher in AD patients with intense pruritus compared to those without (Salomon and Baran 2008). Another study showed that CGRP biased immunity towards a Th2 pattern by upregulating IL-13 and HLA-DR expression in circulating cutaneous lymphocyte-associated antigen-positive CLA⁺ T cells in AD patients, while it did not in healthy controls (Antunez et al., 2009). CGRP also increased the IL-13/IFN γ ratio after co-culture, also suggesting an immunomodulatory role in AD.

6.3. Rosacea

Rosacea is a common cutaneous vascular disorder primarily affecting the face with redness, inflammation, frequently papules and pustules and occasionally edema. Triggering factors include stress, menopause, and alcohol consumption, as well as environmental factors such as extreme temperatures, excessive sun exposure, and food items such as spices and caffeine as well as temperature hot food or beverage (Crawford et al., 2004). Many patients experience flushing with burning or stinging. Although the pathophysiology of flushing remains unclear, neuropeptides are likely involved. By gene expression analysis, mRNA for several neuropeptides were upregulated in rosacea-CALCA (alpha CGRP), CALCB (beta CGRP), and TAC1 (SP) (Helfrich et al., 2015). Compared with control samples, the level of alpha CGRP was elevated almost 10-fold, beta CGRP was elevated 7-fold, and SP was elevated 28-fold in patients with the erythematotelangiectatic subtype of rosacea (ETR). CGRP likely contributes to flushing by vasodilation. Levels of alpha CGRP and SP were significantly increased in patients with ETR compared to patients with telangiectatic photoaging (TP). It is likely that neurogenic inflammatory processes are active in rosacea, as activation of TRP, as mentioned previously, results in release of vasoactive neuropeptides such as SP, CGRP, and VIP, which regulate local blood flow as well as induce MC degranulation resulting in elevated levels of pro-inflammatory cytokines (IL-1, IL-3, IL-8), chemokines (CCL2, CXCL9, CXCL10, CCL5, CXCL8) and TNF- α (Kulka et al., 2008; Gerber et al., 2011; Schwab et al., 2011; Helfrich et al., 2015).

6.4. Contact dermatitis

A study investigated the role of CGRP in established CHS, immediate immunologic reaction, and irritant contact dermatitis. CHS was elicited by a patch test with nickel sulfate 0.2%, 0.4%, and/or 0.8% in water in 19 nickel-allergic patients, and irritant contact dermatitis was induced by using benzalkonium chloride (1%) in water solution in 21 subjects. CGRP is present in free sensory nerve fibers in both the dermis and epidermis, surrounding blood vessels and hair follicles. CGRP influenced the sensation of itch and pain from the skin to the CNS via sensory c-fibers (Wallengren 1993). CGRP is expressed in approximately 45% of dorsal root ganglion neurons, mainly in small-diameter unmyelinated C-fibers (Sann and Pierau 1998; Ruscheweyh et al., 2007). As above, CGRP-positive nerve fibers are in close proximity to LCs in the epidermis and regulates their functions (Hosoi et al., 1993; Fox et al., 1997; Misery 1998). CGRP has been observed to regulate the antigen-presenting ability of the LC and to inhibit the induction phase of CHS in mice to a

Th1-dominant hapten (Asahina et al., 1995; Mikami et al., 2011).

With mechanical stress, sensory c-fibers are stimulated to release both CGRP and SP, and the interaction between these two factors help determine the physiologic outcome (Brain and Williams 1988; Wallengren and Wang 1993). However, there is contradicting evidence as to whether CGRP plays a role in the symptoms of irritant contact dermatitis, a more immediate inflammatory process than CHS. Whereas the aforementioned study (Wallengren and Wang 1993) failed to show that either CGRP or CGRP₈₋₃₇ has any significant effects on the pathophysiology of irritant contact dermatitis, other studies have reported that local administration of CGRP augmented irritant contact dermatitis from croton oil in mice (Gutwald et al., 1991), and that topical application of CGRP reduced irritant contact dermatitis from croton oil, arachidonic acid, and phorbol esters (Clementi et al., 1994). Perhaps CGRP plays a role in delayed inflammatory processes such as CHS, but has no effect on immediate immunologic reactions such as irritant contact dermatitis. However, interpretation is difficult as experiments differed in design and neuropeptide dose.

6.5. *Candida* skin invasion

Nociceptors are important in mediating protective skin immunity against *Candida albicans*. *Candida* invasion of murine skin triggers nociceptor neurons to release CGRP in the dermis, which then induces IL-23 production by CD301b⁺ dermal DCs. IL-23, in turn, stimulates gamma-

delta T cells to produce IL-17A and IL-22, resulting in host resistance to the infection (Kashem et al., 2015). Repeated injections of CGRP during infection in nociceptor-deficient mice restored the defense against *Candida albicans* (Kashem et al., 2015). This circuit is similar to that described for the imiquimod murine model of psoriasiform dermatitis (Riol-Blanco et al., 2014). Perhaps CGRP is the factor released by nerves that induce dermal DCs to produce IL-23 in that model.

7. Conclusion

There is abundant evidence demonstrating roles for CGRP in the functional relationship between the nervous and immune systems. Many studies demonstrate that CGRP regulates various inflammatory processes in human skin, as summarized in Fig. 1. This review highlights the importance of CGRP immunoregulation and presents emerging clinical and preclinical evidence suggesting CGRP's putative role in various cutaneous disorders, as summarized in Fig. 2. As described in the review, nociceptors, as a specialized subset of sensory neurons that respond to various noxious stimuli, act as primary responders to damaged tissue or pathogens. A recent study shows that nociceptors can even mediate the immune response to bacterial pathogens and microbial products during infection, as they can release neuropeptides such as CGRP to modulate appropriate inflammatory responses. In a mouse model of necrotizing fasciitis, it was demonstrated that CGRP inhibits neutrophilic killing of *Streptococcus pyogenes* (Pinho-Ribeiro et al., 2018). Although beyond

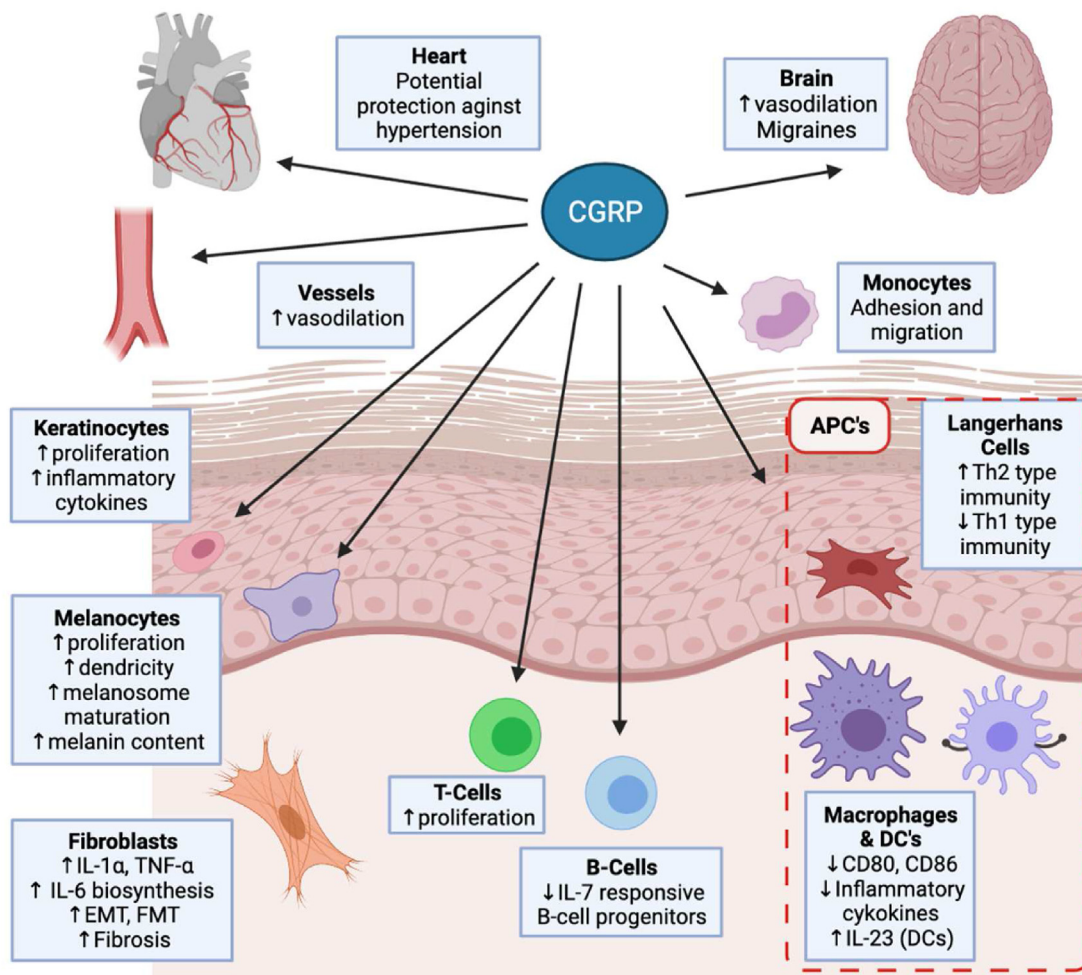


Fig. 1. Effect of CGRP on the heart, the brain, the skin and vessels. CGRP impacts monocytes, macrophages, LCs, dendritic cells, endothelial cells, vascular smooth muscle and neutrophils, along with epidermal cells such as keratinocytes, melanocytes, and fibroblasts, likely contributing to a number of disease states, as described in the text. EMT, epithelial-mesenchymal transition; FMT, fibroblast to myofibroblast transdifferentiation; APC, antigen presenting cell; LC, Langerhans Cell; DC, dendritic cell. Created with BioRender.com. (single column fitting image).

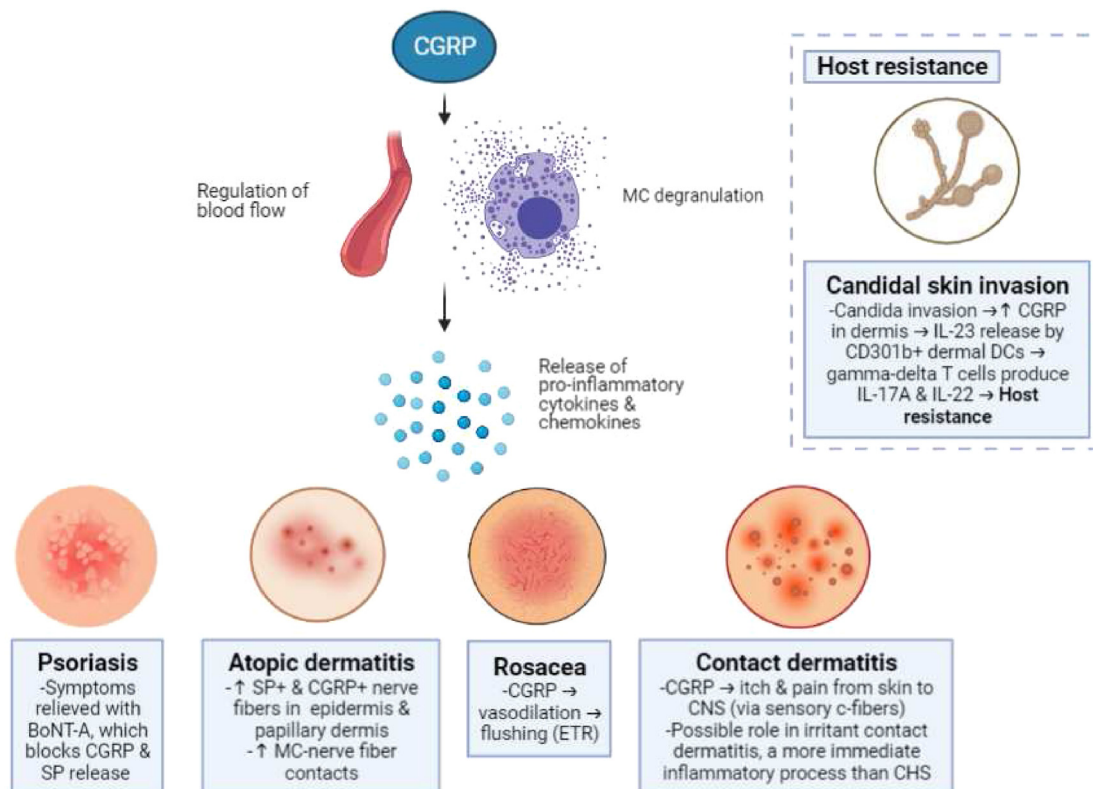


Fig. 2. Probable Roles of CGRP in inflammatory skin disorders. TRPA1, transient receptor potential ankyrin 1; TRPV1, transient receptor potential vanilloid 1; CGRP, calcitonin gene-related peptide; MC, mast cell; ETR, erythematotelangiectatic subtype of rosacea; CNS, central nervous system; CHS, contact hypersensitivity; DC, dendritic cells; BoNT-A, botulinum neurotoxin A. Created with BioRender.com. (single column fitting image).

the scope of our current review, the area of neuropeptide actions on anti-microbial immunity is a new and important area of research. Future studies will provide further insights into the etiology and pathomechanisms of psoriasis, atopic dermatitis, rosacea, contact dermatitis, and other inflammatory processes in the skin. Pharmacodynamic models are needed to evaluate CGRP receptor antagonists and agonists in vivo for actions in inflammatory skin disorders. The potential for an effective, specific cutaneous anti-inflammatory drug lacking significant side-effects is great. Topical versions of CGRP antagonists or agonists, if effective, would hold particular promise for novel and possibly safer approaches to the treatment of inflammatory cutaneous disorders.

Declaration of competing interest

RDG is on the scientific advisory boards of Elysium Health and Hoth Therapeutics. He is also on the Industry Advisory Board of Gore Range Capital and has research agreements with Leo Pharma, the Leo Foundation, Galderma, Pfizer and Elysium Health.

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