REVIEW

TRPV1 and SP: key elements for sepsis outcome?

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Sensory neurons play important roles in many disorders, including inflammatory diseases, such as sepsis. Sepsis is a potentially lethal systemic inflammatory reaction to a local bacterial infection, affecting thousands of patients annually. Although associated with a high mortality rate, sepsis outcome depends on the severity of systemic inflammation, which can be directly influenced by several factors, including the immune response of the patient. Currently, there is a lack of effective drugs to treat sepsis, and thus there is a need to develop new drugs to improve sepsis outcome. Several mediators involved in the formation of sepsis have now been identified, but the mechanisms underlying the pathology remain poorly understood. The transient receptor potential vanilloid 1 (TRPV1) receptor and the neuropeptide substance P (SP) have recently been demonstrated as important targets for sepsis and are located on sensory neurones and non-neuronal cells. Herein, we highlight and review the importance of sensory neurones for the modulation of sepsis, with specific focus on recent findings relating to TRPV1 and SP, with their distinct abilities to alter the transition from local to systemic inflammation and also modify the overall sepsis outcome. We also emphasize the protective role of TRPV1 in this context.

LINKED ARTICLES

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Abbreviations

CBS, cystathionine beta-synthase; CGRP, calcitonin gene related peptide; CLP, cecal ligation and puncture; CSE, cystathionine γ -lyase; ICAM-1, intercellular adhesion molecule 1; IFN, interferon; IL-1 β , IL-1 beta; IL-6, IL 6; KO, knock-out; LTB₄, leukotriene B₄; MCP-1, monocyte chemotactic protein 1; MIP-2, macrophage inflammatory protein 2; NK, neurokinin; NK₁₋₃, NK receptor subtype 1–3; NKA, neurokinin A; NKB, neurokinin B; NPY, neuropeptide Y; PIP₂, phosphatidylinositol 4,5-bisphosphate; PPT1, preprotachykinin 1 protein; PPT2, preprotachykinin 2 protein; RANTES, regulated upon activation, normal T-cell expressed, and secreted; SP, substance P; TAC1, tachykinin 1 gene; TAC2, tachykinin 2 gene; TAC3, tachykinin 3 gene; TLR, toll-like receptor; TRP, transient receptor potential; TRPA, transient receptor potential ankyrin; TRPC, transient receptor potential canonical; TRPM, transient receptor potential melastatin; TRPML, transient receptor potential mucolipin; TRPN, transient receptor potential NOMPC; TRPP, transient receptor potential polycystin; TRPV, transient receptor potential vanilloid; WT, Wild Type

Introduction

In the Western world, sepsis continues to be a source of significant mortality, being within the top 10 causes of death (Lever and Mackenzie, 2007; Coelho and Martins, 2012). Research into sepsis continues to be popular within scientific communities hoping to gain a better understanding of an exceedingly complex syndrome and develop potential therapeutics. Among the many pathways underlying sepsis, we highlight the importance of sensory neurones. Recent

findings demonstrate the ability of TRPV1 to modulation of sepsis, which is associated with its ability to trigger neuropeptide release when stimulated. Such findings have augmented the interest in the role of sensory neurones and neuropeptides in this disorder. In light of these findings, we provide a summary of the current clinical challenges in sepsis, followed by a review of two mediators of particular interest, the TRPV1 receptor and the neuropeptide SP, which have demonstrated both protective and detrimental effects respectively in animal models of sepsis.

Clinical aspects of sepsis

Sepsis comprises a complex systemic response, generally initiated by infection. Local infection can originate from any part of the body, including the peritoneal cavity (Hernández-Palazón *et al.*, 2012). Without treatment, sepsis can rapidly lead to multi-organ dysfunction, commonly including the lungs, kidney, circulatory system, liver and brain. Sepsis comprises several phases, starting with an overwhelming systemic pro-inflammatory response, followed by an immune-suppressive phase, with both being damaging to the host (Giamarellos-Bourboulis and Raftogiannis, 2012). It has a complex and heterogeneous pathophysiology, which is still under intensive study; however, over-exuberant production of both pro- and anti-inflammatory mediators are thought to play equally damaging roles. Symptoms and clinical severity of sepsis can vary widely among individuals, leading to a 'spectrum' of illness that can be difficult to define and treat (Lever and MacKenzie, 2007). Symptoms include fever, tachycardia and haemodynamic shock, which can be fatal and lead to multi-organ failure if not treated rapidly. Several biomarkers of sepsis severity and outcome have been identified by the scientific community, with only C-reactive protein and procalcitonin being commonly used in a clinical setting (Lichtenstern *et al.*, 2012). The lack of a specific marker is partially due to the heterogeneity of the condition, likely stemming from differences in bacterial strain and host physiology, importantly including the patient's immune response. Sepsis continues to be a major contributor to mortality in developed countries, with increasing incidence and a high mortality, largely due to the currently poor selection of treatments available and difficulties in the diagnosis of affected organ systems and causative bacterial strain. A recent review of the clinical biomarkers and diagnosis of sepsis is provided by Coelho and Martins (2012). Sepsis can be divided into three to four broad and overlapping conditions (Lever and Mackenzie, 2007). The first stage is septic inflammation and sepsis, characterized by fever/hypothermia, tachycardia, increased plasma coagulation markers, glucose, C-reactive protein, creatinine and pro-calcitonin, among other markers. Inflammatory markers are often quite general and some, such as white blood cell counts, can be either raised or depleted, hindering differential diagnosis. This stage is not generally associated with mortality but demands rapid identification of the causative bacterial strain and intravenous antibacterial treatment to prevent sepsis progression. Progression of severe sepsis occurs where organ dysfunction is evident, due to the uncontrolled pro-inflammatory environment. This can later turn into septic shock, associated with hypoperfusion and poor immune function. These latter stages are associated with significant mortality. Treatment options for sepsis are currently limited to addressing the bacterial infection and short-term corrections of organ failure with medical interventions. Significant efforts by the scientific community have yet to lead to targeted treatment strategies for sepsis; however, improvements in diagnostic tests and criteria may lead to better clinical handling of sepsis. Identification of important biochemical and molecular pathways in sepsis will now be key in the development of effective treatments. Several studies have demonstrated the ability of sensory neurones

and neuropeptides to modify sepsis pathogenesis, suggesting that they may be potential therapeutic targets for the future.

Sensory neurones

Sensory neurones comprise small diameter C-fibre and A δ fibres. They possess slow action potential conduction, being non-myelinated or sparsely myelinated respectively. Virtually all tissues are innervated with sensory neurones deriving from dorsal root ganglia in the spinal cord or from cranial nerves, such as the vagus nerve. Sensory nerves are predominantly responsible for the detection of noxious stimuli, expressing a range of receptors that can be activated by harmful substances, such as irritants (for review, see: Fernandes *et al.*, 2012a). Upon activation they show dual functionality, conducting the danger signal to higher centres, often associated with the feeling of pain, and also antidromically releasing inflammation modulating substances into the tissue (Sann and Pierau, 1998). Several of these substances are active peptides – termed neuropeptides (Brain and Cox, 2006).

Sensory neurones are involved in a very diverse range of activities, spanning from development, to physiological maintenance of homeostasis, to disease pathogenesis and resolution (for review, see Alawi and Keeble, 2010). Their wide innervation and ability to release active substances into the tissue upon stimulation makes them uniquely suited to modulation of the tissue-specific microenvironment, whereas their link to the central nervous system can bring about additional systemic effects. Determination of their reactivity depends solely on their expression of surface receptors. An ever-increasing selection of receptors have been demonstrated on sensory neurones, including toll-like receptors (TLR) (Ochoa-Cortes *et al.*, 2010), leukotriene receptors (Andoh and Kuraishi, 2005), neuropeptide receptors (including that for SP) (Andoh *et al.*, 1996), complement receptors (Jang *et al.*, 2010) and prostaglandin receptors (Durrenberger *et al.*, 2006) – all demonstrating the potential for recruitment of sensory neurones in to active inflammatory disorders. In this context, TRPV1 occupies a very special niche, integrating neuronal and non-neuronal inflammatory pathways that play roles in sepsis.

Transient receptor potential (TRP) channels

TRP channels comprise a large superfamily of membrane expressed cation channels. To date, there are more than 30 members, divided into seven subfamilies: the TRP 'canonical' (TRPC) family, the TRP 'melastatin' (TRPM) family, the TRP 'vanilloid' (TRPV) family, the TRP 'polycystin' (TRPP) family, the TRP 'mucolipin' (TRPML) family, the TRP 'ankyrin' (TRPA) family and finally, the TRP 'NOMPC' (TRPN) family (Pedersen *et al.*, 2005; Premkumar and Abooj, 2012). Each of these families contains a number of numerically named receptors, in the order of their date of identification. All TRP channels pass cations upon activation, producing transduction in response to external stimuli; however, differential

agonist profiles and wide expression patterns provide a distinct functional niche for each TRP channel. Several of the TRP channels are expressed on sensory neurones, including TRPV1, TRPA1 and TRPM8, which are well-known irritant receptors but are also activated by changes in temperature and products of inflammation (Huang *et al.*, 2006b).

TRPV1

TRPV1 is likely to be the most well-studied TRP channel. For many years, sensory neurones were known to be selectively activated by capsaicin, a pungent substance found in varying levels within chilli peppers. The ability for capsaicin to activate, and subsequently desensitize sensory neurones was used as a valuable tool to investigate the actions of these nerves. Furthermore, administration of high doses of capsaicin in neonates has been used as a neurotoxin to selectively ablate sensory neurones (Wall, 1982). Studies had previously suggested the presence of a capsaicin receptor on nociceptive neurones (Szolcsányi and Jancsó-Gábor, 1975); however, it was not until 1997 that Caterina *et al.* (Caterina *et al.*, 1997) identified and published its molecular identity, then known as VR1. The receptor was subsequently identified in humans by Hayes *et al.* (2000). TRPV1 has a structure similar to other TRP channels, comprising of six transmembrane domains, with intracellular amino and carboxy terminals. A short hydrophobic sequence between transmembrane domains 5 and 6 forms a pore loop. When four TRPV1 subunits come together, the resultant tetramer forms a non-selective cation channel (Kuzhikandathil *et al.*, 2001). Passage of cations through this channel, particularly calcium, forms the basis of TRPV1 intracellular signalling. A recent review by Ho *et al.* (2012) describes the intracellular signalling of TRPV1 and how this can lead to further receptor sensitization. Both amino and carboxy terminals of TRPV1 comprise sites allowing channel modulation by various substances, including kinases (Zhang *et al.*, 2008), phosphatidylinositol 4,5-bisphosphate (PIP₂) (Ufret-Vincenty *et al.*, 2011) and calcium cations (Samways and Egan, 2011). Transmembrane domains 3 and 4 are thought to hold the capsaicin binding site (Gavva *et al.*, 2004). In 2000, the first TRPV1 knock-out (KO) strains were reported by Davis *et al.* and Caterina *et al.* Davis *et al.* (2000) presented mice lacking TRPV1 transmembrane domains 2–4, whereas Caterina *et al.* (2000) removed part of transmembrane domain 5, alongside the *p*-loop and sixth transmembrane domain. Both models showed loss of functional TRPV1, resulting in reduced neuronal sensitivity to vanilloids, such as capsaicin, heat and acid. TRPV1KO mice have now become a central component of sensory neurone research and are readily available in a wide range of institutions and also commercially.

TRPV1 is a polymodal receptor, and a growing number of endogenous and exogenous agonists for TRPV1 have now been identified (Fernandes *et al.*, 2012a). Endogenous agonists include endovanilloids such as anandamide (Caterina *et al.*, 2000), lipoxygenase products such as leukotriene B₄ (LTB₄) (Hwang *et al.*, 2000), and reactive oxygen species (hydrogen peroxide, H₂O₂; Keeble *et al.*, 2009). TRPV1 can also be sensitized by several endogenous mediators, reducing its activation threshold. These mediators can modulate

TRPV1 via their own receptors which are co-expressed on the sensory neurone. This includes prostaglandin E₂ (PGE₂), bradykinin and nerve growth factor, among many others (see review by Huang *et al.*, 2006a). Interestingly, several of these mediators also play an active role in sepsis (Table 1). Sensitization mechanisms often include increases the activity of protein kinase A or C (Zhang *et al.*, 2008) and can induce activation of TRPV1 in a physiological tissue environment.

Since the identification of the TRPV1 receptor in sensory neurones (mainly in peptidergic neurons), several other tissues have been shown to express the receptor. These include other neurones, such as those in the central nervous system, where TRPV1 has been identified in neurones of the substantia nigra, hippocampus, hypothalamus, locus coeruleus and cortex (Mezey *et al.*, 2000). However, the role TRPV1 plays in these centres is not yet clear. TRPV1 has also shown varying levels of expression in a diverse array of non-neuronal tissues, including smooth muscle, bladder urothelium, endothelial cells, leukocytes, pancreatic β -cells, lymphocytes, liver and keratinocytes (see recent review by Fernandes *et al.*, 2012a). In all tissue types, activation of TRPV1 leads to influx of cations (Tominaga *et al.*, 1998) and leads to cell-specific intracellular transduction and a variety of cellular responses. With all these expression sites in mind, the complexity of actions attributed to TRPV1 is potentially huge. However, the site of predominant expression remains the sensory neurone, where the strongest of TRPV1-mediated actions are attributed. On the sensory nerve, activation of TRPV1 is firmly associated with the release of neuropeptides and the formation of neurogenic inflammation in the surrounding tissue. To date, more than 100 neuropeptides have been identified in a neuropeptide database at <http://www.neuropeptides.nl>, each with unique activity on cells, both resident and recruited to the tissue. The two classical neuropeptides released upon TRPV1 activation are SP and calcitonin gene related peptide (CGRP) (Lin *et al.*, 2007). Classically, during acute inflammation, both of these neuropeptides are considered pro-inflammatory, acting via receptors on the microvasculature to induce plasma extravasation and vasodilatation respectively. Together they also act to increase recruitment of leukocytes to the tissue (Holzer, 1998). However, in a more physiological setting, release of these neuropeptides can have important roles in homeostasis, for example in the control of glomerular filtration in the kidney (Li and Wang, 2008). In the context of more chronic or systemic inflammation, including sepsis, the plasma level of neuropeptides can increase, introducing another distinct layer to their actions (Beer *et al.*, 2002).

TRPV1 activation is closely allied with the pro-inflammatory components of several diseases, including rheumatoid arthritis (Russell *et al.*, 2009), airway and gastrointestinal diseases (Pan *et al.*, 2010; Delescluse *et al.*, 2012), and also painful conditions arising as a consequence of cancer (Lautner *et al.*, 2011), musculoskeletal inflammation (Ro *et al.*, 2009) and diabetic neuropathy (Hong and Wiley, 2005). These findings have led to the development of several TRPV1 antagonists for clinical use (Voight and Kort, 2010); however, finding a selective antagonist with minor side effects has been challenging. Capsazepine has been used for some time as a reversible, competitive TRPV1 antagonist, reversing inflammatory and neuropathic pain in animal

Table 1

Endogenous activators of TRPV1 and their role in sepsis

Endogenous TRPV1 activators released in sepsis	Role in sepsis progression
Direct activators	
Anandamide (Zygmunt <i>et al.</i> , 1999; Smart <i>et al.</i> , 2000)	Anandamide mediates LPS-induced NO release (Vercelli <i>et al.</i> , 2009) and hypotension in septic shock induced by LPS (Varga <i>et al.</i> , 1998; Bátkai <i>et al.</i> , 2004). The anandamide antagonist AM281 reduces mortality in rats with CLP-induced sepsis (Kadoi <i>et al.</i> , 2005).
Lipoxygenase products (e.g. LTB ₄) (Hwang <i>et al.</i> , 2000)	LTB ₄ receptor blockade reduces NO, increases bacterial load and reduces survival in mice with sepsis caused by CLP (Rios-Santos <i>et al.</i> , 2003).
ROS (e.g. H ₂ O ₂) (Keeble <i>et al.</i> , 2009)	Increased levels of H ₂ O ₂ are produced so the phagocytes are able to kill pathogens (Henricks <i>et al.</i> , 1986; Mayer, 1998)
Endogenous modulators (via activation of intracellular pathways)	
Bradykinin (Chuang <i>et al.</i> , 2001)	Increased circulating levels of kallikrein are present in patients with early sepsis and their levels are correlated with sepsis severity (Asmis <i>et al.</i> , 2008)
PAR-2 agonists (Amadesi <i>et al.</i> , 2004)	The role of PAR-2 in sepsis is rather controversial. Pawlinski and Mackman (2004) demonstrated that PAR-2 KO mice exhibited reduced lipopolysaccharide-induced interleukin-6 expression and increased survival. On the other hand, Kazerani <i>et al.</i> (2004) suggested that PAR-2 activation does not contribute to LPS-induced multi-organ dysfunction. Similarly, it was suggested that PAR-2 inhibition alone does not affect inflammation or survival in LPS-treated mice, but also requires thrombin inhibition.
PGE ₂ (Schnitzler <i>et al.</i> , 2008)	PGE ₂ is released from liver and peritoneal macrophages obtained from mice with CLP-induced sepsis (Ayala and Chaudry, 1996). In a similar model, PGE ₂ treatment increased survival in CLP-septic mice (Nicolette <i>et al.</i> , 2008)
NGF (Chuang <i>et al.</i> , 2001)	LPS-treated human macrophages overexpress NGF and its receptors (Caroleo <i>et al.</i> , 2001). Similarly, NGF is up-regulated in human dendritic cells challenged with LPS (Noga <i>et al.</i> , 2008). In addition, NGF attenuates neuronal death following LPS treatment (Ansari <i>et al.</i> , 2011).

Several TRPV1 activators are produced endogenously during sepsis and may modulate the progression of the condition. Some of these are detailed in the table.

models (Walker *et al.*, 2003). However, in 2004, Gunthorpe *et al.* published the development of a more selective and potent TRPV1 antagonist named SB366791, which improves on capsaizepine's poor selectivity profile and ability to block TRPV1 activation by only some modalities (Gunthorpe *et al.*, 2004). Identification of TRPV1 antagonists continues to be of great interest to academia and industry, but discussions of these stepwise advances are beyond the scope of this review. Several of the clinically developed antagonists have entered clinical trials but have shown potentially dangerous side effects including hyperthermia and insensitivity to noxious heat (see review of 2008 and 2009 patent applications for TRPV1 antagonists by Voight and Kort, 2010 and literature review by Gavva, 2008). Current basic research utilizes a range of TRPV1 antagonists, including AMG 9810, BCTC and SB705498 (Gavva *et al.*, 2005; Tékus *et al.*, 2010), which display varying pharmacokinetic and pharmacodynamics characteristics.

There are also growing reports of protective effects of TRPV1 activity in several diseases, including ischaemia-reperfusion injury (Huang *et al.*, 2009), hypertension (Yang *et al.*, 2010) and sepsis (Fernandes *et al.*, 2012b). This paradoxical role of TRPV1 has been reviewed recently by Alawi and Keeble (2010). These findings, combined with the increasing reports of non-neuronal TRPV1 expression,

demand us to take a step back and examine the consequences of TRPV1 antagonizing drugs. Sustained efforts to expand the research field have provided an impressive array of experimental tools to investigate the role of TRPV1 activity in both physiological and pathological settings. These tools have also been important in investigating the role of TRPV1 in sepsis.

TRPV1 and its role in sepsis

A role for TRPV1 has been suggested in sepsis. The expression and suggested function of TRPV1 in organs relevant to sepsis is summarized in Table 2. The first study demonstrating the involvement of this receptor in sepsis was conducted in rats, where pre-treatment with the TRPV1 agonist capsaicin increased survival (Bryant *et al.*, 2003). Lipopolysaccharide (LPS)-induced fever was also shown to be reduced in rats pre-treated with capsaicin (Romanovsky, 2004). However, it is important to consider that capsaicin would initially activate TRPV1 but then desensitize the neuronal fibres, leading to a loss of signalling mediated by TRPV1 and many other neuronal receptors, which may have distinct roles in the response to sepsis. These would include other TRP channels (Almeida *et al.*, 2006; Konno *et al.*, 2012), neuropeptides (Beer *et al.*, 2002; Westphal *et al.*, 2006; Neunaber *et al.*, 2011), ghrelin

Table 2

The expression and functional relevance of TRPV1, SP and NK receptors during abdominal sepsis

Tissue	Relevance in abdominal sepsis	TRPV1 expression	SP expression	NK receptor expression
Immune cells of the peritoneal cavity	Resident and infiltrating inflammatory cells manage the initial bacterial load	<ul style="list-style-type: none"> • Lymphocytes (Saunders <i>et al.</i>, 2007) • Macrophages (Rogers <i>et al.</i>, 2006; Fernandes <i>et al.</i>, 2012b) <p><i>Function</i></p> <ul style="list-style-type: none"> → Phagocytosis, thus control of bacterial load (Guptill <i>et al.</i>, 2011; Fernandes <i>et al.</i>, 2012b). → Mediator release (Fernandes <i>et al.</i>, 2012b). 	<ul style="list-style-type: none"> • Lymphocytes (Cantalupo <i>et al.</i>, 2008) • Macrophages (Ho <i>et al.</i>, 1997) • Neutrophils (Tuncer <i>et al.</i>, 2004) <p><i>Function</i></p> <ul style="list-style-type: none"> → Bacterial phagocytosis (Fernandes <i>et al.</i>, 2012b). → Activation of immune cells (Katsanos <i>et al.</i>, 2008). → Inflammatory mediator release (Sipka <i>et al.</i>, 2010). 	<ul style="list-style-type: none"> • Lymphocytes (Orsal <i>et al.</i>, 2006; Kitamura <i>et al.</i>, 2012) • Macrophages (Fernandes <i>et al.</i>, 2012b) • Mast cells (Okada <i>et al.</i>, 1999) • Neutrophils (Gallicchio <i>et al.</i>, 2009) <p><i>Function</i></p> <ul style="list-style-type: none"> → Release of inflammatory mediators (Foreman <i>et al.</i>, 1983; Katsanos <i>et al.</i>, 2008). → Regulation of apoptosis by NK₁ (Fernandes <i>et al.</i>, 2012b).
Intestine	Gut movement reduces bacterial growth	<ul style="list-style-type: none"> • Sensory neurones (Zhang <i>et al.</i>, 2004) <p><i>Function</i></p> <ul style="list-style-type: none"> → Modulation of neuropeptide release and muscle tone (Matsumoto <i>et al.</i>, 2011). → Potential regulation of bacterial translocation in abdominal sepsis. 	<ul style="list-style-type: none"> • Sensory neurones (Höckfelt <i>et al.</i>, 2001) <p><i>Function</i></p> <ul style="list-style-type: none"> → SP expression is reduced in the gut following peritonitis (Jacob <i>et al.</i>, 2007). → Potential regulation of bacterial translocation and growth in abdominal sepsis. 	<ul style="list-style-type: none"> • Expression of NK₁₋₃ on several cell types (Holzer and Holzer-Petsche, 1997; Improta and Broccardo, 2006). <p><i>Function</i></p> <ul style="list-style-type: none"> → Facilitation of gut peristalsis (Holzer and Holzer-Petsche, 1997; Höckfelt <i>et al.</i>, 2001). → Potential regulation of bacteria translocation and growth in abdominal sepsis.
Vasculature	Plays an important role in sepsis related hypotension	<ul style="list-style-type: none"> • Smooth muscle (Kark <i>et al.</i>, 2008) • Endothelial cells (Ching <i>et al.</i>, 2011) <p><i>Function</i></p> <ul style="list-style-type: none"> → Vessel contraction (Kark <i>et al.</i>, 2008). → Vessel dilation (Ching <i>et al.</i>, 2011). → Protection from hypotension (Clark <i>et al.</i>, 2007; Fernandes <i>et al.</i>, 2012b). 	<ul style="list-style-type: none"> • Sensory neurones innervating blood vessels (Höckfelt <i>et al.</i>, 2001) <p><i>Function</i></p> <ul style="list-style-type: none"> → Increased circulating levels of SP are associated with negative consequences on sepsis outcome (Beer <i>et al.</i>, 2002). → Vessel dilation, vascular permeability and migration (Nakagawa <i>et al.</i>, 1995; Mechiche <i>et al.</i>, 2003). 	<ul style="list-style-type: none"> • Vascular smooth muscle (NK₁) • Endothelial cells (NK₁) <p><i>Function</i></p> <ul style="list-style-type: none"> → Vessel contraction to maintain myogenic tone (Scotland <i>et al.</i>, 2004). → Vessel dilation and vascular permeability (Mechiche <i>et al.</i>, 2003). → Up-regulation of adhesion molecules and leukocyte migration (Nakagawa <i>et al.</i>, 1995).
Lungs	A key site of organ failure	<ul style="list-style-type: none"> • Sensory neurones (Dinh <i>et al.</i>, 2004) <p><i>Function</i></p> <ul style="list-style-type: none"> → Mediates neuropeptide release, potential lung oedema and bronchoconstriction (Jia and Lee, 2007). → Reduction of lung function. 	<ul style="list-style-type: none"> • Autonomic and sensory neurones innervating respiratory tracts (Dinh <i>et al.</i>, 2004; Joachim <i>et al.</i>, 2006). <p><i>Function</i></p> <ul style="list-style-type: none"> → Preprotachykinin gene deletion protects against lung injury (Puneet <i>et al.</i>, 2006) and mortality (Hegde <i>et al.</i>, 2010) in sepsis. 	<ul style="list-style-type: none"> • Smooth muscle cells (NK₁ and NK₂) • Endothelial cells (NK₁) <p><i>Function</i></p> <ul style="list-style-type: none"> → Bronchoconstriction (Murai <i>et al.</i>, 1992). → Lung oedema (Helyes <i>et al.</i>, 2010).
Liver	A key site of organ failure	<ul style="list-style-type: none"> • Hepatocytes (Rychkov and Barritt, 2011). • Sensory neurones (Miao <i>et al.</i>, 2008) <p><i>Function</i></p> <ul style="list-style-type: none"> → Possible role on liver failure? 	<ul style="list-style-type: none"> • Sensory neurones innervating the liver (Fehér <i>et al.</i>, 1992). <p><i>Function</i></p> <ul style="list-style-type: none"> → Possible role on liver failure? 	<ul style="list-style-type: none"> • Liver bile duct epithelium (Glaser <i>et al.</i>, 2011) <p><i>Function</i></p> <ul style="list-style-type: none"> → Possible role on liver failure?

Primary local infection in the abdominal cavity is common in sepsis. This principle forms the basis of many experimental models. TRPV1, SP and NK receptors are expressed on a variety of cells/tissues that are important for the transition from local infection to systemic infection – forming sepsis. They also play a role in multiple organ damage, contributing to sepsis lethality. This table highlights the expression and relevant function of these mediators in several organs which play a key role in regulating the pathogenesis and outcome of sepsis. Relevant references are given within the table.

(Cheyuo *et al.*, 2012) and NO (Berg *et al.*, 2011), amongst others. Subsequently, the protective role of TRPV1 in sepsis was confirmed in experiments using TRPV1KO mice. It has since been shown that TRPV1 is an essential component in the inflammatory response to bacterial infection (Clark *et al.*, 2007; Guptill *et al.*, 2011; Fernandes *et al.*, 2012b). TRPV1KO mice with LPS-induced sepsis exhibited increased hypotension and hypothermia compared with WT controls (Clark *et al.*, 2007). The same study also showed that TRPV1KO mice treated with LPS presented with increased levels of TNF α and nitrative stress in their peritoneal lavage fluid in addition to marked liver failure compared with WT mice, denoted by the raised plasma levels of aspartate-amino transferase. Although this study suggested a lethal outcome for sepsis in the absence of TRPV1, in 2008, Wang and collaborators demonstrated a greater hypotension and diminished survival in septic WT mice pre-treated with the TRPV1 antagonist capsazepine. These findings were also consistent in the more physiologically relevant sepsis model of cecal ligation and puncture (CLP), where TRPV1KO mice exhibited increased mortality when compared with septic WT mice (Guptill *et al.*, 2011). Similarly, prolonged treatment with capsazepine or the selective TRPV1 antagonist SB366791 has been shown to cause increased organ failure (Fernandes *et al.*, 2012b) and mortality in septic WT mice (Guptill *et al.*, 2011). Conversely, some detrimental findings have been described, as Iida *et al.* (2005) showed that TRPV1KO mice with LPS-induced sepsis presented with reduced late phase fever compared with wild type (WT) counterparts. The mechanisms underlying this response were yet to be clarified, as are the key differences from other studies, which have generally resulted in detrimental effects of TRPV1KO in mouse models of sepsis.

Although increasing evidence suggests TRPV1 is a protective receptor in response to infectious stimuli, little is known about the underlying mechanisms. In fact, TRPV1 and TLR4 receptors are found co-localized in human capsaicin-sensitive trigeminal sensory nerves (Wadachi and Hargreaves, 2006), suggesting that afferent neurons innervating infected tissue may be able to directly detect bacterial infection. Interestingly, TLR4 is known to activate PKC (Aksoy *et al.*, 2004) which could in turn sensitize TRPV1 receptors. Indeed, a TLR4-dependent mechanism of TRPV1 sensitization has since been demonstrated (Diogenes *et al.*, 2011). Downstream effects of TRPV1 activation could modulate the inflammatory response observed in sepsis. This in turn may lead to further TRPV1 activation by inflammatory mediators. In sepsis, an example of this positive feedback occurs between ROS [H₂O₂ and superoxide (O₂⁻)] generation and TRPV1. H₂O₂ is known to activate TRPV1 (Keeble *et al.*, 2009) while O₂⁻ production has been linked to TRPV1 up-regulation (Puntambekar *et al.*, 2005; Starr *et al.*, 2008). Furthermore, both H₂O₂ and O₂⁻ release occur upon TRPV1 activation (Fernandes *et al.*, 2012b). ROS are known to have important anti-microbial actions, providing further links between TRPV1 and bacterial load during sepsis. Previously, Clark *et al.* (2007) suggested that TRPV1 protection to sepsis was due to mechanisms involving the modulation of NO and TNF α production. In addition, recent data obtained from studies from CLP-induced sepsis models suggest that the disruption TRPV1 activity (either by the use of antagonists or by genetic deletion) results in a poor immune response to intestinal pathogens, and thus, increased bacteria survival

(Guptill *et al.*, 2011; Fernandes *et al.*, 2012b). It has been suggested that in the absence of functional TRPV1 at the primary site of infection (e.g. the peritoneal cavity), there is a disruption of macrophage-mediated immune response (Fernandes *et al.*, 2012b). A study performed by Chen and colleagues (2003) showed that incubation of macrophages with the TRPV1 antagonist capsazepine reduced a series of mediators released from macrophages stimulated with LPS, such as NO, interferon (IFN)- γ and PGE₂ *in vitro*. Indeed, it was later demonstrated that peritoneal-derived macrophages from TRPV1KO mice show reduced ability to phagocytose and are not able to generate and release reactive oxygen species (H₂O₂ and O₂⁻) and NO (Fernandes *et al.*, 2012b). In addition, these cells undergo increased apoptosis (Fernandes *et al.*, 2012b). Overall, several pieces of evidence by both Guptill *et al.* (2011) and Fernandes *et al.* (2012b) suggest that the lack of TRPV1 triggers a defective immune response to bacteria, culminating in an exaggerated transition from local infection to a systemic and uncontrollable infection. To add another layer of complexity to this scenario, recent data suggests a loss of TRPV1-mediated protection in ageing mice subjected to LPS-induced sepsis (Wanner *et al.*, 2012). However, the same was not observed in animals with sepsis caused by CLP. This difference of outcome observed in both experimental models was attributed to the use of aseptic-(LPS) and septic-(CLP) induced systemic inflammatory responses (Wanner *et al.*, 2012).

SP

SP was first identified in 1931 by Von Euler and Gaddum (Von Euler and Gaddum, 1931) as a factor present in the brain and gut. Tissue extracts were able to constrict rabbit intestine in an atropine insensitive manner. Later, Pernow (1953) described the distribution of SP in discrete areas of the brain, in dorsal root ganglia and in peripheral nerves, among other locations. Over the next 30 years, SP was demonstrated to be a sensory neurotransmitter.

SP is a decapeptide and a key member of the mammalian tachykinin family. Six members of the family exist, deriving from the two mammalian genes, tachykinin 1 (TAC1) gene producing the preprotachykinin 1 protein (PPT1) and the tachykinin 2 (TAC2) (rodent) or 3 (human) gene, producing the preprotachykinin 2 protein (PPT2). The six members are called SP, neurokinin A (NKA), NKB, neuropeptide Y (NPY), haemokinin and endokinin. The PPT1 protein can form four different splice variants, encoding different tachykinin proteins, whereas the PPT2 protein forms only a single tachykinin product. Figure 1 shows splice variants and resultant tachykinin production from PPT proteins as well as their respective preferred receptors. All tachykinins can be identified by their shared 5 amino acid sequence at the carboxy terminus. For a review of the tachykinin family and receptors, see Pennefather *et al.* (2004) and for further classification information, see the British Journal of Pharmacology's Guide to Receptors and Channels (Alexander *et al.*, 2011).

Neurokinin 1 (NK₁) receptor

Tachykinin receptors are G-protein coupled and exist in three main subtypes named neurokinin (NK) receptor 1–3 (NK_{1–3}).

Figure 1

Tachykinin gene encoding and receptor preference. The key tachykinins SP, NKA and NKB are encoded in TAC1 or TAC2 (rodent)/3 (human) genes, where different mRNA splice variants of PPT1 and PPT2 protein products can occur (α to γ). All tachykinins can bind to the three main NK receptors, but with different affinity for each, creating a situation of preferential agonists. NK receptors can signal independently, or their signalling can converge to become synergistic or antagonistic. This figure is adapted from that in Fernandes *et al.* (2009).

All receptors can be activated by all tachykinin members, but show differential selectivity (Pennefather *et al.*, 2004). SP preferentially signals through the NK₁ receptor. This receptor is widely expressed on both peripheral tissues; including smooth muscle, the lungs, the bladder, bone marrow and within the central nervous system (Huang and Korlipara, 2010). It is predominantly linked to Gq-protein signalling, mediating calcium mobilization (Quartara and Maggi, 1997). This has cell-specific effects, such as contraction of smooth muscle (Bury and Mashford, 1977), retraction of endothelial cells leading to tissue oedema (Sawyer *et al.*, 2011) and endothelial dependent vasodilation (Beny *et al.*, 1986). SP also forms part of the pain signalling pathways in the spinal cord (Baranauskas and Nistri, 1998). The first NK₁ antagonist was developed in 1991 by Pfizer, named CP-96345, initiating the now well-developed stream of NK antagonists poised to combat an increasingly wide range of indications. Over the last 20 years, more than 300 patents have been granted for NK₁ antagonists alone, with over a dozen entering clinical trials (Huang and Korlipara, 2010). These trials reveal the potential role for SP/NK₁ in several disease areas including affective disorders, asthma/unwanted airway constriction, emesis, tinnitus, painful diabetic neuropathy, migraine, gastrointestinal disturbances and overactive bladder/urinary

incontinence. A full review of the clinical status of NK₁ antagonists can be found in Huang and Korlipara (2010). Despite much effort from the pharmaceutical industry to develop NK₁ antagonists, few have reached the clinic. So far, only aprepitant and its prodrug fosaprepitant dimeglumine have been approved by the Food and Drug Administration (Patel and Lindley, 2003). In spite of this, several NK₁ antagonists have become common in the experimental literature, and are successfully utilized in animal disease models. Of these, CP-96345 (IC₅₀ in low nM, Snider *et al.*, 1991) and SR140333 (IC₅₀ in the mid- pM range, Croci *et al.*, 1995) are the most commonly used. Thus, several potent and selective antagonists of the SP/NK₁ interaction exist and continue to be developed by the pharmaceutical industry, demonstrating the potential that this modulation holds for therapeutic benefit.

Alongside the development of SP antagonists, efforts have been made to develop and characterize mice lacking either the PPT1 protein or specific NK receptors. NK₁KO mice are viable and healthy, albeit some psychological differences from WT mice (De Felipe *et al.*, 1998; Laird *et al.*, 2001). They respond normally to several mechanical stimuli but show reduced initial pain reflexes, leukocyte recruitment and oedema in response to several chemical stimuli, including

capsaicin (Ahluwalia *et al.*, 1998; Zimmer *et al.*, 1998; Laird *et al.*, 2000; De Swert *et al.*, 2009). PPT1KO mice, lacking both SP and NKA, are more widely used than NK₁KO mice in the study of sepsis. They similarly show reduced oedema and acute reflexes to noxious chemical stimuli (Cao *et al.*, 1998). Interestingly, PPT1KO mice have been used to suggest that hydrogen sulphide (H₂S) and PPT proteins act together to upregulate NF- κ B and TLR4 in a murine model of acute pancreatitis (Tamizhselvi *et al.*, 2011). PPT1KO mice also experience reduced lung injury in this model (Bhatia *et al.*, 2003), eluding to potential parallels with sepsis.

SP in sepsis

In recent years, there has been growing interest in the role SP plays in sepsis. The expression and suggested function of SP and NK receptors in organs relevant to sepsis is summarized in Table 2. NK₁ activation is known to enhance inflammation via increases in endothelial permeability, vasodilation and inflammatory cell recruitment (Maggi, 1997; Katz *et al.*, 2003; O'Connor *et al.*, 2004). In agreement with these findings, several authors have demonstrated tachykinins to be involved in the pathogenesis of several inflammatory diseases, including pancreatitis (Bhatia *et al.*, 2003), airway inflammation (Groneberg *et al.*, 2004), inflammatory bowel disease (Margolis and Gershon, 2009), arthritis (Keeble and Brain, 2004) and cystitis (Duffy, 2004). Indeed, during inflammatory conditions the levels of SP are known to increase, for example in bronchial lavage following lung injury (Espirito *et al.*, 1992) and in the blood during systemic inflammations, such as sepsis (Beer *et al.*, 2002). These findings suggest that inhibition of SP/NK₁ interaction may be therapeutically beneficial during inflammatory diseases.

The potential roles for SP in sepsis are wide ranging. It induces many inflammatory actions relevant to sepsis progression, most of which are attributed to activation of the NK₁ receptor. SP is well known as an inducer of neurogenic inflammation, which shows hallmarks of vasodilation, oedema and leukocyte infiltration. All of these actions can be induced by SP acting on the NK₁ receptor (O'Connor *et al.*, 2004), and are detrimental in sepsis. NK₁ activation on endothelial cells induces cell retraction, leading to oedema, and also the production of vasodilators such as NO and prostacyclin (Katz *et al.*, 2003), which contribute to hypotension. NK₁ activation can also induce inflammatory mediator transcription, including chemokines, cytokines and adhesion molecules in several cell types (Maggi, 1997). SP is also known to prime neutrophils for chemotactic responses to chemokines, inducing the expression of chemokine receptors, a response that can be inhibited with NK₁ antagonists (Sun *et al.*, 2007). These actions of SP are detrimental during sepsis as they exacerbate the inflammation and lead to fatal organ damage. Oedema and vasodilation can contribute to the dangerous hypotension and decrease in lung function, which is associated with poor outcome from sepsis.

SP can both stimulate and inhibit gastrointestinal tract motility. NK₁ activation facilitates motor activity via the interstitial cells of cajal, involved in the production of basal levels of peristalsis. However, SP can also depress motor activity via production of inhibitory transmitter such as NO.

Increased levels of SP in the gut can lead to increases in gut secretions, along with activation of resident macrophages and mast cells, provoking the release of inflammatory mediators. A review of tachykinins in the gut is provided within Hökfelt *et al.*, 2001. During sepsis, inhibition of gut motility is detrimental as it allows the growth and translocation of bacteria out of the tract (De Winter and De Man, 2010) and exacerbates the inflammatory reaction against them.

In 2006, Puneet *et al.* were the first to demonstrate that PPT1 deletion was protective during CLP-induced sepsis. Mice showed reduced morbidity and mortality, alongside reduced systemic inflammation. SP was significantly increased in both the lung and plasma, one hour after CLP surgery in WT mice. This is in agreement with studies from septic patients, showing an increased plasma level of SP is a predictor of lethality (Beer *et al.*, 2002). PPT1KO mice showed significantly reduced lung, liver and kidney neutrophil infiltration and bacterial load, alongside reduced lung oedema. They also exhibited lower levels of the CC chemokine monocyte chemotactic protein 1 (MCP-1) and the CXC chemokine macrophage inflammatory protein 2 (MIP-2). This demonstrates the potential for SP and/or NKA to exacerbate sepsis. The role of SP was then strengthened by later studies from this group, showing the NK antagonist SR140333 to have similar detrimental effects on lung injury in CLP-induced sepsis (Hegde *et al.*, 2007). In this study, vehicle-treated mice showed significantly more lung damage, indicated by increased leukocyte infiltration, oedema, chemokine and cytokine levels than in antagonist-treated mice. Additionally, MIP-2 and MCP-1, regulated upon activation, normal t-cell expressed, and secreted (RANTES), IL-1 β and IL-6 levels in the lung were reduced by NK₁ antagonism, alongside the expression of the adhesion molecules intercellular adhesion molecule 1 (ICAM-1), E-selectin and P-selectin. A follow-up study showed similar findings were exclusively due to NK₁ activation, as an NK₂ selective antagonist showed no beneficial effects (Hegde *et al.*, 2010a). Following similar principles, another publication showed protection in PPT1KO mice during LPS-induced sepsis. These mice showed protection from lung, liver and kidney inflammation and injury (Ng *et al.*, 2008). Together, these studies suggest that SP release during sepsis activates the endothelium and inflammatory cells, exacerbating inflammation via recruitment of leukocytes and induction of inflammatory mediator expression. In Hegde *et al.* (2010b), the authors show NK₁ antagonism to reduce PKC, NF- κ B, activator protein 1 and extracellular signal-regulated kinase (ERK) activation in lung homogenates, suggesting NK₁ activation may trigger a pro-inflammatory cascade and exacerbate lung inflammation. The activity of both resident and recruited cell types may be involved in this process due to the wide expression pattern of the NK₁ receptor. Leukocytes may also contribute to the production of chemokines and cytokines following NK₁ stimulation (Lotz *et al.*, 1988; Maggi, 1997). Hegde *et al.* (2010a) have conducted microarray analysis of WT and PPT1KO mouse lungs following CLP-induced sepsis. In this study, they found that PPT1KO mice showed reduced pro-inflammatory mediator expression, and also elevated anti-inflammatory mediator expression, most notably the IL-1 receptor antagonist gene. This suggested that SP/NK₁ may be responsible for sepsis lethality, contributing to the uncontrolled and

damaging tissue inflammation seen in the early stages of the condition, but also participating in the later immunosuppressive phase, where most mortality occurs (Shimaoka and Park, 2008).

The source of SP was not fully investigated in these studies; however, TLR receptors are known to be expressed on sensory neurones (Wadachi and Hargreaves, 2006), potentially triggering nerve activation and release of SP by bacteria products. This explanation would fit well the findings of high SP in the lung only one hour after CLP (Puneet *et al.*, 2006), where anti-dromal neuronal activation at secondary sites may occur before significant bacterial translocation. Additionally, at six hours post-LPS injection, WT mice show large magnitude increases in SP in the lung, liver and kidney, but a smaller magnitude increase in plasma (Ng *et al.*, 2008). This additionally suggests that SP is released from sources within the inflammatory site or at sites with high sensory neurone density and leaks into the circulation. Other potential sources of SP include leukocytes, who also express NK₁ receptors (Lai *et al.*, 1998), thus potentially providing both paracrine and autocrine stimulation. Recently, the activation of NK₁ receptors by SP on macrophages was suggested to participate in TRPV1-mediated protection to CLP-induced sepsis by regulating phagocytosis (Fernandes *et al.*, 2012b).

An area of research attracting increasing interest is that of H₂S. This is now recognized to be the third gaseotransmitter, alongside carbon monoxide and NO. It is produced by the enzymes cystathione γ -lyase (CSE), mostly found in the vasculature, and cystathione β -synthase (CBS), largely found in the central nervous system (Li *et al.*, 2009). H₂S is known to activate sensory neurones, leading to neuropeptide release in several tissues, including the lung (Trevisani *et al.*, 2005) and bladder (Patacchini *et al.*, 2004; 2005). The level of H₂S in vascular tissues has shown clear increases in models of LPS and CLP-induced sepsis in rats (Hui *et al.*, 2003), along with plasma levels in septic patients (Li *et al.*, 2005). H₂S donors have also been shown to aggravate inflammation and organ damage in murine CLP-induced sepsis, due to activation of NF- κ B and up-regulation of inflammatory genes (Zhang *et al.*, 2007a). Building on these findings, Zhang *et al.* (2007b) used PPT1WT and KO mice pre-treated with an inhibitor of H₂S formation to show that H₂S exacerbated CLP-induced lung inflammation and damage in a manner dependent on PPT1-derived proteins. In addition, they showed that PPT1 deletion has no effect on the endogenous generation of H₂S, suggesting that H₂S induces SP release, thus aggravating septic lung damage. However, Ang *et al.* (2011) have since demonstrated that TRPV1 is also involved in this process, as a TRPV1 antagonist is able to inhibit H₂S-induced SP production in a model of CLP-induced sepsis. This resulted in reduced ERK and NF- κ B activation, associated with reduced cytokines and chemokines and reductions in lung and liver damage compared with vehicle-treated mice. H₂S is also reported to be an agonist of the TRPA1 receptor, a TRP channel co-expressed with TRPV1 and also associated with the release of neuropeptides (Bodkin and Brain, 2011). The role of TRPA1 in sepsis has yet to be elucidated. These findings bring in yet another layer of complexity, contrasting with the previously discussed protective roles of TRPV1 and sensory neurones in sepsis.

Future aspects

The study of sepsis is continually evolving; however, our understanding of the pathogenesis is still incomplete. This review has described the evidence, largely from animal models, demonstrating an important role for sensory neurones in sepsis outcome. Surprisingly, the roles of TRPV1 and SP in sepsis seem contradictory, suggesting that they may have independent roles within a larger signalling network activated during sepsis, possibly including H₂S. Further studies in human models of sepsis will be needed to determine if the associations identified in animal models are accurate in the clinical setting. Potentially, measurement of neuropeptide levels could be a useful clinical indicator of sepsis progression, though this has yet to be rigorously tested. Pharmacological modulators of TRP channels and neuropeptide receptors may also be useful as therapeutic agents; a hypothesis for which this review shows substantial evidence. Collectively, this review suggests that novel and exciting sepsis therapeutics could be developed by exploiting the protective actions of sensory neurones or blocking detrimental pathways; however, further studies will be needed to completely understand the roles of sensory neurones in sepsis before the best therapeutic avenue can be identified.

Conclusions

Sepsis is a relatively common and life-threatening condition; the treatment of which represents a largely unmet therapeutic need. In this review, we provide a summary of the findings linking sensory neurone-related proteins to the modulation of sepsis; focusing specifically on the emerging roles of TRPV1 and SP in disease pathogenesis. Substantial evidence demonstrates that TRPV1 activity can regulate the immune response to infection, having an overall protective role in sepsis outcome. TRPV1 receptor activity has been shown in several studies to be associated with improvement of sepsis outcome, potentially playing an important role in the clearance of bacteria. However, SP, a neuropeptide typically released upon neuronal TRPV1 activation, shows evidence of detrimental effects in sepsis. Its production and activation of the NK₁ receptor is associated with pro-inflammatory mediator production and end organ damage. Despite recent progress in understanding the role of the sensory neurone/neuropeptide axis in sepsis, many questions remain, particularly in regard to the role of other TRP channels, neuropeptides and related mediators.

Conflict of interest

Authors declare no conflicts of interest.

References

- Ahluwalia A, De Felipe C, O'Brien J, Hunt SP, Perretti M (1998). Impaired IL-1 β -induced neutrophil accumulation in tachykinin NK1 receptor knockout mice. *Br J Pharmacol* 124: 1013–1015.

- Aksoy E, Goldman M, Willems F (2004). Protein kinase C epsilon: a new target to control inflammation and immune-mediated disorders. *Int J Biochem Cell Biol* 36: 183–188.
- Alawi K, Keeble J (2010). The paradoxical role of the transient receptor potential vanilloid 1 receptor in inflammation. *Pharmacol Ther* 125: 181–195.
- Alexander SPH, Mathie A, Peters JA (2011). Guide to Receptors and Channels (GRAC), 5th edition. *Br J Pharmacol* 164: S1–S324.
- Almeida MC, Steiner AA, Branco LG, Romanovsky AA (2006). Cold-seeking behavior as a thermoregulatory strategy in systemic inflammation. *Eur J Neurosci* 23: 3359–3367.
- Amadesi S, Nie J, Vergnolle N, Cottrell GS, Grady EF, Trevisani M *et al.* (2004). Protease-activated receptor 2 sensitizes the capsaicin receptor transient receptor potential vanilloid receptor 1 to induce hyperalgesia. *J Neurosci* 24: 4300–4312.
- Andoh T, Kuraishi Y (2005). Expression of BLT1 leukotriene B₄ receptor on the dorsal root ganglion neurons in mice. *Brain Res Mol Brain Res* 137: 263–266.
- Andoh T, Nagasawa T, Kuraishi Y (1996). Expression of tachykinin NK1 receptor mRNA in dorsal root ganglia of the mouse. *Brain Res Mol Brain Res* 35: 329–332.
- Ang SF, Moolchhala SM, MacAry PA, Bhatia M (2011). Hydrogen sulfide and neurogenic inflammation in polymicrobial sepsis: involvement of substance P and ERK-NF- κ B signaling. *PLoS ONE* 6: e24535.
- Ansari N, Khodaghali F, Amini M, Shaerzadeh F (2011). Attenuation of LPS-induced apoptosis in NGF-differentiated PC12 cells via NF- κ B pathway and regulation of cellular redox status by an oxazine derivative. *Biochimie* 93: 899–908.
- Asmis LM, Asmis R, Sulzer I, Furlan M, Lämmle B (2008). Contact system activation in human sepsis – 47kD HK, a marker of sepsis severity? *Swiss Med Wkly* 138: 142–149.
- Ayala A, Chaudry IH (1996). Immune dysfunction in murine polymicrobial sepsis: mediators, macrophages, lymphocytes and apoptosis. *Shock* 6: S27–S38.
- Baranauskas G, Nistri A (1998). Sensitization of pain pathways in the spinal cord: cellular mechanisms. *Prog Neurobiol* 54: 349–365.
- Bátkai S, Pacher P, Járαι Z, Wagner JA, Kunos G (2004). Cannabinoid antagonist SR-141716 inhibits endotoxic hypotension by a cardiac mechanism not involving CB1 or CB2 receptors. *Am J Physiol Heart Circ Physiol* 287: H595–H600.
- Beer S, Weighardt H, Emmanuilidis K, Harzenetter MD, Matevossian E, Heidecke CD *et al.* (2002). Systemic neuropeptide levels as predictive indicators for lethal outcome in patients with postoperative sepsis. *Crit Care Med* 30: 1794–1798.
- Beny JL, Brunet PC, Huggel H (1986). Effect of mechanical stimulation, substance P and vasoactive intestinal polypeptide on the electrical and mechanical activities of circular smooth muscles from pig coronary arteries contracted with acetylcholine: role of endothelium. *Pharmacology* 33: 61–68.
- Berg RM, Møller K, Bailey DM (2011). Neuro-oxidative-nitrosative stress in sepsis. *J Cereb Blood Flow Metab* 31: 1532–1544.
- Bhatia M, Slavin J, Cao Y, Basbaum AI, Neoptolemos JP (2003). Preprotachykinin-A gene deletion protects mice against acute pancreatitis and associated lung injury. *Am J Physiol Gastrointest Liver Physiol* 284: G830–G836.
- Bodkin JV, Brain SD (2011). Transient receptor potential ankyrin 1: emerging pharmacology and indications for cardiovascular biology. *Acta Physiol* 203: 87–98.
- Brain SD, Cox HM (2006). Neuropeptides and their receptors: innovative science providing novel therapeutic targets. *Br J Pharmacol* 147: S202–S211.
- Bryant P, Shumate M, Yumet G, Lang CH, Vary TC, Cooney RN (2003). Capsaicin-sensitive nerves regulate the metabolic response to abdominal sepsis. *J Surg Res* 112: 152–161.
- Bury RW, Mashford ML (1977). A pharmacological investigation of synthetic substance P on the isolated guinea-pig ileum. *Clin Exp Pharmacol Physiol* 4: 453–461.
- Cantalupo L, Cioni C, Annunziata P (2008). Expression of preprotachykinin-A mRNA isoforms and substance P production in T lymphocytes of human healthy subjects. *Neurosci Lett* 434: 191–194.
- Cao YQ, Mantyh PW, Carlson EJ, Gillespie AM, Epstein CJ, Basbaum AI (1998). Primary afferent tachykinins are required to experience moderate to intense pain. *Nature* 392: 390–394.
- Caroleo MC, Costa N, Bracci-Laudiero L, Aloe L (2001). Human monocyte/macrophages activate by exposure to LPS overexpress NGF and NGF receptors. *J Neuroimmunol* 113: 193–201.
- Caterina MJ, Schumacher MA, Tominaga M, Rosen TA, Levine JD, Julius D (1997). The capsaicin receptor: a heat-activated ion channel in the pain pathway. *Nature* 389: 816–824.
- Caterina MJ, Leffler A, Malmberg AB, Martin WJ, Trafton J, Petersen-Zeitz KR *et al.* (2000). Impaired nociception and pain sensation in mice lacking the capsaicin receptor. *Science* 288: 306–313.
- Chen CW, Lee ST, Wu WT, Fu WM, Ho FM, Lin WW (2003). Signal transduction for inhibition of inducible nitric oxide synthase and cyclooxygenase-2 induction by capsaicin and related analogs in macrophages. *Br J Pharmacol* 140: 1077–1087.
- Cheyuo C, Jacob A, Wang P (2012). Ghrelin-mediated sympathoinhibition and suppression of inflammation in sepsis. *Am J Physiol Endocrinol Metab* 302: E265–E272.
- Ching LC, Kou YR, Shyue SK, Su KH, Wei J, Cheng LC *et al.* (2011). Molecular mechanisms of activation of endothelial nitric oxide synthase mediated by transient receptor potential vanilloid type 1. *Cardiovasc Res* 91: 492–501.
- Chuang HH, Prescott ED, Kong H, Shields S, Jordt SE, Basbaum AI *et al.* (2001). Bradykinin and nerve growth factor release the capsaicin receptor from PtdIns(4,5)P₂-mediated inhibition. *Nature* 411: 957–962.
- Clark N, Keeble J, Fernandes ES, Starr A, Liang L, Sugden D *et al.* (2007). The transient receptor potential vanilloid 1 (TRPV1) receptor protects against the onset of sepsis after endotoxin. *FASEB J* 13: 3747–3755.
- Coelho FR, Martins JO (2012). Diagnostic methods in sepsis: the need of speed. *Rev Assoc Med Bras* 58: 498–504.
- Croci T, Emonds-Alt X, Le Fur G, Manara L (1995). In vitro characterization of the non-peptide tachykinin NK1 and NK2-receptor antagonists, SR140333 and SR48968 in different rat and guinea-pig intestinal segments. *Life Sci* 56: 267–275.
- Davis JB, Gray J, Gunthorpe MJ, Hatcher JP, Davey PT, Overend P *et al.* (2000). Vanilloid receptor-1 is essential for inflammatory thermal hyperalgesia. *Nature* 405: 183–187.
- De Felipe C, Herrero JF, O'Brien JA, Palmer JA, Doyle CA, Smith AJ *et al.* (1998). Altered nociception, analgesia and aggression in mice lacking the receptor for substance P. *Nature* 392: 394–397.
- De Swert KO, Bracke KR, Demoor T, Brusselle GG, Joos GF (2009). Role of the tachykinin NK1 receptor in a murine model of cigarette smoke-induced pulmonary inflammation. *Respir Res* 10: 37.

- De Winter BY, De Man JG (2010). Interplay between inflammation, immune system and neuronal pathways: effect on gastrointestinal motility. *World J Gastroenterol* 16: 5523–5535.
- Delescluse I, Mace H, Adcock J (2012). Inhibition of airway hyperresponsiveness by Trpv1 antagonists (SB705498 and PF-04065463) in the unanaesthetised, ovalbumin-sensitised guinea-pig. *Br J Pharmacol* 166: 1822–1832.
- Dinh QT, Groneberg DA, Peiser C, Mingomataj E, Joachim RA, Witt C *et al.* (2004). Substance P expression in TRPV1 and trkA-positive dorsal root ganglion neurons innervating the mouse lung. *Respir Physiol Neurobiol* 144: 15–24.
- Diogenes A, Ferraz CC, Akopian AN, Henry MA, Hargreaves KM (2011). LPS sensitizes TRPV1 via activation of TLR4 in trigeminal sensory neurons. *J Dent Res* 90: 759–764.
- Duffy RA (2004). Potential therapeutic targets for neurokinin-1 receptor antagonists. *Expert Opin Emerg Drugs* 1: 9–21.
- Durrenberger PF, Facer P, Casula MA, Yiangou Y, Gray RA, Chessell IP *et al.* (2006). Prostanoid receptor EP1 and Cox-2 in injured human nerves and a rat model of nerve injury: a time-course study. *BMC Neurol* 6: 1.
- Espiritu RF, Pittet JF, Matthay MA, Goetzl EJ (1992). Neuropeptides in pulmonary edema fluid of adult respiratory distress syndrome. *Inflammation* 16: 509–517.
- Fehér E, Fodor M, Fehér J (1992). Ultrastructural localization of somatostatin- and substance P-immunoreactive nerve fibers in the feline liver. *Gastroenterology* 102: 287–294.
- Fernandes ES, Schmidhuber SM, Brain SD (2009). Sensory-nerve-derived neuropeptides: possible therapeutic targets. *Handb Exp Pharmacol* 194: 393–416.
- Fernandes ES, Fernandes MA, Keeble JE (2012a). The functions of TRPA1 and TRPV1: moving away from sensory nerves. *Br J Pharmacol* 166: 510–521.
- Fernandes ES, Liang L, Smillie SJ, Kaiser F, Purcell R, Rivett DW *et al.* (2012b). TRPV1 deletion enhances local inflammation and accelerates the onset of systemic inflammatory response syndrome. *J Immunol* 188: 5741–5751.
- Foreman JC, Jordan CC, Oehme P, Renner H (1983). Structure-activity relationships for some substance P-related peptides that cause wheal and flare reactions in human skin. *J Physiol* 335: 449–465.
- Gallicchio M, Benetti E, Rosa AC, Fantozzi R (2009). Tachykinin receptor modulation of cyclooxygenase-2 expression in human polymorphonuclear leucocytes. *Br J Pharmacol* 156: 486–496.
- Gavva NR (2008). Body-temperature maintenance as the predominant function of the vanilloid receptor TRPV1. *Trends Pharmacol Sci* 29: 550–557.
- Gavva NR, Klionsky L, Qu Y, Shi L, Tamir R, Edenson S *et al.* (2004). Molecular determinants of vanilloid sensitivity in TRPV1. *J Biol Chem* 279: 20283–20295.
- Gavva NR, Tamir R, Qu Y, Klionsky L, Zhang TJ, Immke D *et al.* (2005). AMG 9810 [(E)-3-(4-t-butylphenyl)-N-(2,3-dihydrobenzo[b][1,4] dioxin-6-yl)acrylamide], a novel vanilloid receptor 1 (TRPV1) antagonist with antihyperalgesic properties. *J Pharmacol Exp Ther* 313: 474–484.
- Giamarellos-Bourboulis EJ, Raftogiannis M (2012). The immune response to severe bacterial infections: consequences for therapy. *Expert Rev Anti Infect Ther* 10: 369–380.
- Glaser S, Gaudio E, Renzi A, Mancinelli R, Ueno Y, Venter J *et al.* (2011). Knockout of the neurokinin-1 receptor reduces cholangiocyte proliferation in bile duct-ligated mice. *Am J Physiol Gastrointest Liver Physiol* 301: G297–G305.
- Groneberg DA, Quarcoo D, Frossard N, Fischer A (2004). Neurogenic mechanisms in bronchial inflammatory diseases. *Allergy* 59: 1139–1152.
- Gunthorpe MJ, Rami HK, Jerman JC, Smart D, Gill CH, Soffin EM *et al.* (2004). Identification and characterisation of SB366791, a potent and selective vanilloid receptor (VR1/TRPV1) antagonist. *Neuropharmacology* 46: 133–149.
- Guptill V, Cui X, Khaibullina A, Keller JM, Spornick N, Mannes A *et al.* (2011). Disruption of the transient receptor potential vanilloid 1 can affect survival, bacterial clearance, and cytokine gene expression during murine sepsis. *Anesthesiology* 114: 1190–1199.
- Hayes P, Meadows HJ, Gunthorpe MJ, Harries MH, Duckworth DM, Cairns W *et al.* (2000). Cloning and functional expression of a human orthologue of rat vanilloid receptor-1. *Pain* 88: 205–215.
- Hegde A, Zhang H, Moolchhala SM, Bhatia M (2007). Neurokinin-1 receptor antagonist treatment protects mice against lung injury in polymicrobial sepsis. *J Leukoc Biol* 82: 678–685.
- Hegde A, Tamizhselvi R, Manikandan J, Melendez AJ, Moolchhala SM, Bhatia M (2010a). Substance P in polymicrobial sepsis: molecular fingerprint of lung injury in preprotachykinin-A/-mice. *Mol Med* 16: 188–198.
- Hegde A, Koh YH, Moolchhala SM, Bhatia M (2010b). Neurokinin-1 receptor antagonist treatment in polymicrobial sepsis: molecular insights. *Int J Inflamm* 2010: 601098.
- Helyes Z, Elekes K, Sándor K, Szitter I, Kereskai L, Pintér E *et al.* (2010). Involvement of preprotachykinin A gene-encoded peptides and the neurokinin 1 receptor in endotoxin-induced murine airway inflammation. *Neuropeptides* 44: 399–406.
- Henricks PA, Verhoef J, Nijkamp FP (1986). Modulation of phagocytic cell function. *Vet Res Commun* 10: 165–188.
- Hernández-Palazón J, Fuentes-García D, Burguillos-López S, Domenech-Asensi P, Sansano-Sánchez TV, Acosta-Villegas F (2012). Analysis of organ failure and mortality in sepsis due to secondary peritonitis. *Med Intensiva* doi:pii: S0210-5691(12)00250-1. 10.1016/j.medint.2012.07.010
- Ho KW, Ward NJ, Calkins DJ (2012). TRPV1: a stress response protein in the central nervous system. *Am J Neurodegener Dis* 30: 1–14.
- Ho WZ, Lai JP, Zhu XH, Uvaydova M, Douglas SD (1997). Human monocytes and macrophages express substance P and neurokinin-1 receptor. *J Immunol* 159: 5654–5660.
- Höckfelt T, Pernow B, Wahren J (2001). Substance P: a pioneer amongst neuropeptides. *J Intern Med* 249: 27–40.
- Holzer P (1998). Neurogenic vasodilatation and plasma leakage in the skin. *Gen Pharmacol* 30: 5–11.
- Holzer P, Holzer-Petsche U (1997). Tachykinins in the gut. Part I. Expression, release and motor function. *Pharmacol Ther* 73: 173–217.
- Hong S, Wiley JW (2005). Early painful diabetic neuropathy is associated with differential changes in the expression and function of vanilloid receptor 1. *J Biol Chem* 280: 618–627.
- Huang J, Zhang X, McNaughton PA (2006a). Inflammatory pain: the cellular basis of heat hyperalgesia. *Curr Neuropharmacol* 4: 197–206.
- Huang J, Zhang X, McNaughton PA (2006b). Modulation of temperature-sensitive TRP channels. *Semin Cell Dev Biol* 17: 638–645.

- Huang SC, Korlipara VL (2010). Neurokinin-1 receptor antagonists: a comprehensive patent survey. *Expert Opin Ther Pat* 20: 1019–1045.
- Huang W, Rubinstein J, Prieto AR, Thang LV, Wang DH (2009). Transient receptor potential vanilloid gene deletion exacerbates inflammation and atypical cardiac remodeling after myocardial infarction. *Hypertension* 53: 243–250.
- Hui Y, Du J, Tang C, Bin G, Jiang H (2003). Changes in arterial hydrogen sulfide (H₂S) content during septic shock and endotoxin shock in rats. *J Infect* 47: 155–160.
- Hwang SW, Cho H, Kwak J, Lee SY, Kang CJ, Jung J (2000). Direct activation of capsaicin receptors by products of lipoxygenases: endogenous capsaicin-like substances. *Proc Natl Acad Sci U S A* 97: 6155–6160.
- Iida T, Shimizu I, Nealen ML, Campbell A, Caterina M (2005). Attenuated fever response in mice lacking TRPV1. *Neurosci Lett* 378: 28–33.
- Improta G, Broccardo M (2006). Tachykinins: role in human gastrointestinal tract physiology and pathology. *Curr Drug Targets* 7: 1021–1029.
- Jacob P, Mueller MH, Hahn J, Wolk I, Mayer P, Nagele U *et al.* (2007). Alterations of neuropeptides in the human gut during peritonitis. *Langenbecks Arch Surg* 392: 267–271.
- Jang JH, Clark JD, Li X, Yorek MS, Usachev YM, Brennan TJ (2010). Nociceptive sensitization by complement C5a and C3a in mouse. *Pain* 148: 343–352.
- Jia Y, Lee LY (2007). Role of TRPV receptors in respiratory diseases. *Biochim Biophys Acta* 1772: 915–927.
- Joachim RA, Cifuentes LB, Sagach V, Quarcoo D, Hagen E, Arck PC, Fischer A, Klapp BF, Dinh QT (2006). Stress induces substance P in vagal sensory neurons innervating the mouse airways. *Clin Exp Allergy* 36: 1001–1010.
- Kadoi Y, Hinohara H, Kunimoto F, Kuwano H, Saito S, Goto F (2005). Effects of AM281, a cannabinoid antagonist, on systemic haemodynamics, internal carotid artery blood flow and mortality in septic shock in rats. *Br J Anaesth* 94: 563–568.
- Kark T, Bagi Z, Lizanecz E, Pásztor ET, Erdei N, Czikora A (2008). Tissue-specific regulation of microvascular diameter: opposite functional roles of neuronal and smooth muscle located vanilloid receptor-1. *Mol Pharmacol* 73: 1405–1412.
- Katsanos GS, Anogeianaki A, Orso C, Tete S, Salini V, Antinolfi PL (2008). Impact of substance P on cellular immunity. *J Biol Regul Homeost Agents* 22: 93–98.
- Katz LM, Marr CM, Elliott J (2003). Characterisation of the response of equine digital arteries and veins to substance P. *J Vet Pharmacol Ther* 26: 361–368.
- Kazerani HR, Plevin R, Kawagoe J, Kanke T, Furman BL (2004). Lack of effect of proteinase-activated receptor-2 (PAR-2) deletion on the pathophysiological changes produced by lipopolysaccharide in the mouse: comparison with dexamethasone. *J Pharm Pharmacol* 56: 1015–1020.
- Keeble JE, Brain SD (2004). A role for substance P in arthritis? *Neurosci Lett* 361: 176–179.
- Keeble JE, Bodkin JV, Liang L, Wodarski R, Davies M, Fernandes ES *et al.* (2009). Hydrogen peroxide is a novel mediator of inflammatory hyperalgesia, acting via transient receptor potential vanilloid 1-dependent and independent mechanisms. *Pain* 141: 135–142.
- Kitamura H, Kobayashi M, Wakita D, Nishimura T (2012). Neuropeptide signaling activates dendritic cell-mediated type 1 immune responses through neurokinin-2 receptor. *J Immunol* 188: 4200–4208.
- Konno M, Shirakawa H, Iida S, Sakimoto S, Matsutani I, Miyake T *et al.* (2012). Stimulation of transient receptor potential vanilloid 4 channel suppresses abnormal activation of microglia induced by lipopolysaccharide. *Glia* 60: 761–770.
- Kuzhikandathil EV, Wang H, Szabo T, Morozova N, Blumberg P, Oxford GS (2001). Functional analysis of capsaicin receptor (vanilloid receptor subtype 1) multimerization and agonist responsiveness using a dominant negative mutation. *J Neurosci* 21: 8697–8706.
- Lai JP, Douglas SD, Ho WZ (1998). Human lymphocytes express substance P and its receptor. *J Neuroimmunol* 86: 80–86.
- Laird JM, Olivar T, Roza C, De Felipe C, Hunt SP, Cervero F (2000). Deficits in visceral pain and hyperalgesia of mice with a disruption of the tachykinin NK1 receptor gene. *Neuroscience* 98: 345–352.
- Laird JM, Roza C, De Felipe C, Hunt SP, Cervero F (2001). Role of central and peripheral tachykinin NK1 receptors in capsaicin-induced pain and hyperalgesia in mice. *Pain* 90: 97–103.
- Lautner MA, Ruparel SB, Patil MJ, Hargreaves KM (2011). In vitro sarcoma cells release a lipophilic substance that activates the pain transduction system via TRPV1. *Ann Surg Oncol* 18: 866–871.
- Lever A, Mackenzie I (2007). Sepsis: definition, epidemiology, and diagnosis. *BMJ* 335: 879–883.
- Li J, Wang DH (2008). Increased GFR and renal excretory function by activation of TRPV1 in the isolated perfused kidney. *Pharmacol Res* 57: 239–246.
- Li L, Bhatia M, Zhu YZ, Zhu YC, Ramnath RD, Wang ZJ *et al.* (2005). Hydrogen sulfide is a novel mediator of lipopolysaccharide-induced inflammation in the mouse. *FASEB J* 19: 1196–1198.
- Li L, Hsu A, Moore PK (2009). Actions and interactions of nitric oxide, carbon monoxide and hydrogen sulphide in the cardiovascular system and in inflammation—a tale of three gases! *Pharmacol Ther* 123: 386–400.
- Lichtenstein C, Brenner T, Bardenheuer HJ, Weigand MA, Lin Q (2012). Predictors of survival in sepsis: what is the best inflammatory marker to measure? *Curr Opin Infect Dis* 25: 328–336.
- Lin Q, Li D, Xu X, Zou X, Fang L (2007). Roles of TRPV1 and neuropeptidergic receptors in dorsal root reflex-mediated neurogenic inflammation induced by intradermal injection of capsaicin. *Mol Pain* 3: 30.
- Lotz M, Vaughan JH, Carson DA (1988). Effect of neuropeptides on production of inflammatory cytokines by human monocytes. *Science* 241: 1218–1221.
- Maggi CA (1997). The effects of tachykinins on inflammatory and immune cells. *Regul Pept* 70: 75–90.
- Margolis KG, Gershon MD (2009). Neuropeptides and inflammatory bowel disease. *Curr Opin Gastroenterol* 25: 503–511.
- Matsumoto K, Hosoya T, Tashima K, Namiki T, Murayama T, Horie S (2011). Distribution of transient receptor potential vanilloid 1 channel-expressing nerve fibers in mouse rectal and colonic enteric nervous system: relationship to peptidergic and nitrergic neurons. *Neuroscience* 172: 518–534.
- Mayer AM (1998). Therapeutic implications of microglia activation by lipopolysaccharide and reactive oxygen species generation in septic shock and central nervous system pathologies: a review. *Medicina (B Aires)* 58: 377–385.

- Mechiche H, Koroglu A, Candenas L, Pinto FM, Birembaut P, Bardou M *et al.* (2003). Neurokinins induce relaxation of human pulmonary vessels through stimulation of endothelial NK1 receptors. *J Cardiovasc Pharmacol* 41: 343–355.
- Mezey E, Tóth ZE, Cortright DN, Arzubi MK, Krause JE, Elde R *et al.* (2000). Distribution of mRNA for vanilloid receptor subtype 1 (VR1), and VR1-like immunoreactivity, in the central nervous system of the rat and human. *Proc Natl Acad Sci U S A* 97: 3655–3660.
- Miao X, Liu G, Xu X, Xie C, Sun F, Yang Y *et al.* (2008). High expression of vanilloid receptor-1 is associated with better prognosis of patients with hepatocellular carcinoma. *Cancer Genet Cytogenet* 186: 25–32.
- Murai M, Morimoto H, Maeda Y, Fujii T (1992). Effects of the tripeptide substance P antagonist, FR113680, on airway constriction and airway edema induced by neurokinins in guinea-pigs. *Eur J Pharmacol* 217: 23–29.
- Nakagawa N, Sano H, Iwamoto I (1995). Substance P induces the expression of intercellular adhesion molecule-1 on vascular endothelial cells and enhances neutrophil transendothelial migration. *Peptides* 16: 721–725.
- Neunaber C, Zeckey C, Andruszkow H, Frink M, Mommsen P, Krettek C *et al.* (2011). Immunomodulation in polytrauma and polymicrobial sepsis – where do we stand? *Recent Pat Inflamm Allergy Drug Discov* 5: 17–25.
- Ng SW, Zhang H, Hegde A, Bhatia M (2008). Role of preprotachykinin-A gene products on multiple organ injury in LPS-induced endotoxemia. *J Leukoc Biol* 83: 288–295.
- Nicolette R, Lima KdeM, Júnior JM, Jose PJ, Sanz MJ, Faccioli LH (2008). Prostaglandin E₂-loaded microspheres as strategy to inhibit phagocytosis and modulate inflammatory mediators release. *Eur J Pharm Biopharm* 70: 784–790.
- Noga O, Peiser M, Altenähr M, Schmeck B, Wanner R, Dinh QT *et al.* (2008). Selective induction of nerve growth factor and brain-derived neurotrophic factor by LPS and allergen in dendritic cells. *Clin Exp Allergy* 38: 473–479.
- O'Connor TM, O'Connell J, O'Brien DI, Goode T, Bredin CP, Shanahan F (2004). The role of substance P in inflammatory disease. *J Cell Physiol* 201: 167–180.
- Ochoa-Cortes F, Ramos-Lomas T, Miranda-Morales M, Spreadbury I, Ibeakanma C, Barajas-Lopez C *et al.* (2010). Bacterial cell products signal to mouse colonic nociceptive dorsal root ganglia neurons. *Am J Physiol Gastrointest Liver Physiol* 299: G723–G732.
- Okada T, Hirayama Y, Kishi S, Miyayasu K, Hiroi J, Fujii T (1999). Functional neurokinin NK-1 receptor expression in rat peritoneal mast cells. *Inflamm Res* 48: 274–279.
- Orsal AS, Blois S, Labuz D, Peters EM, Schaefer M, Arck PC (2006). The progesterone derivative dydrogesterone down-regulates neurokinin 1 receptor expression on lymphocytes, induces a Th2 skew and exerts hypoalgesic effects in mice. *J Mol Med* 84: 159–167.
- Pan XQ, Gonzalez JA, Chang S, Chacko S, Wein AJ, Malykhina AP (2010). Experimental colitis triggers the release of substance P and calcitonin gene-related peptide in the urinary bladder via TRPV1 signaling pathways. *Exp Neurol* 225: 262–273.
- Patacchini R, Santicioli P, Giuliani S, Maggi CA (2004). Hydrogen sulfide (H₂S) stimulates capsaicin-sensitive primary afferent neurons in the rat urinary bladder. *Br J Pharmacol* 142: 31–34.
- Patacchini R, Santicioli P, Giuliani S, Maggi CA (2005). Pharmacological investigation of hydrogen sulfide (H₂S) contractile activity in rat detrusor muscle. *Eur J Pharmacol* 509: 171–177.
- Patel L, Lindley C (2003). Aprepitant – a novel NK1-receptor antagonist. *Expert Opin Pharmacother* 4: 2279–2296.
- Pawlinski R, Mackman N (2004). Tissue factor, coagulation proteases, and protease-activated receptors in endotoxemia and sepsis. *Crit Care Med* 32: S293–S297.
- Pedersen SF, Owsianik G, Nilius B (2005). TRP channels: an overview. *Cell Calcium* 38: 233–252.
- Pennefather JN, Lecci A, Candenas ML, Patak E, Pinto FM, Maggi CA (2004). Tachykinins and tachykinin receptors: a growing family. *Life Sci* 74: 1445–1463.
- Pernow B (1953). Distribution of substance P in the central and peripheral nervous system. *Nature* 171: 746.
- Premkumar LS, Abooj M (2012). TRP channels and analgesia. *Life Sci* dx.doi.org/10.10016/j.lfs.2012.08.010.
- Puneet P, Hegde A, Ng SW, Lau HY, Lu J, Mochhala SM *et al.* (2006). Preprotachykinin-A gene products are key mediators of lung injury in polymicrobial sepsis. *J Immunol* 176: 3813–3820.
- Puntambekar P, Mukherjee D, Jajoo S, Ramkumar V (2005). Essential role of Rac1/NADPH oxidase in nerve growth factor induction of TRPV1 expression. *J Neurochem* 95: 1689–1703.
- Quartara L, Maggi CA (1997). The tachykinin NK1 receptor. Part I: ligands and mechanisms of cellular activation. *Neuropeptides* 31: 537–563.
- Rios-Santos F, Benjamim CF, Zavery D, Ferreira SH, Cunha FdeQ (2003). A critical role of leukotriene B₄ in neutrophil migration to infectious focus in cecal ligation and puncture sepsis. *Shock* 19: 61–65.
- Ro JY, Lee JS, Zhang Y (2009). Activation of TRPV1 and TRPA1 leads to muscle nociception and mechanical hyperalgesia. *Pain* 144: 270–277.
- Rogers DP, Wyatt CR, Walz PH, Drouillard JS, Mosier DA (2006). Bovine alveolar macrophage neurokinin-1 and response to substance P. *Vet Immunol Immunopathol* 112: 290–295.
- Romanovsky AA (2004). Signaling the brain in the early sickness syndrome: are sensory nerves involved? *Front Biosci* 9: 494–504.
- Russell FA, Fernandes ES, Courade JP, Keeble JE, Brain SD (2009). Tumour necrosis factor alpha mediates transient receptor potential vanilloid 1-dependent bilateral thermal hyperalgesia with distinct peripheral roles of interleukin-1beta, protein kinase C and cyclooxygenase-2 signalling. *Pain* 142: 264–274.
- Rychkov GY, Barritt GJ (2011). Expression and function of TRP channels in liver cells. *Adv Exp Med Biol* 704: 667–686.
- Samways DS, Egan TM (2011). Calcium-dependent decrease in the single-channel conductance of TRPV1. *Pflugers Arch* 462: 681–691.
- Sann H, Pierau FK (1998). Efferent functions of C-fiber nociceptors. *Z Rheumatol* 57: 8–13.
- Saunders CI, Kunde DA, Crawford A, Geraghty DP (2007). Expression of transient receptor potential vanilloid 1 (TRPV1) and 2 (TRPV2) in human peripheral blood. *Mol Immunol* 44: 1429–1435.
- Sawyer I, Smillie SJ, Bodkin JV, Fernandes E, O'Byrne KT, Brain SD (2011). The vasoactive potential of kisspeptin-10 in the peripheral vasculature. *PLoS ONE* 26: e14671.
- Schnizler K, Shutov LP, Van Kanegan MJ, Merrill MA, Nichols B, McKnight GS *et al.* (2008). Protein kinase A anchoring via AKAP150 is essential for TRPV1 modulation by forskolin and prostaglandin E₂ in mouse sensory neurons. *J Neurosci* 28: 4904–4917.

- Scotland RS, Chauhan S, Davis C, De Felipe C, Hunt S, Kabir J *et al.* (2004). Vanilloid receptor TRPV1, sensory C-fibers, and vascular autoregulation: a novel mechanism involved in myogenic constriction. *Circ Res* 95: 1027–1034.
- Shimaoka M, Park EJ (2008). Advances in understanding sepsis. *Eur J Anaesthesiol* 42: 146–153.
- Sipka A, Langner K, Seyfert HM, Schuberth HJ (2010). Substance P alters the in vitro LPS responsiveness of bovine monocytes and blood-derived macrophages. *Vet Immunol Immunopathol* 136: 219–226.
- Smart D, Gunthorpe MJ, Jerman JC, Nasir S, Gray J, Muir AI *et al.* (2000). The endogenous lipid anandamide is a full agonist at the human vanilloid receptor (hVR1). *Br J Pharmacol* 129: 227–230.
- Snider RM, Constantine JW, Lowe JA 3rd, Longo KP, Lebel WS, Woody HA *et al.* (1991). A potent nonpeptide antagonist of the substance P (NK1) receptor. *Science* 251: 435–437.
- Starr A, Graepel R, Keeble J, Schmidhuber S, Clark N, Grant A *et al.* (2008). A reactive oxygen species-mediated component in neurogenic vasodilatation. *Cardiovasc Res* 78: 139–147.
- Sun J, Ramnath RD, Bhatia M (2007). Neuropeptide substance P upregulates chemokine and chemokine receptor expression in primary mouse neutrophils. *Am J Physiol Cell Physiol* 293: C696–C704.
- Szolcsányi J, Jancsó-Gábor A (1975). Sensory effects of capsaicin congeners I. Relationship between chemical structure and pain-producing potency of pungent agents. *Arzneimittelforschung* 25: 1877–1881.
- Tamizhselvi R, Shrivastava P, Koh YH, Zhang H, Bhatia M (2011). Preprotachykinin-A gene deletion regulates hydrogen sulfide-induced toll-like receptor 4 signalling pathway in cerulein-treated pancreatic acinar cells. *Pancreas* 40: 444–452.
- Tékus V, Bölcskei K, Kis-Varga A, Dézsi L, Szentirmay E, Visegrády A *et al.* (2010). Effect of transient receptor potential vanilloid 1 (TRPV1) receptor antagonist compounds SB705498, BCTC and AMG9810 in rat models of thermal hyperalgesia measured with an increasing-temperature water bath. *Eur J Pharmacol* 641: 135–141.
- Tominaga M, Caterina MJ, Malmberg AB, Rosen TA, Gilbert H, Skinner K *et al.* (1998). The cloned capsaicin receptor integrates multiple pain-producing stimuli. *Neuron* 21: 531–543.
- Trevisani M, Patacchini R, Nicoletti P, Gatti R, Gazzieri D, Lissi N *et al.* (2005). Hydrogen sulfide causes vanilloid receptor 1-mediated neurogenic inflammation in the airways. *Br J Pharmacol* 145: 1123–1131.
- Tuncer LI, Alaçam T, Oral B (2004). Substance P expression is elevated in inflamed human periradicular tissue. *J Endod* 30: 329–332.
- Ufret-Vincenty CA, Klein RM, Hua L, Angueyra J, Gordon SE (2011). Localization of the PIP2 sensor of TRPV1 ion channels. *J Biol Chem* 286: 9688–9698.
- Varga K, Wagner JA, Bridgen DT, Kunos G (1998). Platelet- and macrophage-derived endogenous cannabinoids are involved in endotoxin-induced hypotension. *FASEB J* 12: 1035–1044.
- Vercelli CA, Aisemberg J, Billi S, Cervini M, Ribeiro ML, Farina M *et al.* (2009). Anandamide regulates lipopolysaccharide-induced nitric oxide synthesis and tissue damage in the murine uterus. *Reprod Biomed Online* 18: 824–831.
- Voight EA, Kort ME (2010). Transient receptor potential vanilloid-1 antagonists: a survey of recent patent literature. *Expert Opin Ther Pat* 20: 1107–1122.
- Von Euler US, Gaddum JH (1931). An unidentified depressor substance in certain tissue extracts. *J Physiol* 72: 74–87.
- Wadachi R, Hargreaves KM (2006). Trigeminal nociceptors express TLR-4 and CD14: a mechanism for pain due to infection. *J Dent Res* 85: 49–53.
- Walker KM, Urban L, Medhurst SJ, Patel S, Panesar M, Fox AJ *et al.* (2003). The VR1 antagonist capsazepine reverses mechanical hyperalgesia in models of inflammatory and neuropathic pain. *J Pharmacol Exp Ther* 304: 56–62.
- Wall PD (1982). The effect of peripheral nerve lesions and of neonatal capsaicin in the rat on primary afferent depolarization. *J Physiol* 329: 21–35.
- Wanner SP, Garami A, Pakai E, Oliveira DL, Gavva NR, Coimbra CC *et al.* (2012). Aging reverses the role of the transient receptor potential vanilloid-1 channel in systemic inflammation from anti-inflammatory to proinflammatory. *Cell Cycle* 11: 343–349.
- Westphal M, Sander J, Van Aken H, Ertmer C, Stubbe HD, Booke M (2006). Role of adrenomedullin in the pathogenesis and treatment of cardiovascular dysfunctions and sepsis. *Anaesthesist* 55: 171–178.
- Yang D, Luo Z, Ma S, Wong WT, Ma L, Zhong J *et al.* (2010). Activation of TRPV1 by dietary capsaicin improves endothelium-dependent vasorelaxation and prevents hypertension. *Cell Metab* 12: 130–141.
- Zhang H, Zhi L, Moochhala S, Moore PK, Bhatia M (2007a). Hydrogen sulfide acts as an inflammatory mediator in cecal ligation and puncture-induced sepsis in mice by upregulating the production of cytokines and chemokines via NF-kappaB. *Am J Physiol Lung Cell Mol Physiol* 292: L960–L971.
- Zhang H, Hegde A, Ng SW, Adhikari S, Moochhala SM, Bhatia M (2007b). Hydrogen sulfide up-regulates substance P in polymicrobial sepsis-associated lung injury. *J Immunol* 179: 4153–4160.
- Zhang L, Jones S, Brody K, Costa M, Brookes SJ (2004). Thermosensitive transient receptor potential channels in vagal afferent neurons of the mouse. *Am J Physiol Gastrointest Liver Physiol* 286: G983–G991.
- Zhang X, Li L, McNaughton PA (2008). Proinflammatory mediators modulate the heat-activated ion channel TRPV1 via the scaffolding protein AKAP79/150. *Neuron* 59: 450–461.
- Zimmer A, Zimmer AM, Baffi J, Usdin T, Reynolds K, König M *et al.* (1998). Hypoalgesia in mice with a targeted deletion of the tachykinin 1 gene. *Proc Natl Acad Sci U S A* 95: 2630–2635.
- Zygmunt PM, Petersson J, Andersson DA, Chuang H, Sørghard M, Di Marzo V *et al.* (1999). Vanilloid receptors on sensory nerves mediate the vasodilator action of anandamide. *Nature* 400: 452–457.