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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.

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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-1β, IL 1 beta; IL-6, IL 6; KO, knock-out; LTB_4, leukotriene B_4; MCP-1, monocyte chemotactic protein 1; MIP-2, macrophage inflammatory protein 2; NK, neurokinin; NK_{1-3}, NK receptor subtype 1–3; NKA, neurokinin A; NKB, neurokinin B; NPY, neuropeptide Y; PIP_2, 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 in to 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 in to 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 Aδ 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 in to 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-biphosphate (PIP_2) (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 (LTB_4) (Hwang *et al*., 2000), and reactive oxygen species (hydrogen peroxide, H_2O_2; 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 E_2 (PGE_2), 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 s 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 lead 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 *et al.*, 1999; Smart *et al.*, 2000)	Anandamide mediates LPS-induced NO release (Vercelli *et al.*, 2009) and hypotension in septic shock induced by LPS (Varga *et al.*, 1998; Bátkai *et al.*, 2004). The anandamide antagonist AM281 reduces mortality in rats with CLP-induced sepsis (Kadoi *et al.*, 2005).
Lipoxygenase products (e.g. LTB_4) (Hwang *et al.*, 2000)	LTB_4 receptor blockade reduces NO, increases bacterial load and reduces survival in mice with sepsis caused by CLP (Rios-Santos *et al.*, 2003).
ROS (e.g. H_2O_2) (Keeble *et al.*, 2009)	Increased levels of H_2O_2 are produced so to the phagocytes are able to kill pathogens (Henricks *et al.*, 1986; Mayer, 1998)
Endogenous modulators (via activation of intracellular pathways)	
Bradykinin (Chuang *et al.*, 2001)	Increased circulating levels of kallikrein are present in patients with early sepsis and their levels are correlated with sepsis severity (Asmis *et al.*, 2008)
PAR-2 agonists (Amadesi *et al.*, 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 *et al.* (2004) suggested suggest 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 (Schnizler *et al.*, 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 (Nicolete *et al.*, 2008)
NGF (Chuang *et al.*, 2001)	LPS-treated human macrophages overexpress NGF and its receptors (Caroleo *et al.*, 2001). Similarly, NGF is up-regulated in human dendritic cells challenged with LPS (Noga *et al.*, 2008). In addition, NGF attenuates neuronal death following LPS treatment (Ansari *et al.*, 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 capsazepine'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	• Lymphocytes (Saunders *et al.*, 2007) • Macrophages (Rogers *et al.*, 2006; Fernandes *et al.*, 2012b) *Function* → Phagocytosis, thus control of bacterial load (Guptill *et al.*, 2011; Fernandes *et al.*, 2012b). → Mediator release (Fernandes *et al.*, 2012b).	• Lymphocytes (Cantalupo *et al.*, 2008) • Macrophages (Ho *et al.*, 1997) • Neutrophils (Tuncer *et al.*, 2004) *Function* → Bacterial phagocytosis (Fernandes *et al.*, 2012b). → Activation of immune cells (Katsanos *et al.*, 2008). → Inflammatory mediator release (Sipka *et al.*, 2010).	• Lymphocytes (Orsal *et al.*, 2006; Kitamura *et al.*, 2012) • Macrophages (Fernandes *et al.*, 2012b) • Mast cells (Okada *et al.*, 1999) • Neutrophils (Gallicchio *et al.*, 2009) *Function* → Release of inflammatory mediators (Foreman *et al.*, 1983; Katsanos *et al.*, 2008). → Regulation of apoptosis by NK_1 (Fernandes *et al.*, 2012b).
Intestine	Gut movement reduces bacterial growth	• Sensory neurones (Zhang *et al.*, 2004) *Function* → Modulation of neuropeptide release and muscle tone (Matsumoto *et al.*, 2011). → Potential regulation of bacterial translocation in abdominal sepsis.	• Sensory neurones (Hökfelt *et al.*, 2001) *Function* → SP expression is reduced in the gut following peritonitis (Jacob *et al.*, 2007). → Potential regulation of bacterial translocation and growth in abdominal sepsis.	• Expression of NK_{1-3} on several cell types (Holzer and Holzer-Petsche, 1997; Improta and Broccardo, 2006). *Function* → Facilitation of gut peristalsis (Holzer and Holzer-Petsche, 1997; Hökfelt *et al.*, 2001). → Potential regulation of bacteria translocation and growth in abdominal sepsis.
Vasculature	Plays an important role in sepsis related hypotension	• Smooth muscle (Kark *et al.*, 2008) • Endothelial cells (Ching *et al.*, 2011) *Function* → Vessel contraction (Kark *et al.*, 2008). → Vessel dilation (Ching *et al.*, 2011). → Protection from hypotension (Clark *et al.*, 2007; Fernandes *et al.*, 2012b).	• Sensory neurones innervating blood vessels (Hökfelt *et al.*, 2001) *Function* → Increased circulating levels of SP are associated with negative consequences on sepsis outcome (Beer *et al.*, 2002). → Vessel dilation, vascular permeability and migration (Nakagawa *et al.*, 1995; Mechiche *et al.*, 2003).	• Vascular smooth muscle (NK_1) • Endothelial cells (NK_1) *Function* → Vessel contraction to maintain myogenic tone (Scotland *et al.*, 2004). → Vessel dilation and vascular permeability (Mechiche *et al.*, 2003). → Up-regulation of adhesion molecules and leukocyte migration (Nakagawa *et al.*, 1995).
Lungs	A key site of organ failure	• Sensory neurones (Dinh *et al.*, 2004) *Function* → Mediates neuropeptide release, potential lung oedema and bronchoconstriction (Jia and Lee, 2007). → Reduction of lung function.	• Autonomic and sensory neurones innervating respiratory tracts (Dinh *et al.*, 2004; Joachim *et al.*, 2006). *Function* → Preprotachykinin gene deletion protects against lung injury (Puneet *et al.*, 2006) and mortality (Hegde *et al.*, 2010) in sepsis.	• Smooth muscle cells (NK_1 and NK_2) • Endothelial cells (NK_1) *Function* → Bronchoconstriction (Murai *et al.*, 1992). → Lung oedema (Helyes *et al.*, 2010).
Liver	A key site of organ failure	• Hepatocytes (Rychkov and Barritt, 2011). • Sensory neurones (Miao *et al.*, 2008) *Function* → Possible role on liver failure?	• Sensory neurones innervating the liver (Fehér *et al.*, 1992). *Function* → Possible role on liver failure?	• Liver bile duct epithelium (Glaser *et al.*, 2011) *Function* → 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 TNFα 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 [H_2O_2 and superoxide (O_2^-)] generation and TRPV1. H_2O_2 is known to activate TRPV1 (Keeble *et al.*, 2009) while O_2^- production has been linked to TRPV1 up-regulation (Puntambekar *et al.*, 2005; Starr *et al.*, 2008). Furthermore, both H_2O_2 and O_2^- 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 TNFα 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 PGE_2 *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 (H_2O_2 and O_2^-) 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 (NK_1) receptor

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

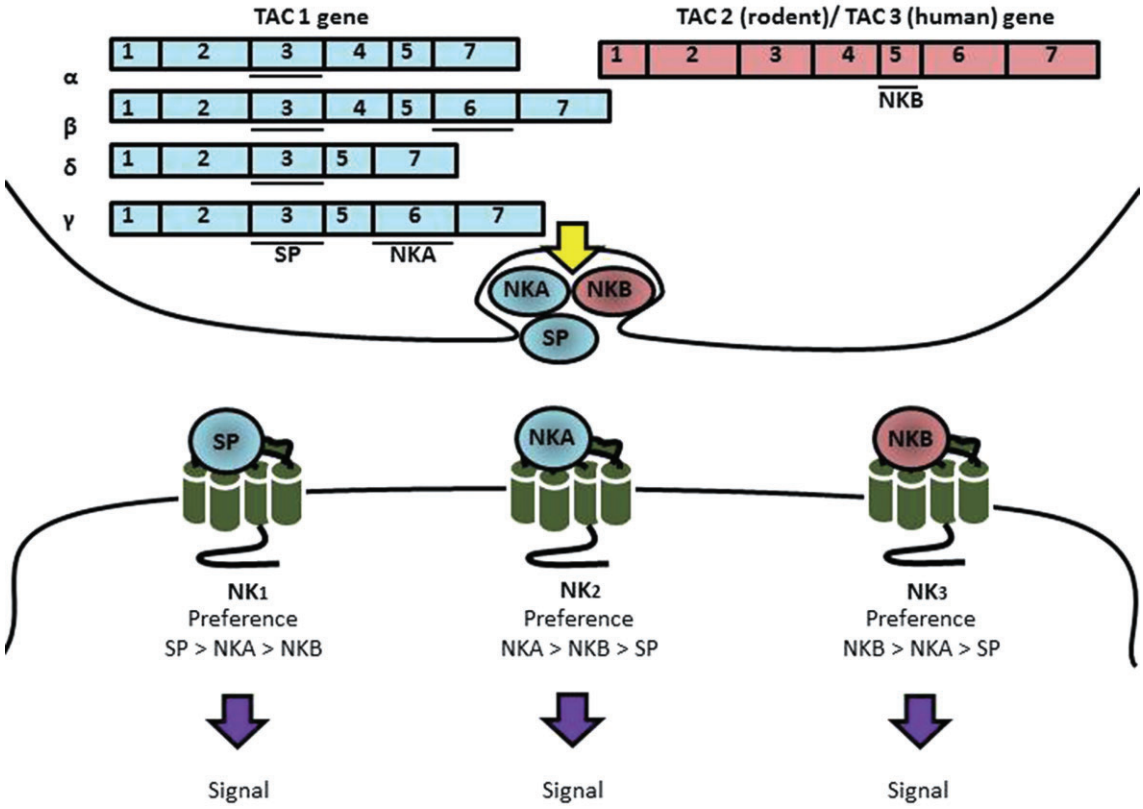

Figure 1

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 NK_1 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 NK_1 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 NK_1 antagonists alone, with over a dozen entering clinical trials (Huang and Korlipara, 2010). These trials reveal the potential role for SP/NK_1 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 NK_1 antagonists can be found in Huang and Korlipara (2010). Despite much effort from the pharmaceutical industry to develop NK_1 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 NK_1 antagonists have become common in the experimental literature, and are successfully utilized in animal disease models. Of these, CP-96345 (IC_{50} in low nM, Snider *et al.*, 1991) and SR140333 (IC_{50} in the mid- pM range, Croci *et al.*, 1995) are the most commonly used. Thus, several potent and selective antagonists of the SP/NK_1 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. NK_1KO 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 NK_1KO 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 (H_2S) and PPT proteins act together to upregulate NF-κB 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. NK_1 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 (Espiritu *et al.*, 1992) and in the blood during systemic inflammations, such as sepsis (Beer *et al.*, 2002). These findings suggest that inhibition of SP/NK_1 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 NK_1 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 NK_1 receptor (O'Connor *et al.*, 2004), and are detrimental in sepsis. NK_1 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. NK_1 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 NK_1 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. NK_1 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-1β and IL-6 levels in the lung were reduced by NK_1 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 NK_1 activation, as an NK_2 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 NK_1 antagonism to reduce PKC, NF-κB, activator protein 1 and extracellular signal-regulated kinase (ERK) activation in lung homogenates, suggesting NK_1 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 NK_1 receptor. Leukocytes may also contribute to the production of chemokines and cytokines following NK_1 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/NK_1 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 imunosupressive 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 NK_1 receptors (Lai *et al.*, 1998), thus potentially providing both paracrine and autocrine stimulation. Recently, the activation of NK_1 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 H_2S. 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). H_2S 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 H_2S 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). H_2S donors have also been shown to aggravate inflammation and organ damage in murine CLP-induced sepsis, due to activation of NF-κB 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 H_2S formation to show that H_2S 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 H_2S, suggesting that H_2S 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 H_2S-induced SP production in a model of CLP-induced sepsis. This resulted in reduced ERK and NF-κB activation, associated with reduced cytokines and chemokines and reductions in lung and liver damage compared with vehicle-treated mice. H_2S 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 H_2S. 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 NK_1 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.

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