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Targeting neural reflex circuits in immunity to treat kidney disease

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Abstract

Neural pathways regulate immunity and inflammation via the inflammatory reflex and specific molecular targets can be modulated by stimulating neurons. Neuroimmunomodulation by nonpharmacological methods is emerging as a novel therapeutic strategy for inflammatory diseases, including kidney diseases and hypertension. Electrical stimulation of vagus neurons or treatment with pulsed ultrasound activates the cholinergic anti-inflammatory pathway (CAP) and protects mice from acute kidney injury (AKI). Direct innervation of the kidney, by afferent and efferent neurons, might have a role in modulating and responding to inflammation in various diseases, either locally or by providing feedback to regions of the central nervous system that are important in the inflammatory reflex pathway. Increased sympathetic drive to the kidney has a role in the pathogenesis of hypertension, and selective modulation of neuroimmune interactions in the kidney could potentially be more effective for lowering blood pressure and treating inflammatory kidney diseases than renal denervation. Use of optogenetic tools for selective stimulation of specific neurons has enabled the identification of neural circuits in the brain that modulate kidney function via activation of the CAP. In this Review we discuss evidence for a role of neural circuits in the control of renal inflammation as well as the therapeutic potential of targeting these circuits in the settings of AKI, kidney fibrosis and hypertension.

The prevalence of kidney disease is increasing worldwide[1,2]. In the USA, estimates suggest that more than 20 million people have kidney disease, of whom nearly 700,000 have reached end-stage renal disease (ESRD) requiring dialysis or transplantation[2]. The incidence of acute

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kidney injury (AKI) is also increasing[3,4]. AKI is associated with high mortality, morbidity, risk of chronic kidney disease (CKD) and ESRD[5]. As a consequence of gaps in our understanding of the pathophysiology of AKI, limited clinical and pathological data, adverse effects of pharmacological agents[6,7], and a lack of data in good animal models[8], effective treatment of AKI in well-designed clinical trials remains elusive. No approved pharmacological agents exist for the prevention and treatment of AKI, thus novel therapies and innovative approaches are needed.

Neuroimmunomodulation is an important area of therapeutics that is based on the bidirectional control by the brain of the physiological functions of various organ systems, including the cardiovascular, digestive, respiratory, and immune systems. Advances in the elucidation of neural circuits that control immunity and inflammation[9–12] offer new approaches to therapies for kidney disease[13]. An NIH initiative on peripheral nerve control of organ function (Stimulating Peripheral Activity to Relieve Conditions) aims to catalyse the development of next-generation therapies based on neuromodulatory control of organ function[14].

Accumulating evidence exists of the value in using electrodes to modulate nerve signalling as a new nonpharmacologic method for the control of hypertension, heart failure, obesity, epilepsy, inflammation, diabetes mellitus, bronchoconstriction (forming the basis of anticholinergic treatment of chronic obstructive pulmonary disease), migraine and other diseases[15–18]. In particular, vagus nerve stimulation (VNS) attenuates inflammation, and preliminary early clinical trials show efficacy of VNS for the treatment of rheumatoid arthritis[19] and Crohn disease[20]. To date, however, none of the published clinical studies of VNS include kidney disease.

Collaborative, multidisciplinary approaches have the potential to shed new light on the pathogenesis of AKI and other kidney diseases, as well as on kidney-related diseases such as hypertension, and could lead to innovative therapeutic interventions. In this Review, we high-light the molecular and cellular basis for neural control of immunity as a paradigm to guide novel approaches for the treatment of kidney disease.

Regulation of immunity by neural reflexes

The nervous and immune systems have long been studied independently. Over the last few decades, however, considerable advances have led to the understanding that these two systems are inextricably linked to maintain normal homeostasis as well as to respond to stress and pathophysiological disorders[21].

In the 19th century, the germ theory advanced by Louis Pasteur[22], and later by Robert Koch[23], demonstrated that pathogens cause disease. Subsequently, Claude Bernard described the milieu or environment necessary to maintain equilibrium and health[24], and Lewis Thomas elegantly described the importance of host sensing of bacteria and the host response to bacterial products, such as lipopolysaccharide (LPS)[25]. During sepsis, immediate activation of both pro-inflammatory and anti-inflammatory immune responses occurs and the balance of these pathways is important for favourable outcomes[26]. A hyper-

inflammatory pathway in the absence of the counterbalancing anti-inflammatory pathway might lead to overwhelming inflammation and death. Thus, the immediate early anti-inflammatory response seems to be critical to maintain balance.

A well-known mechanism of the neuroimmune control of inflammation is dependent upon the hypothalamic–pituitary–adrenal axis[27]. During stress, the pituitary gland produces adrenocorticotropic hormone and the adrenal glands are stimulated to release hormones that affect almost all types of immune cells. These immune cells perform immunosuppressive and anti-inflammatory functions through various genomic and non-genomic mechanisms[27].

A seminal study by Linda Watkins provided early evidence that the nervous system also directly initiates the response to inflammation[28]. She demonstrated that IL-1β-induced hyperthermia could be blocked by subdiaphragmatic vagotomy, indicating that the afferent limb of the vagus nerve is necessary to induce the febrile response to intraperitoneal injection of IL-1β. Sensory neurons in close proximity to immune cells in the periphery respond to inflammatory products and send signals to the central nervous system (CNS)[29–31]. Afferent sensory nerve fibres also detect bacterial products (pathogen-associated molecular patterns), pro-inflammatory cytokines, immunoglobulins and ATP[32].

The sensory afferent vagus nerve expresses IL-1β receptors[33], tumour necrosis factor (TNF) receptors[34], Fc receptors[35], Toll-like receptor 4 and P2X purinergic receptors[36,37]. Upon activation, this nerve sends signals to and activates neurons of the brainstem nucleus tractus solitarius[30,38,39], which is one of its primary terminal fields[40]. This activation culminates in activation of efferent vagus nerve signals that suppress monocyte and/or macrophage production of inflammatory cytokines such as TNF and IL-6[9], and attenuate inflammation in the liver, heart[41], pancreas[42], gastrointestinal tract[43–45] and kidney[13]. This vagus nerve circuit is referred to as the inflammatory reflex. VNS has been exploited to modulate the immune system[46] and is being studied as a nonpharmacological tool for neuroimmunomodulation in disorders including myocardial infarction, colitis, pancreatitis, ischaemia–reperfusion injury, sepsis and arthritis[47].

The cholinergic anti-inflammatory pathway

Once bacteria or bacterial products penetrate the initial barriers and gain access to the blood, the next line of defence is the reticuloendothelial system — tissues including those of the spleen, liver, lung, and peritoneum[48] that contain phagocytic myeloid cells (presumably macrophages) and are the terminal target of the inflammatory reflex. The spleen is a major component of the reticuloendothelial system and an important source of TNF production as evidenced by the finding that VNS-induced inhibition of TNF production is attenuated in splenectomized animals[49].

The efferent arm of the inflammatory reflex, which mediates inhibition of systemic inflammation by VNS, is termed the cholinergic-anti-inflammatory pathway (CAP)[9]. This pathway also requires the spleen[49,50]. Vagus efferent neurons are cholinergic and upon activation release acetylcholine from their nerve terminals. Although the spleen contains acetylcholine, vagus nerve fibres, which originate in the brainstem in the dorsal motor

nucleus of the vagus, do not innervate the spleen[51,52]. Noradrenergic nerve fibres in the spleen, which originate in the coeliac ganglion and produce noradrenaline as their primary neurotransmitter, terminate in the white pulp around splenic T cells[50,51]. Despite the absence of cholinergic innervation, splenic acetylcholine levels increase following inflammatory reflex stimulation[53].

Some immune cells, such as T cells, dendritic cells and macrophages, can synthesize and secrete neurotransmitters and express neurotransmitter receptors that permit control of the immune response to infection by the CNS and peripheral nervous system[54]. Rosas-Ballina *et al.* found that $CD4^+$ T cells provide a link between VNS-mediated activation of the inflammatory reflex, sympathetic innervation of the spleen and increased acetylcholine levels[53]. In response to noradrenaline, $CD4^+$ T cells release acetylcholine[53], likely via β-adrenergic receptor stimulation[55]. In mice, VNS produced a rapid increase in acetylcholine levels in the spleen that peaked within 20 min[53].

To identify the cells that produce acetylcholine in the spleen, Rosas-Ballina *et al.* used mice that express enhanced green fluorescent protein (eGFP) under the control of transcriptional regulatory elements for choline acetlytransferase (ChAT), which catalyses the biosynthesis of acetylcholine[53]. Using flow cytometry analysis, they showed that $CD4^+$ T cells that express ChAT (ChAT-eGFP $^+$ T cells) can be defined phenotypically as $CD44^{high}CD62L^{low}$ memory T cells. In dual labelling studies, neuronal synapses expressing synaptophysin were localized adjacent to ChAT-eGFP $^+$ T cells within the white pulp of the spleen, providing an anatomical basis for splenic nerve fibres interacting with acetylcholine-producing T cells. Acetylcholine released from these T cells is thought to bind to macrophages in the spleen[53].

Macrophages express α7 nicotinic acetylcholine receptors (α7nAChR), and VNS or nicotine, which is an α7nAChR agonist, suppress LPS-induced increases in serum TNF levels and splenic TNF content, or macrophage TNF release, respectively[56]. Moreover, VNS failed to inhibit LPS-induced increases in serum TNF in α7nAChR-deficient mice[56]. Thus acetylcholine-synthesizing splenic CD4 $^+$ T cells link vagus nerve signals with the anti-inflammatory role of the spleen[53] (FIG. 1). The cellular mechanism underlying α7nAChR-induced suppression of TNF production involves inhibition of STAT3 phosphorylation and sequestration of NF-κB[21,57,58]. Although many of the functional components of the CAP have been defined, ongoing studies of these mechanisms suggest that the principles of reflex control of immunity can be exploited in other tissues[32].

The inflammatory reflex pathway in AKI

Despite the critical role of inflammation in the pathogenesis of AKI, few studies have addressed the role of the vagus nerve or the inflammatory reflex pathway in this setting. In rodents, pretreatment with nicotine or the nicotine analogue GTS-21 attenuated renal ischaemia–reperfusion injury (IRI)[59] or septic AKI[60], suggesting that nicotinic acetylcholine receptors might mediate an anti-inflammatory response after kidney injury. Preclinical studies of VNS and pulsed ultrasound application have also provided evidence of a role of the CAP in protection from AKI.

Vagus nerve stimulation

In mice, electrical stimulation of vagus afferent or efferent nerves 24 h before IRI markedly attenuated kidney injury and caused a decrease in plasma TNF levels[13]. This protective effect could be abolished by splenectomy 7 days before VNS. The protective effect of VNS was also lost in mice deficient in α7nAChR, and conditioned α7nAChR splenocytes from VNS-treated donor mice transferred protection when injected into naive recipients subjected to IRI. These findings demonstrate that α7nAChR positive splenocytes are required for VNS-induced attenuation of AKI and systemic inflammation.

AKI has an important role in determining outcomes in transplantation. In particular, brain death of the donor results in the release of pro-inflammatory mediators and an increase in adhesion molecules that leads to inflammation and pretransplantation injury to peripheral organs, including the kidney[61]. The inflammatory milieu in the deceased donor could, therefore, contribute to shortened graft survival in the recipient[61].

Hoeger and co-workers showed that in rats, VNS attenuated the pro-inflammatory response to brain death (that is, an increase in serum TNF levels and in the expression of pro-inflammatory genes in the small intestine, liver, kidney and heart)[61]. Moreover, VNS of brain-dead donor rats before kidney transplantation resulted in improved recipient and organ survival[61,62]. At 16 weeks post-transplantation, serum creatinine levels were significantly lower in recipients of kidneys from donors that had undergone VNS than in recipients of kidneys from donors that had not undergone VNS[62]. Moreover, histological analysis showed that kidneys from rats that had undergone VNS had reduced vasculopathy and tubulopathy compared with controls. These findings suggest that VNS of deceased kidney donors before transplantation could potentially lead to improved outcomes in the recipient, but this hypothesis has not yet been evaluated clinically. This concept also raises questions of whether VNS in transplant recipients might also be beneficial, and whether performing VNS in both donors and recipients might further increase the efficacy of the intervention.

VNS therapy using a device that is surgically implanted to stimulate the vagus nerve was approved for the treatment of medically refractory epilepsy in Europe in 1994 and in the USA by the FDA in 1997 (REF. 63). In addition, the FDA approved VNS therapy for treatment-resistant depression in 2005 (REF. 63). As of August 2014, over 100,000 VNS devices had been implanted in more than 75,000 patients worldwide[64]. Clinical trials of VNS for the treatment of a wide variety of disorders, such as heart failure, hypertension, inflammation and diabetes, are on-going.

Two non-invasive external devices have now been developed to stimulate the vagus nerve through the skin[63,64]. Transcutaneous VNS can be accomplished using a dedicated intra-auricular electrode (similar to an earphone) that stimulates the auricular branch of the vagus nerve[64]. In addition, a transcutaneous device has been developed that can deliver a proprietary, low-voltage electrical signal to the cervical vagus nerve[64]. In 2016, transcutaneous cervical VNS was reported to protect against cerebral ischaemic injury in rats[65]. In addition, a pilot trial showed that VNS using a gammaCore® transcutaneous device could downregulate inflammatory cytokine release in healthy individuals[66]. These findings

suggest that a non-invasive vagus nerve stimu lator could be safely applied in clinical practice and should be evaluated as a potential preventive therapy for ischaemic AKI and other inflammatory conditions.

Ultrasound stimulation

Similar to VNS, delivery of pulsed ultrasound to the spleen using a clinical ultrasound machine could prevent AKI in mice[67,68]. A single ultrasound application 1–2 days before IRI suppressed systemic inflammation and attenuated AKI. The efficacy waned in a time-dependent manner when ultrasound was applied up to 7 days before IRI[68]. The mechanism of this persistent activation state is unknown, but the effect can be thought of as analogous to that of a vaccine that protects against tissue injury resulting from AKI or sepsis, as well as against the systemic dysregulated immune response in these conditions. A protective effect of ultrasound in AKI has also been shown in a model of sepsis induced by caecal ligation and puncture[69].

Several findings suggest that ultrasound-induced protection of the kidney from IRI occurs through activation of the CAP[67,68]. First, the spleen is required for this protective effect as evidenced by its abrogation in mice that were splenectomized 7 days before ultrasound treatment[68]. Second, chemical sympathectomy of the spleen using direct splenic injections of 6-hydroxydopamine (a neurotoxin that destroys cate cholaminergic neurons[70]) 14 days before ultrasound abolished the protective effect[69], indicating a requirement for innervation of the spleen. Third, the protective effect of ultrasound was absent in *Rag1*$^{-/-}$ mice, which lack T cells and B cells, but could be reconstituted by adoptive transfer of CD4^{+} T cells[68]. Fourth, a series of experiments demonstrated that α7nAChR-positive splenocytes were necessary for the protective effect of ultrasound[69]. This protective effect was observed in chimeric mice that expressed α7nAChR in bone-marrow-derived cells, but not in those that lacked α7nAChR expression in these cells. Moreover, splenocytes that were isolated from ultrasound-treated wild-type donor mice protected wild-type recipients from IRI, whereas splenocytes from ultrasound-treated *α7nAChR*$^{-/-}$ donor mice did not confer such protection[69]. Finally, the protective effect of ultrasound was absent in mice that were treated with α-bungarotoxin, which blocks α7nAChRs, and was mimicked in mice treated with an α7nAChR agonist[68]. Taken together, these results strongly suggest that similar to VNS, ultrasound-mediated protection from IRI is due to activation of the CAP, and that stimu lation of the CAP using ultrasound is a promising nonpharmacological and non-invasive strategy for prevention of AKI.

CNS regulation of the inflammatory reflex

In addition to activating the inflammatory reflex pathway by signals in the periphery (involving neurons of the peripheral nervous system), evidence from early studies suggests that the brain can control the inflammatory reflex. For example, in rats, intracerebroventricular injection of the anti-inflammatory agent CNI-1493 (a tetravalent guanylhydrazone) suppressed carrageenan-induced paw oedema and inflammation[71]. These effects of CNI-1493 were abrogated by atropine, a muscarinic acetylcholine receptor (mAChR) antagonist, or by bilateral cervical vagotomy. These findings are consistent with

activation of the inflammatory reflex pathway from sites in the CNS and demonstrate the requirement for an intact vagus nerve in mediating the central effects of CNI-1493. Similarly intracerebroventricular injection of a mAChR agonist blocked endotoxin-induced systemic inflammation in rats[72]. These studies demonstrate an important ability of the CNS to control the inflammatory reflex pathway; however, they do not specifically identify regions that regulate this pathway.

Role of C1 neurons

C1 neurons reside in the medullary reticular formation and are glutamatergic, catecholaminergic and peptidergic[73–75]. These neurons have several properties that make them good candidates for a potential role as part of an integrative centre for the neuroimmune reflex in the CNS. Stress responses mobilize the autonomic nervous system, especially the sympathetic division[73–75], and C1 neurons are important for central regulation of autonomic function (particularly cardiovascular function) and also seem to be sensors for various autonomic physical stressors. They project to sympathetic preganglionic neurons in the spinal cord and innervate a variety of brain regions, including the dorsal motor nucleus of the vagus and the paraventricular nucleus of the hypothala mus. Furthermore, subsets of C1 cells are activated by circulating IL-1 and LPS[73], suggesting that they could regulate the immune system by controlling the corticotropin-releasing factor/adrenocorticotropic hormone/corticosterone cascade or the autonomic nervous system.

To investigate whether C1 neurons control the inflammatory reflex pathway to attenuate inflammation and AKI, Abe *et al.* used optogenetic technology[76] (described below). Using transgenic mice that selectively expressed channel rhodopsin-2 in C1 neurons, they showed that optogenetic stimulation of these neurons protected the kidneys from IRI. This C1 neuron-activated protection was dependent on the spleen, β2-adrenergic receptors and α7nAChRs, suggesting that it was mediated by the CAP. Additional experiments suggested that C1 neuron-mediated CAP activation occurred through activation of a sympathetic pathway[76]. These findings suggest that the CNS controls the inflammatory reflex in part through C1 neurons (FIG. 1).

Neural circuits in the kidney

In addition to a role of inflammatory reflexes, including the CAP, in modulating the response to AKI[13,68,69,76], direct innervation of the kidney might be important in regulating immunity and inflammation. Anatomical and physiological evidence suggest that neural circuits, including afferent and efferent innervation of the kidney, provide pathways for regulation of kidney function and disease states by the peripheral nervous system, and for feedback within the kidney and likely to the CNS[77,78] (FIG. 2).

Efferent sympathetic renal neurons arborize in a widely distributed pattern in the kidney, with noradrenergic terminals contacting the vasculature and tubules, particularly along the proximal tubules[79]. Increased renal sympathetic nerve activity (RSNA), and hence increased noradrenaline release, decrease renal blood flow and increase sodium retention and renin release[80,81].

Terminal fields of afferent renal sensory neurons, whose cell bodies reside in the dorsal root ganglion[82], have a much sparser distribution than sympathetic efferents. Sensory nerve fibres in the kidney contain substance P[83,84] and calcitonin gene-related protein (CGRP)[84] and are mechanosensitive and chemosensitive[85–87]. Afferent renal sensory neurons project to the dorsal horn of the spinal cord[88], where they synapse with neurons projecting to regions of the brainstem and hypothalamus, and perhaps directly to the brainstem[89], thus providing pathways for feedback to the CNS. At present, whether sensory information from the kidney can activate the inflammatory reflex is not known. However these sensory afferents have been shown to respond to various stimuli, such as bradykinin, substance P, capsaicin, and prostaglandins[90,91]. Sensory afferents, including vagus afferents[92], are glutamatergic, which enables them to be discriminated from cholinergic vagus efferents, as has been elegantly shown in the lung[93]. Within the kidney, interactive relationships exist between sympathetic renal efferent and sensory renal afferent nerves; these reno-renal reflexes have been studied in various disease states, such as hypertension and diabetes[81,90,94]. RSNA results in the release of noradrenaline, which increases renal afferent nerve activity and provides feedback to inhibit RSNA.

No evidence exists of parasympathetic innervation of the kidney (that is, vagus efferents). By contrast, evidence for vagus afferents in the kidney is controversial and requires additional investigation. Retrograde tract tracing studies in rats revealed that the nodose ganglion (the inferior ganglion of the vagus nerve) contains cell bodies of neurons that project to the kidney[95,96]. These results suggest the presence of vagus afferents in the kidney; however, further studies are needed to determine their function. Moreover, these vagus afferents target the nucleus of the solitary tract in the brain, an area that is important for regulation of autonomic function in the periphery[97]. Electrophysiological data showing that neurons in the hypothalamus are excited after stimulation of renal sensory afferents through a pathway that may involve areas of the medulla, suggest that renal sensory afferent information might also be integrated in the hypothalamus[98].

Role of renal nerves in kidney fibrosis

Experimental evidence suggests a role of renal nerves in the development of renal fibrosis. In animal models, renal denervation prevented the development of renal fibrosis after unilateral ureteral obstruction[99] or IRI[100]. Fibrotic and inflammatory responses in these denervated kidneys were, however, observed following local infusion of noradrenaline (which is found in sympathetic efferents) or CGRP (which is found in sensory afferents). These fibrotic responses to noradrenaline and CGRP were blocked by antagonists of their respective receptors, suggesting that neural signalling contributes to the development of renal inflammation and fibrosis. The denervation method used in these studies does not discriminate between sympathetic efferent and sensory afferent nerves; however, the roles of noradrenaline and CGRP, respectively, suggest involvement of both pathways in kidney fibrosis. Future studies with selective denervation of sensory afferents[101,102] are needed to dissect the individual roles of these neural circuits.

Although the findings described above suggest that renal nerves contribute to fibrosis, other endogenous factors leading to an abnormal microenvironment also contribute to the

progression of kidney disease following an acute insult[103–105]. Such factors include, but are not limited to, capillary rarefaction and hypoxia[106,107], altered fatty acid oxidation[108], inflammatory cells[109–111], cell cycle arrest[112], mitochondrial function[113], partial epithelial-to-mesenchymal transition[114,115] and the endothelium[116]. The contribution of these factors explains why renal allografts undergo fibrosis despite the renal denervation that occurs during transplantation[117].

Neural-immune mechanisms in hypertension

Regulation of blood pressure involves a complex intertwining of mechanisms involving the sympathetic nervous system (effects on heart rate and vascular tone), the CNS (brainstem mechanisms regulating cardiovascular function), hormones, environmental factors, and the kidney, particularly in terms of renal sodium handling, renin secretion, and the renal vasculature[81,118–121]. Perturbations in these regulatory mechanisms lead to hypertension. Increased sympathetic drive to the kidney in hypertension forms the basis for the experimental and clinical use of renal denervation for blood-pressure lowering, but the contribution from renal sensory afferents in the renorenal reflex is not well understood[122].

Role of the immune system

Considerable evidence exists for a role of the immune system in blood pressure control in animal models[123], and some studies suggest that the immune system might also be important in human hypertension[124] (TABLE 1). Passive transfer studies in rodents have demonstrated that immunosuppression can attenuate hypertension[125–127]. In rats with CKD, elimination of T cells owing to thymectomy or splenectomy prevented the development of hypertension, whereas transfer of lymph node cells from rats with renal infarction induced hyper tension[126]. Similarly, in spontaneously hypertensive rats (SHR), depletion of lymphocytes with anti-thymocyte serum or chronic cyclophosphamide administration attenuated hypertension[128,129]. Moreover, *Rag-1*$^{-/-}$ mice, which are deficient in T cells and B cells, show a blunted increase in blood pressure in response to angiotensin II or deoxycorticosterone acetate salt[130]. This effect could be reversed by adoptive transfer of T cells from wild-type mice.

Cytokines have also been implicated in the pathogenesis of hypertension. T helper type 17 cells produce IL-17, which has a role in immune-mediated diseases such as psoriasis, rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease and asthma[131]. In *Il17*$^{-/-}$ mice, angiotensin II infusion induced an initial increase in blood pressure, but this response was not sustained compared to controls (C57BL/6 mice)[132]. TNF and IL-6 have also been shown to contribute to hypertension in animal models[132–137].

Both TNF and IL-6 were independent risk factors for high blood pressure in a population-based study that included 196 healthy individuals[138]. In addition, a small study that included eight patients with hypertension and either psoriasis or rheumatoid arthritis, showed that treatment with the immunosuppressant myco phenolate mofetil was associated with a significant reduction in blood pressure and urinary excretion of TNF[139]. Together, these

studies provide evidence for a role of the immune system in the pathogenesis of hypertension.

Neuroimmunomodulatory pathways

Interactions between neural circuits and the immune system in hypertension have also been identified. Although increased sympathetic nerve activity seems to have both activating and suppressive effects on the immune system (dependent in part on the effects on immune cells in different locations), direct evidence indicates that increased sympathetic outflow and the resulting increase in noradrenaline levels activates T cells, promotes renal inflammation and contributes to hypertension[140]. These neural-immune mechanisms are mediated at least in part by T cells in the kidney, which have roles in immune-mediated damage[141–143] and salt-sensitive hypertension[144,145]. In a seminal study by Burne, Rabb and co-workers, T cell-deficient *nu/nu* mice were shown to be protected from IRI, an effect that was reversed upon reconstitution of these mice with wild-type T cells[141]. Additional studies have demonstrated that natural killer T cells contribute to early innate-immune-mediated IRI[142].

Renal sympathetic nerves drive T cell infiltration, kidney damage and hypertension[140,146]. In turn, hypertension causes accumulation of oxidized products (γ-ketoaldehydes) in dendritic cells, which promotes dendritic cell cytokine production and activates T cells[146]. Both sympathetic efferents and renal sensory afferents have a role in mediating hypertension. Selective renal denervation studies showed that renal sympathetic nerves are primarily responsible for renal inflammation, whereas afferent nerves mediate salt-induced hypertension[101]. Furthermore, two models of experimental hypertension showed that increased sympathetic splenic nerve activity and T cell recruitment to the kidney were mediated by hypertension-induced activation of a cholinergic–sympathetic immuno modulatory mechanism with marked similarities to the CAP[147]. Interruption of this pathway by selective splenic denervation prevented T cell activation, egress from the spleen, and kidney infiltration, and protected mice from hypertension[147].

These new concepts are provocative but the mechanisms need to be more clearly defined to resolve potential inconsistences[140]. A role for neural-immune mechanisms in the kidney also needs to be confirmed in human hypertension. Perhaps more intriguing, and not yet understood, is the apparent contradiction between the anti-inflammatory role stimulated by increased sympathetic drive to the spleen (the noradrenaline-dependent CAP) and the renal pro-inflammatory response driven by increased sympathetic drive to the kidney. Future investigations are needed to understand mechanisms in the kidney, including the role that other neuromodulators released from afferent and efferent nerve terminals (for example, ATP, nitric oxide and neuro peptides) have in this pro-inflammatory, hypertensive pathway in the kidney as well as feedback mechanisms from sensory afferent pathways to the brain that could drive compensatory mechanisms, perhaps by activating the CAP.

Implications for therapy

Despite the importance of the sympathetic nervous system in the pathophysiology of hypertension, targeting this pathway has been underutilized. From a clinical standpoint,

immunosuppressive drugs that target lympho cytes or specific immunotherapy directed at T cells have been investigated for treatment of hypertension in animals[128,129] and humans[139]. In addition to the obvious limitations of immunosuppression, this approach is complicated by the observation that patients with hypertension show increased susceptibility to secondary infections. Case and Zimmerman suggested that this susceptibility might be related to an immuno suppressive state in lymphoid organs, separate from kidney and vasculature T cell activation, that is driven by the suppressive effects of increased sympathetic drive[148]. Directly targeting the neuroimmune axis in the kidney or the CAP could provide a more selective approach to the treatment of hypertension than broad immunosuppression.

As sympathetic outflow is enhanced in essential hypertension, radiofrequency ablation has been utilized to denervate the kidney[149–151]. In a proof-of-principal study, sympathetic renal denervation was performed in 45 patients with resistant hypertension, but the effect on renal noradrenaline spillover (a measure of sympathetic denervation) was incomplete with a mean decrease of only 47.5%[152]. Despite incomplete denervation, blood-pressure control was substantial with a mean decrease in office blood pressure of 27/17 mmHg (relative to baseline measurement at enrolment) at 12 months after denervation. Follow-up studies demonstrated sustained lowering of blood pressure at 3 years[153].

Notably, the renal denervation procedure ablates both afferent and efferent nerves. Renal afferent nerves project to the hypothalamus and can stimulate sympathetic outflow[81,151,154–156]. In patients with kidney failure on haemodialysis, bilateral nephrectomy corrected hypertension and increased muscle sympathetic nerve activity and calf muscle vascular resistance, demonstrating that the diseased kidneys were the source of the afferent signal[157].

Despite these early, encouraging findings, the SYMPLICITY HTN-3 prospective randomized control trial in 535 patients with resistant hypertension failed to demonstrate a significant blood-pressure lowering effect of radiofrequency renal denervation in comparison to a sham procedure[158]. This result precipitated the termination of other planned studies of renal denervation for the treatment of resistant hypertension. SYMPLICITY HTN-3, while carefully designed to obviate the problems associated with prior studies (such as lack of a sham control group), was limited, however, by problems associated with patient selection (differences in the pathogenesis of obesity-induced hypertension and possible variations in response owing to age and ethnicity) and compliance (lack of confirmation of adherence to antihypertensive medication) as well as by ineffective ablation of renal nerves owing to inexperienced operators. Second-generation multi-electrode devices for renal denervation are currently being tested with the aim of improving efficacy and safety, in part by delivering multiple lesions simultaneously to enable shorter procedure times with a reduced risk of clotting. Further defining the neural circuitry and the underlying molecular mechanisms is important to enable the development of selective strategies for the therapeutic use of renal denervation in hypertension.

Tools to investigate neural pathways

Combining molecular and genetic approaches in a variety of ways, particularly with the introduction of optogenetic techniques, has given neuroscientists, nephro logists and immunologists a powerful toolset with fine resolution for selectively probing specific subsets of phenotypically distinct neurons.

Optogenetic technology enables the use of light for stimulation of specific neurons in transgenic mice. Light-sensitive ion channels (microbial opsins) can be introduced into the neurons of interest using two different techniques. Either Cre-dependent viral vectors harbouring the opsin downstream of a floxed-stop or floxed-inverse cassette are injected into specific brain regions of mice that express Cre recombinase under the control of a specific promoter of interest, or Cretransgenic mice are crossed with mice harbouring the floxed-stop or floxed-inverse cassette. Spatially targeted application of light of a specific wavelength can then be used to open the light-sensitive channels (either membrane cation channels such as channel rhodopsin-2 or chloride channels such as halorhodopsin), enabling selective activation or silencing, respectively, of the opsin-expressing neurons[159,160].

To date, such investigations have mostly focused on the CNS, but these techniques are now being extended to the regulation of organ function by the peripheral nervous system. For example, vagus sensory neurons were found to be divided into several phenotypic subgroups based on specific markers, and optogenetic stimulation of each subgroup modulated the function of the lung, heart, and gastrointestinal tract in different ways[93,161]. This elegant technique could be exploited to finely examine the specific function of phenotypically different neural circuits in the kidney and to more clearly define specific mechanisms underlying the role of the inflammatory reflex in kidney function in injury and disease.

Analogous to optogenetics, Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) uses a chemogenetics approach to selectively activate neural circuits that express mutated mAChRs. These mAChRs (which are introduced using adenoviral or Cre-LoxP techniques) respond to an inactive ligand, clozapine-N-oxide (CNO)[162], or its metabolite clozapine, rather than acetylcholine[163]. Treatment with low-dose CNO, therefore, induces selective activation of neural circuits expressing mAChRs.

Imaging of neural pathways can be enhanced using a transgenic multicolour labelling strategy known as Brainbow[164]. This method uses the Cre-LoxP recombination strategy to label neurons with multiple distinct colours, thus defining specific neural pathways. Use of these approaches in combination with other techniques such as tract tracing will enable precise understanding of neural pathways that mediate physiological functions and disease pathways.

Conclusions

Neuroimmunomodulation of organ function is attracting a great deal of interest as a novel means of treating disease. A growing understanding of the roles of neural circuits, such as the immune reflex pathway and particularly the CAP, as well as of sympathetic efferent and sensory afferent innervation, in kidney function, responses to acute and chronic kidney

injury, and hypertension, is providing new therapeutic approaches, particularly through nonpharmacological, and in some cases non-invasive, techniques.

Stimulating the vagus nerve modulates peripheral nerve activity and suppresses inflammation, and clinical trials examining the effects of VNS in inflammatory disorders, such as rheumatoid arthritis[165] and inflammatory bowel diseases are ongoing[166]. Experimental evidence suggests that VNS and therapeutic ultrasound protect the kidney from acute ischaemic injury by stimulating the CAP[13,67–69]. Furthermore, data suggest that neural pathways mediate inflammation and hyper tension[124] as well as kidney fibrosis[99,100], and that stimulation of C1 neurons in the brainstem activates the CAP[76]. C1 neurons respond to a variety of stimuli, including danger signals, and could be a central component of the immune reflex circuit.

The use of optogenetics, DREADDs and Brainbow labelling in combination with tract tracing, immunofluorescent labelling and electrophysiological techniques is enabling greater understanding of neural circuits that regulate kidney function. These circuits could potentially be manipulated to modulate immune responses in kidney disease. Further elucidation of neuroimmune mechanisms in AKI, kidney disease and hypertension might lead to the identification of neural circuits that could be exploited for therapy.

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Glossary

Vagus nerve
The vagus or 10th cranial nerve is a pair of nerve bundles (right and left) that contains axons of both efferent and afferent neurons. The efferent neurons provide cholinergic input to almost all organs in the periphery and some skeletal muscles. Their cell bodies are located in the medulla oblongata. The cell bodies of afferent neurons are located in the nodose ganglia. These neurons carry the majority of sensory information from visceral organs to the CNS.

Subdiaphragmatic vagotomy
Denervation by surgical transection of both trunks of the vagus nerve either below or caudal to the diaphragm.

Nucleus tractus solitarius
A group of neuronal cell bodies in the brainstem that form an integrative centre for sensory information from the vagus, glossopharyngeal and facial nerves. The nucleus tractus solitarius projects to a wide variety of brain regions, including the hypothalamus, thalamus, and medulla, and participates in circuits that regulate autonomic function.

Coeliac ganglion
A cluster of nerve cells in the abdomen that forms part of the prevertebral sympathetic chain and provides sympathetic innervation to most of the digestive tract. The coeliac ganglion is

regulated by the preganglionic neurons in the intermediolateral cell column of the spinal cord.

Bilateral cervical vagotomy

Bilateral cervical vagotomy is a surgical transection of the vagus nerve at the level of the neck on both sides. This procedure prevents the flow of information through the nerve in both directions (afferent and efferent) between its origin in the CNS and its targets in the periphery.

Retrograde tract tracing

A technique for identifying neuronal pathways that exploits constitutive axonal transport to trace the movement of specialized proteins, markers or viruses (which can be visualized by various means) from their point of exogenous introduction in a target field of interest (synaptic terminals) to the cell bodies of those axons (retrograde transport). By contrast, anterograde tracing traces the transport of markers from the cell body region in the direction of the synapse.

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Key points

- Neural circuits that control immunity and inflammation provide novel targets for the treatment of kidney disease and hypertension
- Activation of the cholinergic anti-inflammatory pathway (CAP) blocks splenic-dependent systemic inflammation and acute kidney injury (AKI); non-invasive, nonpharmacological approaches to activate the CAP include ultrasound application and vagus nerve stimulation
- Neural circuits that directly regulate kidney function or carry sensory feedback from the kidney to the central nervous system could provide additional mechanisms for bidirectional neuroimmunomodulation of kidney disease
- Interactions between neural circuits and the immune system have important roles in the pathogenesis of hypertension and renal fibrosis
- Further defining neuroimmunomodulatory pathways in hypertension could enable the development of selective neuronal stimulatory or inhibitory strategies for lowering blood pressure that could potentially be more effective than renal denervation
- Optogenetic tools provide unprecedented opportunities to dissect the neural pathways that control immunity and inflammation and enable the identification of novel approaches to therapy for kidney diseases

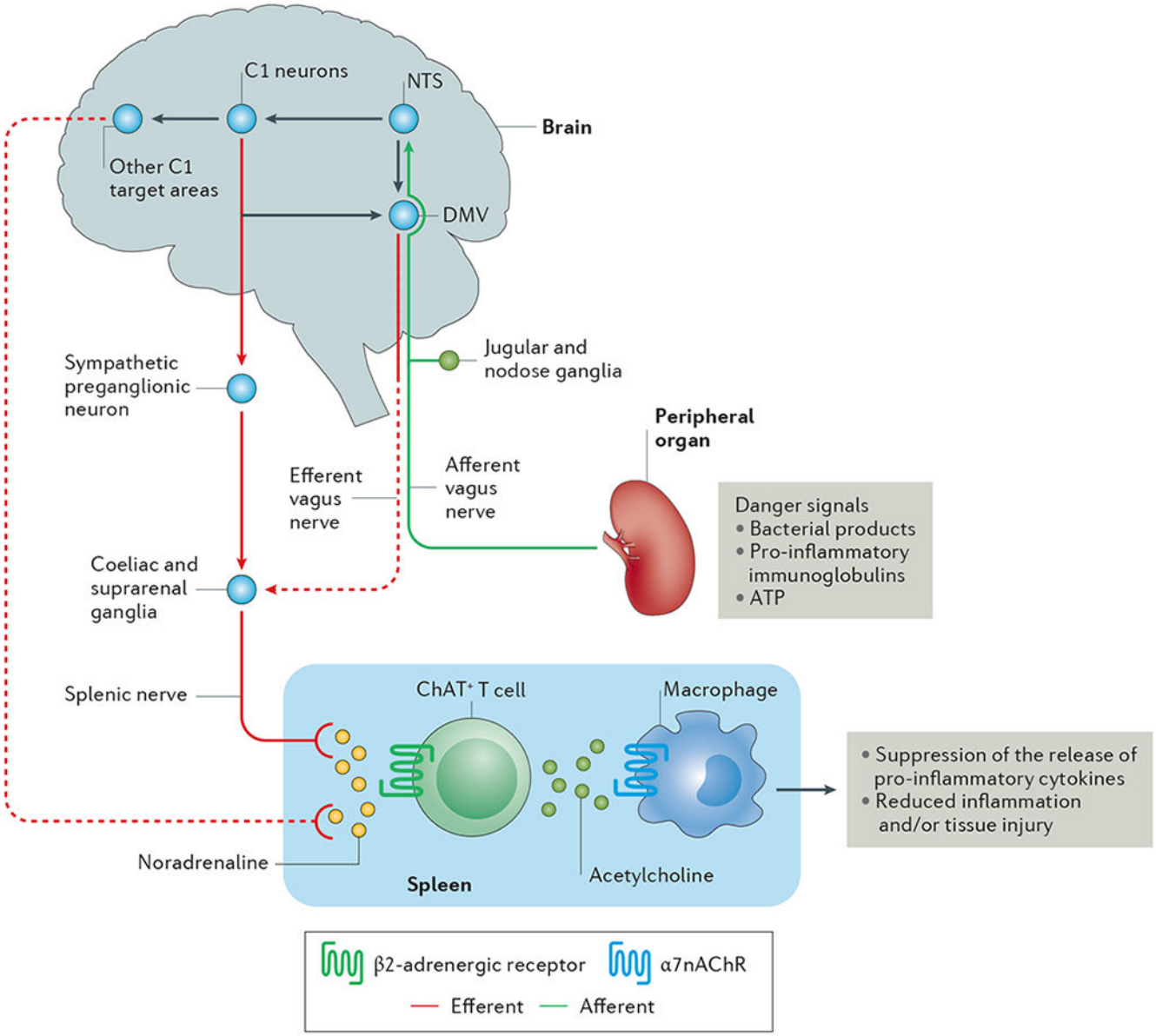

Figure 1 |. The inflammatory reflex.

Afferent vagus nerve fibres transmit danger signals from peripheral organs to the nucleus tractus solitarius (NTS). This signalling leads to activation of the efferent vagus nerve arising in the dorsal motor nucleus of the vagus (DMV), and of the splenic nerve, leading to noradrenaline release in the spleen. This noradrenaline release activates choline acetyltransferase positive ($ChAT^{+}$) T cells, which express β2-Activated $ChAT^{+}$ T cells release acetylcholine, which binds to α7 nicotinic acetylcholine receptors (α7nAChRs) on macrophages, leading to suppression of the release of pro-inflammatory cytokines and reduced inflammation and/or tissue injury. In addition to activation of this cholinergic anti-inflammatory pathway (CAP) by this vagal preganglionic efferent pathway, direct stimulation of brainstem C1 neurons (or indirect stimulation by a variety of physiological stressors) elicits activation of the CAP via a sympathetic efferent pathway[76] that might

involve C1 projections to sympathetic preganglionic neurons (which innervate sympathetic ganglia such as the coeliac and suprarenal ganglia) or other C1 projections in the brain that stimulate a sympathetic pathway. Dashed lines represent unconfirmed pathways, and solid lines represent confirmed pathways.

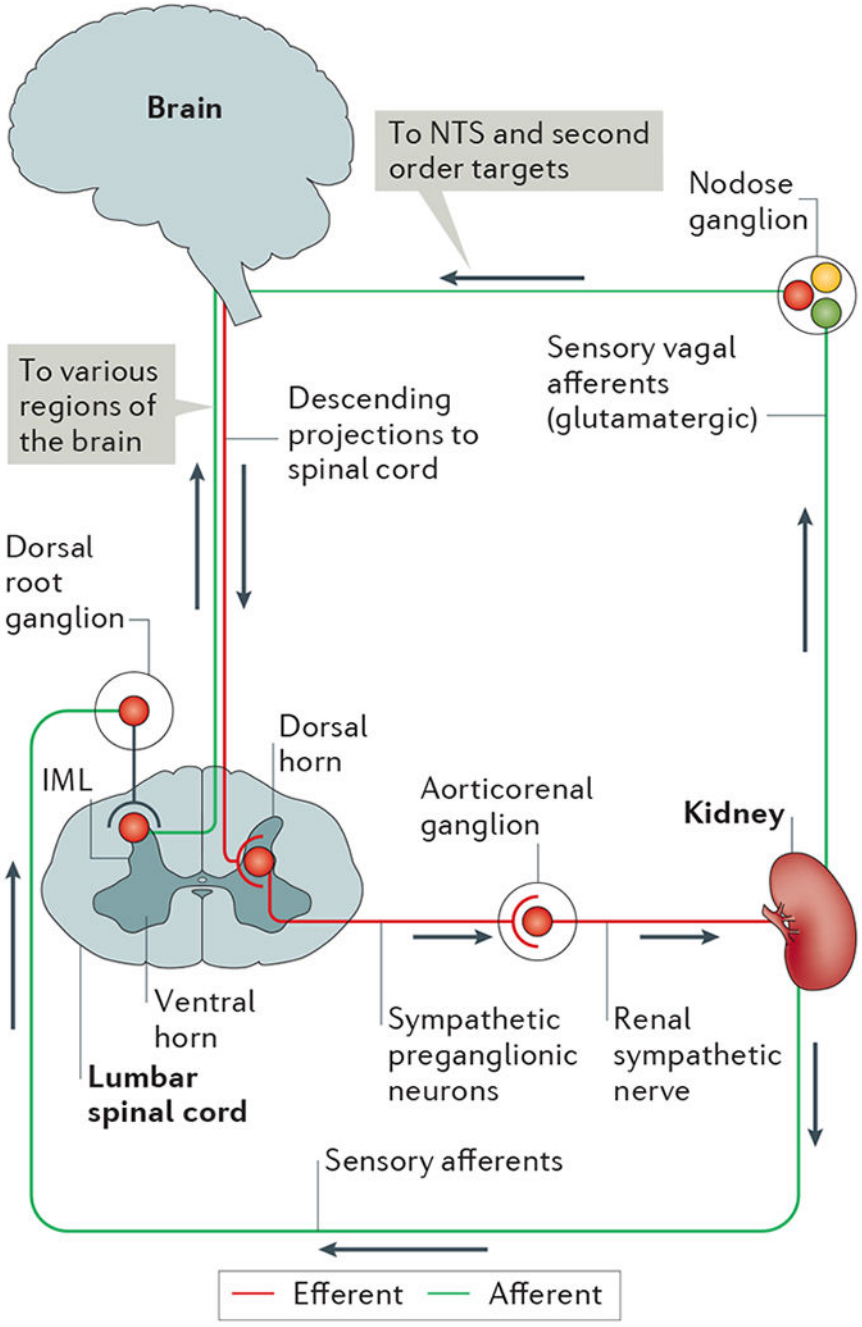

Figure 2 |. Neural circuitry of efferent and afferent innervation in the kidney.

In the efferent pathway, descending projections from the brain (for example, from brainstem and hypothalamic regions) synapse on sympathetic preganglionic neurons in the intermediolateral cell column (IML) of the thoracic and lumbar spinal cord. Sympathetic preganglionic neurons in the lumbar spinal cord project through the ventral horn to the aorticorenal ganglion and activate the renal sympathetic nerve, which innervates the kidney and releases noradrenaline, neuropeptide Y and ATP. Sensory afferents in the kidney, which release substance P and calcitonin gene-related peptide, have their cells bodies in the dorsal

root ganglia and synapse centrally on interneurons in the dorsal horn of the spinal cord that transmit information to various regions of the brain. Although the kidney does not seem to have vagal efferent input, some evidence suggests that vagal afferent neurons arising in the nodose ganglion innervate the kidney, thus providing a pathway for integration with the nucleus tractus solitarius (NTS) and subsequent second order neuronal targets in the brain.

Table 1 |
Therapeutic use of neuromodulation in kidney disease and HTN

Setting	Treatment	Key findings	Refs
Acute kidney injury (CAP)			
Preclinical	Ultrasound	Ultrasound treatment of mice prior to IRI protected kidney structure and function consistent with activation of the CAP	69
	Vagus nerve stimulation	Stimulation of vagal afferents or efferents in mice prior to IRI protected kidney structure and function consistent with activation of the CAP	13
	Optogenetic stimulation of C1 neurons	Optogenetic stimulation of C1 neurons located in the medulla oblongata attenuated IRI by activating the CAP predominantly through a sympathetic pathway	76
Transplantation (CAP)			
Preclinical	Vagus nerve stimulation	VNS activation of the CAP in brain-dead donor rats attenuated the production of inflammatory cytokines in the donors and chronic allograft nephropathy in the recipients	61,62
Renal fibrosis (SNS)			
Preclinical	Renal denervation	Renal nerve stimulation after ureteral obstruction stimulates fibrosis, whereas renal denervation prevents inflammation and fibrosis	99
		Renal denervation at the time of or 1 day after IRI preserved histology, attenuated pro-inflammatory and profibrotic responses and apoptosis, and prevented G2/M cell cycle arrest in the kidney	100
Hypertension (SNS)			
Preclinical	Renal denervation	• In angiotensin II-induced HTN, renal sympathetic nerves contribute to dendritic cell activation, subsequent T cell infiltration and end-organ damage in the kidney • Bilateral renal denervation reduced inflammation and associated renal fibrosis, albuminuria, and nephrinuria	146
		In CKD, rhizotomy from T9 to L1 (a procedure that interrupts the afferent nerve input to the hypothalamus) blocks HTN, indicating that the afferent pathway contributes to HTN	156
Clinical	Bilateral nephrectomy	Bilateral nephrectomy corrected HTN, sympathetic nerve activity and calf vascular resistance, indicating that the kidney was the source of the afferent signal causing HTN	157
	Renal denervation	In a proof-of-principle trial in patients with resistant HTN, renal sympathetic denervation led to a decrease in blood pressure without serious adverse events	152
		The SYMPLICITY HTN-2 trial in patients with treatment-resistant HTN showed that renal denervation resulted in sustained lowering of blood pressure at 3 years compared with medical therapy alone	153
		The SYMPLICITY HTN-3 in patients with resistant HTN showed that renal denervation did not result in a significant reduction in systolic blood pressure at 6 months compared with a sham procedure	158
Cardiorenal syndrome (SNS)			
Preclinical	Renal denervation	SNS had a detrimental effect on renal blood flow and renal vascular resistance in rabbits with heart failure; this effect was prevented by renal denervation	167
CKD and resistant hypertension (SNS)			
Clinical	Renal denervation	In patients with resistant hypertension and stage 3–4 CKD, bilateral renal denervation was safe and effective in lowering blood pressure	168
Resistant hypertension and albuminuria (SNS)			
Clinical	Renal denervation	In patients with resistant HTN, renal denervation reduced blood pressure, renal resistive index, and the incidence of albuminuria without adversely affecting glomerular filtration rate	169

CAP, cholinergic anti-inflammatory pathway; CKD, chronic kidney disease; HTN, hypertension; IRI, ischaemia-reperfusion injury; SNS, sympathetic nervous system.