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AKI and the Neuroimmune Axis

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Summary

Neuroimmune interaction is an emerging concept, wherein the nervous system modulates the immune system and vice versa. This concept is gaining attention as a novel therapeutic target in various inflammatory diseases including acute kidney injury (AKI). Vagus nerve stimulation or treatment with pulsed ultrasound activates the cholinergic anti-inflammatory pathway to prevent AKI in mice. The kidneys are innervated by sympathetic efferent and sensory afferent neurons, and these neurons also may play a role in the modulation of inflammation in AKI. In this review, we discuss several neural circuits with respect to the control of renal inflammation and AKI as well as optogenetics as a novel tool for understanding these complex neural circuits.

Keywords

Acute kidney injury; neuroimmune interaction; cholinergic anti-inflammatory pathway; vagus nerve stimulation; optogenetics

Acute kidney injury (AKI) is an important clinical concern because it is highly prevalent and associated with high mortality and morbidity. AKI episodes can lead to chronic kidney disease (CKD) and end-stage renal disease.[1–4] Although inflammation by immune cells is undoubtedly a critical step in the pathophysiology of AKI, pharmacologic approaches to decrease inflammation in AKI have been unsuccessful in clinical trials.[5,6] The importance of the inter-relationship between the nervous system and the immune system recently was shown, and this neuroimmune interaction is emerging as a therapeutic target for several inflammatory diseases.[7,8] In fact, the kidney is densely innervated by the sympathetic efferent nerves that originate from the brain, descend into the spinal cord, and reach the kidney.[9] The kidney, the pelvic region in particular, also is innervated by the sensory afferent nerves that transmit various signals from the kidney, mainly via the spinal cord, to the brain.[9] In this review, we discuss several neural circuits that are involved in the control of renal inflammation, focusing on AKI, and the therapeutic potential of targeting the neuroimmune interaction in AKI.

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NEUROIMMUNE INTERACTION: AN EMERGING MECHANISM TO MODULATE INFLAMMATION

Felten and colleagues showed sympathetic and peptidergic innervation of the primary and secondary lymphoid organs using histologic evaluation with anterograde and retrograde labeling techniques in the 1980s.[10–13] These studies clearly showed an anatomic inter-relationship between the nervous system and the immune system. Since then, many studies have been conducted to investigate the interaction between the two seemingly independent systems. It is now well known that the function of afferent (sensory) neurons is modulated by immune cells, while afferent neurons and efferent (motor) autonomic neurons alter the function of the immune cells. These afferent and efferent neurons constitute reflex pathways to regulate immune responses and inflammation.

Somatosensory neurons that innervate the skin, muscles, and joints have cell bodies in the dorsal root ganglia (DRG) that project to the spinal cord. Visceral sensory neurons that innervate all the internal organs, such as the lung, heart, liver, kidney, and gastrointestinal tract, have cell bodies in the DRG or the nodose/jugular ganglia; the latter are called the vagus afferent (sensory) neurons. Most central axons of the vagus afferent neurons project to the nucleus tractus solitarius in the medulla oblongata in the brain.[14] In response to infection or tissue injury, peripheral immune cells are activated by pathogen-associated molecular patterns and damage-associated molecular patterns; they then release inflammatory cytokines and chemokines.[15,16] In the local sites of infection or tissue injury, sensory neurons that express pattern recognition receptors and cytokine receptors sense inflammation and transmit signals to the central nervous system (CNS).[7] Conversely, sensory neurons also can alter the inflammatory state. An activation of sensory neurons causes the release of various neuropeptides, such as calcitonin gene-related peptide (CGRP) and substance P from axon terminals at the site of innervation. These peptides bind to their receptors expressed on immune cells and blood vessels to augment or suppress inflammation.[17–19]

Efferent (motor) autonomic neurons also alter immune cell function. Cell bodies of the efferent vagus neurons reside in the dorsal motor nucleus of the vagus nerve and nucleus ambiguus in the medulla oblongata.[14] The efferent vagus neurons synapse on ganglia located very close to the innervated organs and release acetylcholine. Some postganglionic fibers release acetylcholine that binds to the muscarinic acetylcholine receptors in the thoracic and abdominal organs, such as the heart, liver, and gastrointestinal tract, to modulate physiological functions. However, the anti-inflammatory effects of efferent vagus nerve stimulation require nicotinic acetylcholine receptors, which are stimulated by acetylcholine released by immune cells rather than by vagus nerve terminals, as discussed in the following section.

VAGUS NERVE AND THE INFLAMMATORY REFLEX

In 1995, it was found that the febrile response elicited by an intraperitoneal injection of interleukin 1β requires the afferent vagus nerve.[20] In 2002, Bernik et al[21] observed that administering a small amount of a potent anti-inflammatory agent intracerebroventricularly

significantly decreased lipopolysaccharide-induced increases in levels of plasma tumor necrosis factor (TNF), which mainly originates from the spleen, despite negligible systemic concentrations of the anti-inflammatory agent. Cutting the vagus nerve nullified the decrease in the plasma TNF level and electrical stimulation of the vagus nerve decreased plasma TNF. These findings indicated the presence of the inflammatory reflex, wherein the afferent vagus nerve senses peripheral inflammation, and the signal is transmitted through the CNS to the efferent vagus nerve and the spleen to alleviate inflammation.[22] Thereafter, the mechanism of the inflammatory reflex gained interest and increasingly has been explored (Fig. 1).

The inflammatory reflex is initiated through the sensing of local inflammation by the afferent vagus nerve via cytokine receptors and pattern recognition receptors.[23] The signal is transmitted through the CNS to the efferent vagus nerve and the splenic nerve.[24] The interaction between the efferent vagus nerve and the splenic nerve may occur in the celiac, superior mesenteric, or suprarenal ganglia.[10,25–28] Norepinephrine is released by splenic nerve terminals and binds to β2-adrenergic receptors expressed on the choline acetyltransferase—positive T cells in the spleen, resulting in release of acetylcholine from this specific $CD4^+$ $CD44^{high}$ $CD62L^{low}$ memory T-cell subpopulation.[29] Binding of acetylcholine to $\alpha 7$ nicotinic acetylcholine receptors (α7nAChRs) expressed on macrophages that reside close to these T cells leads to suppression of proinflammatory cytokine production (eg, TNFα) by macrophages and reduced inflammation.[24,30] The efferent arm of the inflammatory reflex is called the cholinergic anti-inflammatory pathway (CAP).[22]

INNERVATION OF THE KIDNEY AND INTERACTION BETWEEN THE RENAL SENSORY AFFERENT AND SYMPATHETIC EFFERENT NERVES

The sympathetic innervation reaches all portions of the renal vasculature, with the highest density of innervation in afferent arterioles.[31] Tubules also are innervated by sympathetic nerves to a lesser degree. Norepinephrine released from sympathetic terminals is believed to act on the vasculature and tubules. An increase in efferent renal sympathetic nerve activity (ERSNA) increases the renin secretion rate via stimulation of β1-adrenergic receptors on juxtaglomerular granular cells. An increase in ERSNA also decreases renal blood flow via stimulation of α_{1A}-adrenergic receptors on renal arterial vessels as well as sodium excretion in the urine via stimulation of α_{1B}-adrenergic receptors on the tubular epithelial cells. In contrast to the broad innervation by sympathetic nerves to the kidney, the distribution of sensory nerves in the kidney is localized predominantly in the pelvic region.[32] The sensory nerves enter the pelvis parallel to the renal artery and ureter, terminating as free nerve endings in the pelvic wall. In contrast, the renal artery and vein are innervated to a lesser degree by the sensory nerves, and there are few sensory fibers in the renal parenchyma. Considerable evidence has shown that the mechanosensitive pelvic nerves are activated by increased pelvic pressure (stretch of the pelvic wall) within the physiological range.[33,34] The cell bodies of renal sensory nerves are located mainly in the DRG at the thoracic and lumbar levels,[35,36] and neuronal signals are propagated to the spinal cord and then to specific areas of the brain, including the nucleus tractus solitarius and the rostral ventrolateral medulla.[37]

Unilateral renal denervation (both sensory afferents and sympathetic efferents) not only increased ipsilateral urinary sodium excretion, an expected result of the denervation of sympathetic efferents, but also decreased contralateral urinary sodium excretion, accompanied by increased contralateral ERSNA in normal rats.[38] Stimulation of renal sensory afferents using various methods (eg, increased renal pelvic pressure and pelvic administration of chemical substances) decreased the contralateral ERSNA and increased the contralateral urinary sodium excretion that was abolished by ipsilateral renal denervation.[39–41] These findings suggest that an increase in afferent renal nerve activity (ARNA) suppresses ERSNA, an effect known as the inhibitory renorenal reflex.[42] ARNA also modulates the central sympathetic outflow to the periphery. In contrast, an increase in ERSNA increases ARNA, possibly via a synaptic connection between the sympathetic efferent nerves and the sensory afferent nerves in the pelvic wall (binding of norepinephrine released by the sympathetic efferents to α*1*- and *α*2-adrenergic receptors expressed on the sensory afferents).[43,44] In sum, there is probably a negative feedback system by the sympathetic efferents and sensory afferents in the kidney under normal conditions; an increase in ERSNA increases ARNA, and the increase in ARNA decreases ERSNA through the inhibitory renorenal reflex (Fig. 2A).

In contrast, in pathologic conditions associated with increased sympathetic nervous system activity, such as hypertension, CKD, and heart failure, the inhibitory renorenal reflex is impaired, leading to an excitatory reflex. For example, in two-kidney, one-clip hypertensive rats, denervation of the ipsilateral clipped kidney increased the urinary sodium excretion from the contralateral kidney, accompanied by decreased contralateral ERSNA.[45] Removal of the diseased kidneys significantly reduced blood pressure and muscle sympathetic nerve activity in hemodialysis patients and kidney transplant patients,[46,47] further supporting the notion that diseased kidneys have an excitatory effect on the sympathetic nervous system (Fig. 2B). Limited information is available about the functional status of renal sensory afferents and the renorenal reflex in AKI, although impaired responsiveness of the renal afferent nerves has been reported in acutely injured kidneys at 24 hours after unilateral ischemia-reperfusion or ureteral obstruction.[48,49]

RENAL DENERVATION: A POSSIBLE TREATMENT STRATEGY FOR AKI?

Considerable evidence has shown that sympathetic nerve activity is up-regulated in patients with CKD and end-stage renal disease, often accompanied by hypertension.[46] Renal denervation in human beings with hypertension has been a popular, albeit controversial, research topic for several years.[50–53] Renal denervation was effective in ameliorating kidney inflammation in various animal models, although little information is available regarding its effect in ischemic or septic AKI.[54–56] Surgical bilateral renal denervation performed 2 days before inducing glomerulonephritis significantly ameliorated albuminuria, mesangial microaneurysms, and interstitial macrophage infiltration in a rat model of anti—Thy-1.1 nephritis.[57] Bilateral renal denervation also was effective in decreasing the urinary albumin and renal cortical expression of monocyte chemotactic protein-1 without affecting the blood pressure in a mouse model of systemic lupus erythematosus.[58] The effect of ipsilateral renal denervation with ethanol was investigated in a mouse model of unilateral ureteral obstruction (UUO).[59] Renal denervation 2 days before UUO surgery significantly reduced

neutrophil and macrophage infiltration and fibrosis in the kidney. Furthermore, continuous infusion of norepinephrine or CGRP, but not neuropeptide Y or substance P, into the cortical region of the denervated kidney via a catheter nullified the protective effect of renal denervation in a dose-dependent manner. Unilateral renal denervation or administration of these neurotransmitters did not alter the systolic blood pressure. In the innervated kidneys, the CGRP level was increased significantly up to 24 hours after UUO. The investigators also showed that UUO-induced kidney inflammation and fibrosis required α2-adrenergic and CGRP receptors and that these receptors are expressed in tubular epithelial cells. Similar findings also were shown in a mouse model of unilateral kidney ischemia-reperfusion injury (IRI).[60] In contrast to the protective effect of preventive renal denervation before disease induction, renal denervation at 1 day after UUO and at 3 days after IRI did not ameliorate kidney fibrosis significantly, suggesting that renal nerve activity is important, particularly during the acute phase of injury. These findings suggest that the local actions of both sympathetic efferent and sensory afferent neurons in the kidney play critical roles in kidney inflammation and fibrosis.

CAP IN AKI

The role of CAP in AKI was explored using vagus nerve stimulation (VNS) in a mouse model of renal IRI.[61] Electrical stimulation of the left cervical vagus nerve 24 hours before IRI significantly ameliorated kidney injury, as shown by the decrease in plasma creatinine level and kidney injury molecule-1 expression in the kidney with improved renal histology. As expected, in splenectomized mice or $\alpha 7nAChR^{-/-}$ mice, VNS was not protective, indicating that VNS-mediated protection against kidney IRI is caused by CAP activation. It is noteworthy that the stimulation of either the peripheral or central end of the cut vagus nerve also protected the kidneys. Blocking nerve conduction of the right (contralateral) vagus nerve by local anesthesia (bupivacaine) did not inhibit the protective effect of afferent VNS, suggesting the presence of downstream pathway(s) other than the efferent vagus nerve in the protection against AKI. VNS in brain-dead donor rats was effective in attenuating inflammation in the donors, decreasing immune cell infiltration to the tubules and the arteries in the recipients, and improving long-term renal function and survival of the recipients.[62,63]

Applying pulsed ultrasound to the spleen also appears to exert a protective effect against AKI in a manner similar to that of VNS.[64,65] Ultrasound application using a clinical machine 24 hours before IRI attenuated kidney injury in mice. The protective effect by ultrasound was abolished in splenectomized mice, mice with splenic sympathectomy, $Rag1^{-/-}$ mice, $\alpha 7nAChR^{-/-}$ mice, and mice treated with an antagonist of α7nAChR. Administration of an α7nAChR agonist mimicked the protective effect of ultrasound. Furthermore, bone marrow chimera experiments showed that α7nAChR expression in bone marrow—derived cells is essential for protection by ultrasound. In sum, these findings suggest that the application of pulsed ultrasound protects the kidneys from IRI by activating the CAP. Pulsed ultrasound also ameliorated septic AKI in a cecal ligation and puncture model. However, direct target(s) of pulsed ultrasound are yet to be determined.

Although all of these studies showed that the spleen plays a critical role in CAP activation to protect the kidneys from AKI, the precise interaction between the spleen and the kidney is unknown. One intriguing finding is that adoptive transfer of splenocytes from ultrasound-treated[64] or VNS-treated[61] (but not sham) mice to naive mice was sufficient to protect kidneys of recipient mice from IRI. Thus, activation of CAP may have altered the phenotype of splenocytes and conferred protection.

In addition, interaction of spleen and kidneys during protection may include involvement of the renal nerves. Recent findings on the neuroimmune axis in hypertension may provide a clue regarding the missing link between the two organs in the context of CAP activation in AKI. Hypertension is associated with $CD4^+$ and $CD8^+$ T cell infiltration into the kidney.[66,67] Xiao et al[68] extended their work to investigate the role of renal sympathetic nerves in T cell infiltration into the kidney in angiotensin II—induced hypertension. Bilateral renal denervation with phenol, but not selective renal afferent ablation with capsaicin, ameliorated hypertension and kidney inflammation, as reflected by significant decreases in $CD4^+$ and $CD8^+$ T cell infiltration, fibrosis, and urinary albumin. Moreover, unilateral renal denervation, leading to a partial decrease in blood pressure, ameliorated inflammation only in the denervated kidney, suggesting that suppressed kidney inflammation is not secondary to decreased blood pressure, but directly caused by renal denervation. Moreover, the investigators observed that renal denervation changed the phenotype of dendritic cells in the spleen. Furthermore, mice lacking C—C chemokine receptor type 7, important as a homing signal to secondary lymphoid organs for dendritic cells, showed no $CD4^+$ or $CD8^+$ T cell infiltration into the kidney without activation of dendritic cells in the spleen, while the dendritic cells in the kidney still were activated. These findings, although indirect, support the hypothesis that hypertensive stimuli with renal sympathetic nerve activity activates dendritic cells in the kidney, leading to the migration of these cells to secondary lymphoid organs, such as the spleen, where they, in turn, activate T cells; thereafter, these T cells migrate to the kidney causing inflammation. Another group showed that T cells egress from the spleen and infiltrate the kidney and aorta, eventually causing hypertension in an angiotensin II—infusion model and that the splenic nerve is essential in these steps (Fig. 3).[69] The interplay between the spleen and kidney in the context of AKI clearly merits further exploration.

NONCLASSIC CAP AND OTHER NEUROIMMUNE INTERACTIONS TO REGULATE AKI AND INFLAMMATION

Recently, Abe et al[70] explored the role of the CNS in the neuroimmune interaction and AKI. C1 neurons that reside in the medulla oblongata innervate the dorsal motor nucleus of the vagus, paraventricular nucleus of the hypothalamus, and sympathetic efferent pathways, and mediate autonomic responses to several stressors, including hypotension and hypoxia.[71] The selective stimulation of C1 neurons using the optogenetics technique (described later) protected mice against kidney IRI, which was dependent on the spleen, α7nAChRs, and β2-adrenergic receptors. These results suggest that kidney protection by C1 neuron stimulation involves CAP activation. Interestingly, a short period of physical restraint also protected the kidney from IRI, and selective ablation or inhibition of C1 neurons nullified the protective

effect of restraint stress, indicating that renoprotection by restraint stress is mediated by C1 neurons. Furthermore, the investigators attempted to identify the downstream pathway—vagal efferents, hypothalamic-pituitary-adrenal axis, or sympathetic efferents—involved in kidney protection by C1 neuron stimulation. Ganglionic blockade, but not subdiaphragmatic vagotomy or corticosterone-receptor blockade, significantly attenuated the protection, suggesting that a sympathetic, not a vagus route, to the spleen is crucial for kidney protection by C1 neuron stimulation.

Several studies also have shown that AKI can affect CNS function.[72] Bilateral kidney IRI increased vascular permeability in the brain and the number of pyknotic neurons; it also activated microglial cells in the hippocampus in mice and was accompanied by reduced locomotor activity.[73] Dopamine turnover was decreased in the striatum, mesencephalon, and hypothalamus of rats with bilateral kidney IRI.[74] Although circulating factors such as cytokines and damage-associated molecular patterns may be responsible for these brain changes, signal transmission from activated afferent neurons in the injured kidneys to the CNS also may play an important role.

Dopamine released by the adrenal gland also appears to be involved in vagus nerve—mediated anti-inflammation.[75] Sciatic nerve activation using electroacupuncture alleviated polymicrobial peritonitis induced by cecal ligation and puncture by increasing dopamine production in the adrenal medulla via vagus nerve activation. Dopamine D1 receptors mediated the suppression in the cytokine production induced by dopamine. It is noteworthy that unlike the classic CAP, this sciatic-to-vagus neural circuit did not need the spleen, α7nAChRs, or β2-adrenergic receptors. Recent studies have suggested that gut macrophages are involved in other types of neuroimmune interactions. Matteoli et al[76] showed that efferent vagus nerve interacts with cholinergic myenteric neurons that are in close contact with muscularis macrophages. VNS attenuated surgery-induced intestinal inflammation and improved postoperative intestinal transit. This protective effect of VNS was mediated by α7nAChR on muscularis macrophages and was independent of the spleen and T cells. Gut muscularis macrophages also have been shown to enhance their tissue-protective phenotype in cases of luminal bacterial infection.[77] This alteration was attributed to the activation of sympathetic neurons and norepinephrine signaling to β2-adrenergic receptors on these macrophages. Protective neuroimmune interactions other than the classic CAP also may be present in the kidney.

FUTURE CLINICAL APPLICATION OF NEUROIMMUNE INTERACTION IN AKI

Considering the experimental evidence regarding the effectiveness of neuroimmunomodulation in kidney diseases as discussed earlier (Table 1), targeting the neuroimmune interaction appears to be a promising approach for treating human AKI.[78] In the 1990s, VNS with a surgically implanted stimulator was approved for treating refractory epilepsy in Europe and the United States. The Food and Drug Administration also approved VNS for treatment-resistant depression in 2005. Recently, the Food and Drug Administration approved a noninvasive vagus nerve stimulator for treating episodic cluster headache pain and migraine pain. In addition to these disorders, many clinical trials of VNS are ongoing for determining the optimal treatment modality for various inflammatory

diseases (eg, diabetes and heart failure).[79,80] An implanted stimulator (with cuffs placed around the left cervical vagus nerve, a pulse generator implanted on the chest wall, and a subcutaneously tunneled lead connecting the cuffs and pulse generator) was effective in patients with refractory rheumatoid arthritis.[81] VNS significantly reduced the disease severity for up to 12 weeks with suppressed TNF production. It also was reported that five of seven patients with active Crohn's disease achieved significant clinical remission (decreased disease activity index and improved endoscopic findings) by VNS for 6 months.[82]

Pharmacologic activation of CAP or other anti-inflammatory pathways also appears to be a promising treatment strategy for AKI. Clinical trials of GTS-21, an agonist of α7nAChR, currently are ongoing for Alzheimer's disease and schizophrenia, although the precise mechanisms of its effects still are unclear. In animal studies, administration of nicotine or GTS-21 protects against kidney IRI,[83] lipopolysaccharide-induced AKI,[84] and cisplatin-induced AKI.[85] Torres-Rosas et al[75] reported that dopamine D1 receptor agonists rescued mice with adrenal insufficiency from polymicrobial peritonitis by suppressing systemic inflammation.

We believe that the biggest challenge in research regarding AKI treatment that targets neuroimmunomodulation with a nonpharmacologic or pharmacologic approach is the lack of knowledge regarding the precise underlying mechanisms for the amelioration of AKI by neuroimmunomodulation. For example, with respect to VNS, unanswered questions include the downstream effects of afferent VNS and the link between the spleen and the kidney. Understanding the precise mechanisms of the neuroimmune interaction in AKI is critical to ensure its safe and effective clinical application.

OPTOGENETICS: A NOVEL TECHNIQUE TO UNDERSTAND COMPLEX NEURAL CIRCUITS

As discussed previously, a deeper understanding of the complex neural circuits involved in the pathophysiology of AKI is important. However, the lack of methods for selectively stimulating and inhibiting neurons has been a major obstacle. A novel technique called optogenetics helps in selective stimulation and inhibition of target neurons in vivo by light application.

Optogenetics refers to the use of both optics and genetics for controlling cells, typically neurons, which have been genetically manipulated to express light-sensitive opsins. These opsins include excitatory channelrhodopsin-2 (ChR2)[86–88] and inhibitory halorhodopsin[89] and archaerhodopsin[90] (Fig. 4). For example, ChR2, originally discovered from the green alga *Chlamydomonas reinhardtii,* is a nonselective cation channel and its gate is opened rapidly by the conformational change after blue light application (maximum activation, 470 nm).[91] A report on the application of these unique proteins in the field of neuroscience was published in 2005.[92] Boyden et al introduced ChR2 to mammalian hippocampal neurons with lentivirus in vitro and successfully evoked action potentials only 1 to 2 ms after blue light application to these cells, and the firing was stopped when the light was switched off. Illuminating ChR2-expressing neurons with blue light opens the ChR2 cation channel,

enabling Na^+ to enter the cells, which depolarizes the cell membrane and evokes an action potential.

Since a report regarding the control of neurons using optogenetics in 2005, this technique has been broadly used as an intervention tool. Microinjection of viral vectors into the target area and the Cre-LoxP system enable the specific expression of light-sensitive opsins in in vivo studies. This technique has been applied to study subgroups of vagus afferent neurons that express specific markers.[93] By applying blue laser to the cervical vagus nerve of transgenic mice, wherein ChR2 specifically was expressed in each subgroup of the vagus afferent neurons, Liberles and colleagues showed that selective stimulation of each subgroup modified the function of various organs (eg, lung, heart, gastrointestinal tract) in a different manner.[93,94] For example, the stimulation of P2ry1-positive neurons completely stopped respiration, whereas the stimulation of Npy2r-positive neurons caused rapid/shallow breathing. These findings suggest that subpopulations of vagus neurons may play a critical role in the renoprotective effect of VNS. Thus, optogenetics is a useful tool for studying the roles of complex neural circuits in the neuroimmune interaction in AKI pathophysiology, leading to the clinical application of neuroimmunomodulation to AKI treatment.

CONCLUSIONS

Experimental evidence has suggested that VNS and pulsed ultrasound protect the kidney from AKI by activating CAP, and that renal denervation is effective in ameliorating renal inflammation and possibly AKI. Optogenetics is a useful technique for dissecting complex neural circuits and is applicable in AKI. Further assessment of the neural circuits to control renal inflammation is warranted for future clinical application of neuroimmunomodulation with a nonpharmacologic or pharmacologic approach.

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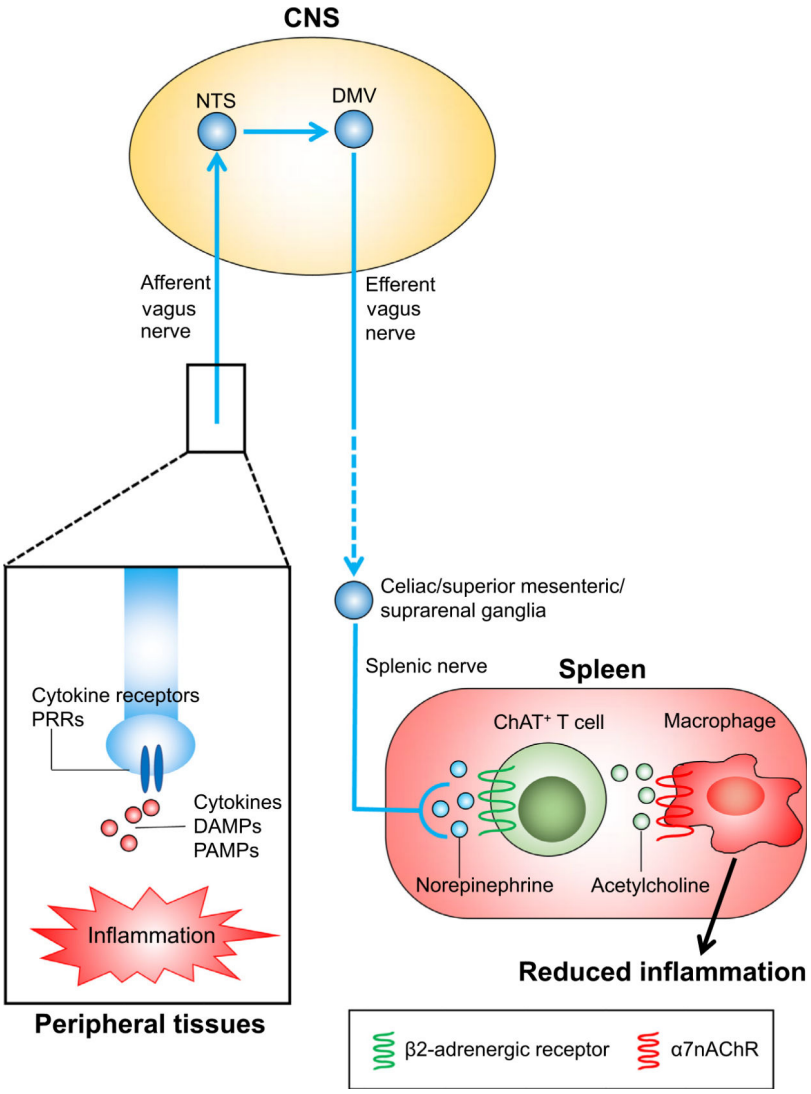

Figure 1.

The inflammatory reflex. When inflammation occurs in peripheral tissues, inflammatory cytokines, damage-associated molecular patterns (DAMPs), and pathogen-associated molecular patterns (PAMPs) bind to cytokine receptors and pattern recognition receptors (PRRs) expressed on the local afferent vagus nerve. The signal is transmitted through the CNS to the efferent vagus nerve and the splenic nerve. Norepinephrine released by splenic nerve terminals binds to $\beta 2$-adrenergic receptors expressed on choline acetyltransferase (ChAT)-positive T cells, causing acetylcholine release from this specific T cell subpopulation. The released acetylcholine binds to $\alpha 7$nAChRs expressed on macrophages located close to these T cells, resulting in suppressed production of the proinflammatory cytokines by the macrophages and reduced inflammation. Abbreviations: DMV, dorsal motor nucleus of the vagus; NTS, nucleus tractus solitarius.

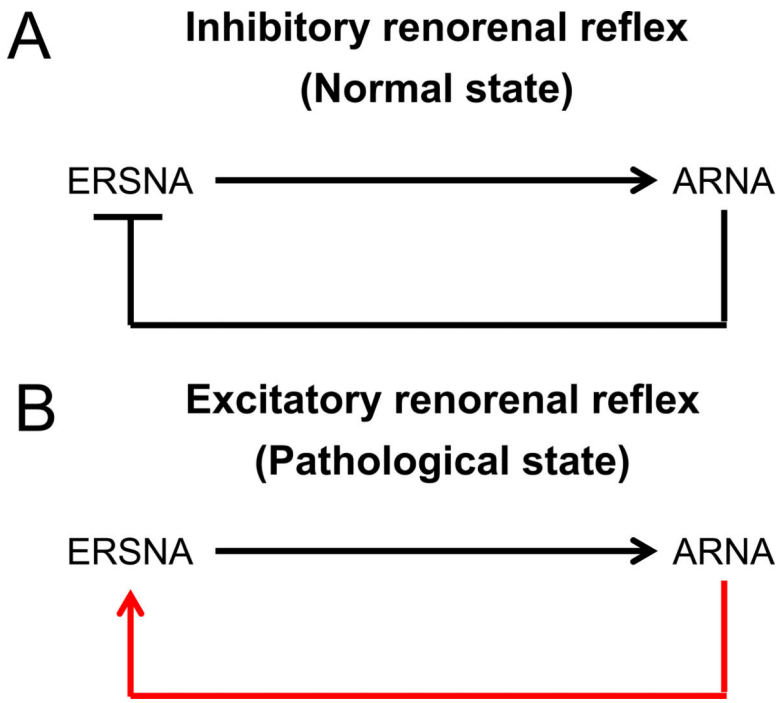

Figure 2.

(A) Inhibitory and (B) excitatory renorenal reflexes. An increase in the ERSNA is known to increase the ARNA. (A) In normal kidneys, an increase in ARNA suppresses ERSNA, providing negative feedback to prevent excessive ERSNA (inhibitory renorenal reflex). (B) In contrast, in the kidneys, under pathologic conditions such as hypertension, CKD, and heart failure, the inhibitory renorenal reflex is suppressed and an excitatory reflex prevails. The afferent renal nerves from the damaged kidneys exert an excitatory influence on ERSNA, forming a vicious cycle leading to excessive ERSNA.

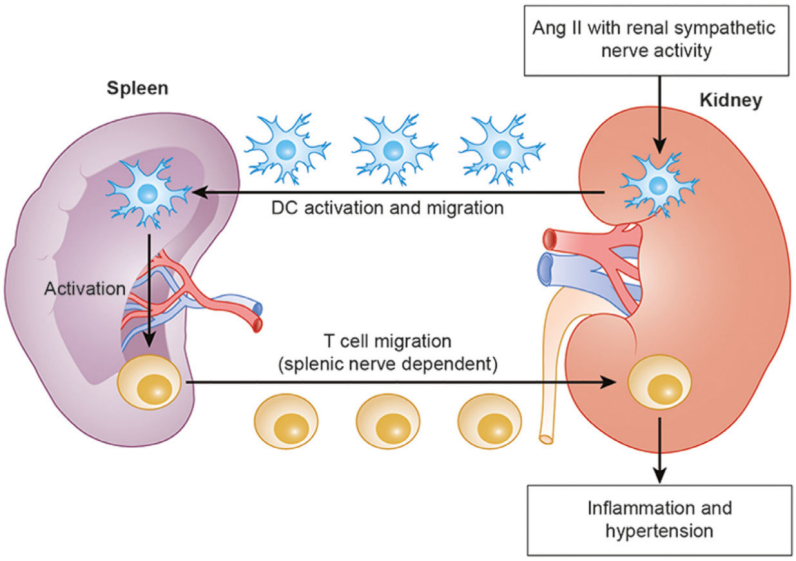

Figure 3.

The hypothesized interaction between the spleen and the kidney for the activation of dendritic cells (DCs) and T cells in angiotensin II (Ang II)-induced hypertension. Ang II with renal sympathetic nerve activity activates DCs in the kidney, leading to the migration of these cells to the spleen, where they, in turn, activate T cells. Thereafter, these activated T cells egress from the spleen and migrate to the kidney causing inflammation and hypertension. The splenic nerve is essential for T cell migration.

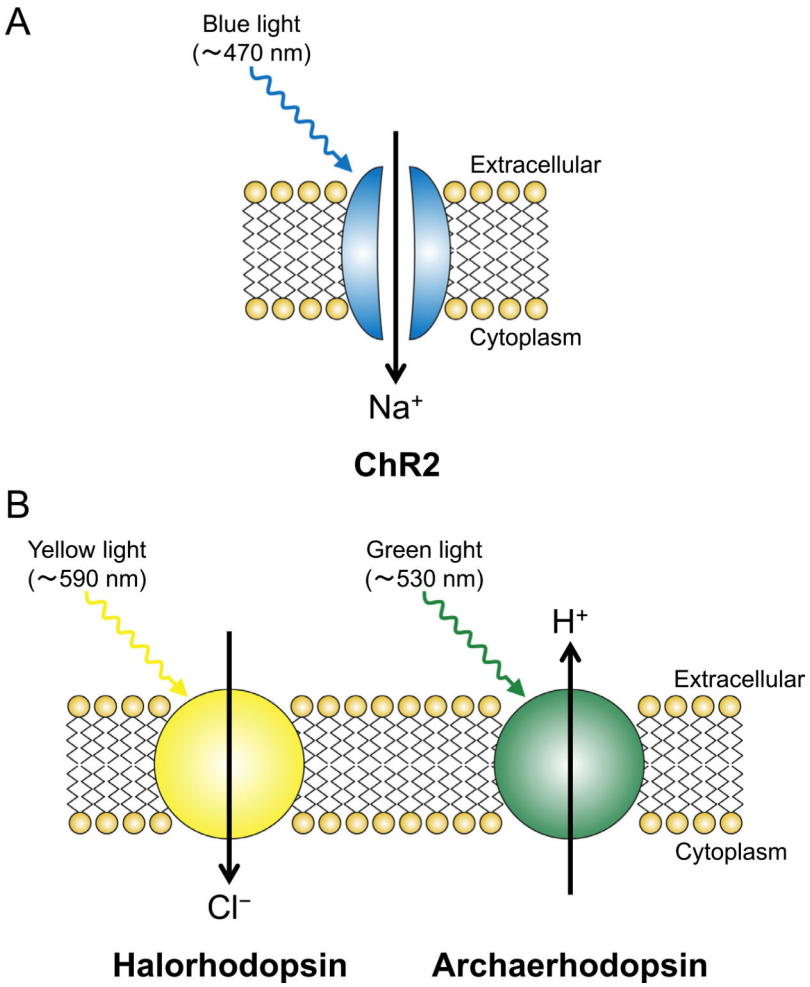

Figure 4.

Schematics of an (A) excitatory light-sensitive opsin, ChR2, and (B) inhibitory light-sensitive opsins, halorhodopsin, and archaerhodopsin. The expression of these opsins does not affect the resting membrane potential because of the lack of ion flux without light application. (A) When ChR2 is illuminated with blue light, the gate of this nonselective cation channel is opened, which allows influx of Na^+ and causes depolarization of the ChR2-expressing neurons. If the spike of Na^+ entry is large enough for the membrane potential to reach the threshold, an action potential is evoked. (B) When halorhodopsin/archaerhodopsin is illuminated with yellow/green light, it functions as an inward Cl^-/outward H^+ pump and causes hyperpolarization of the neurons expressing these opsins, thereby exerting an inhibitory effect.

Table 1.

Experimental Evidence for the Effectiveness of Neuroimmunomodulation in AKI and Other Kidney Diseases

Treatment	Models	Outcomes	References
Renal denervation (both sympathetic and afferent neurons)	Anti–Thy-1.1 nephritis	Decreased urinary albumin, mesangial microaneurysms, and macrophage infiltration	57
	SLE	Decreased urinary albumin and renal cortical expression of MCP-1	58
	UUO/unilateral IRI	Decreased neutrophil and macrophage infiltration and fibrosis	59, 60
	Angiotensin II–induced hypertension	Ameliorated hypertension, renal inflammation (T cell infiltration), renal fibrosis, and albuminuria	68
VNS (CAP activation)	Bilateral IRI	Ameliorated AKI	61
	Kidney transplantation	Improved long-term renal function and survival of the recipients with decreased immune cell infiltration	62, 63
Pulsed ultrasound (CAP activation)	Bilateral IRI/CLP	Ameliorated AKI	64, 65
Stimulation of C1 neurons/physical restraint (CAP activation)	Bilateral IRI	Ameliorated AKI	70
Nicotine/α7nAChR agonists (CAP activation)	Bilateral IRI/LPS/cisplatin	Ameliorated AKI	65, 83–85

Abbreviations: CLP, cecal ligation and puncture; LPS, lipopolysaccharide; MCP-1, monocyte chemotactic protein-1; SLE, systemic lupus erythematosus.