

## Review Article

# Renal disease and neural circuits: brain-kidney crosstalk

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**Abstract:** It has been shown that the neural control of renal function is exerted by the CNS via sympathetic innervations of the kidneys. Developments in neural circuit researches over the past two decades have given us remarkable insight into the renal disorders. Whether the information is neurochemical and neural circuitry structural, a range of renal diseases will undoubtedly benefit from an improved scientific understanding of the pathophysiologic changes that occur in the neural circuits. In this review, we explore the neural circuit mechanisms of renal diseases from experimental and clinical studies. Further studies should be undertaken to elucidate the nature of deep brain stimulation so that we may more effectively apply the neurostimulation to avoid these special complications.

**Keywords:** Renal disease, neural circuits, deep brain stimulation, pseudorabies virus, melanocortinergic circuits, melanocortin-4 receptor

### Introduction

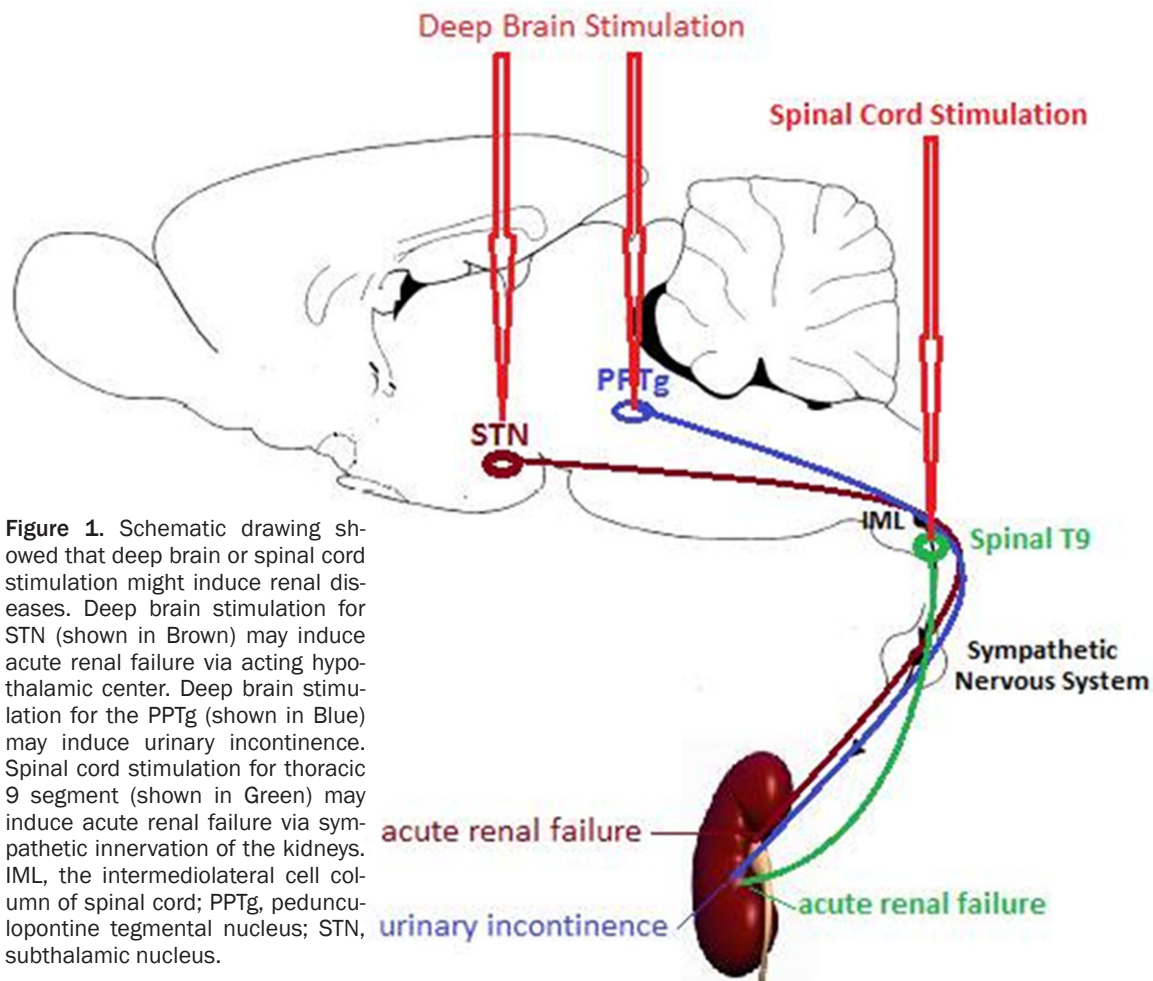
It has been shown that the neural control of renal function is exerted by the CNS via sympathetic innervations of the kidneys [1-4]. Developments in neural circuit researches over the past two decades have given us remarkable insight into the renal disorders [1, 5-8]. Whether the information is neurochemical and neural circuitry structural, a range of renal diseases will undoubtedly benefit from an improved scientific understanding of the pathophysiologic changes that occur in the neural circuits. A better understanding of mechanisms about deep brain stimulation-induced renal diseases should aid development of successful new therapies for renal diseases. In this review, we explore the neural circuit mechanisms of renal diseases from experimental and clinical studies.

### Deep brain stimulation-induced renal diseases

Acute renal disease originated from the CNS is one area where dramatic strides in our understanding of mechanisms have occurred. The

study of Palkovits et al. investigated the effect of experimentally induced acute renal failure (ARF) on neuronal cell activation by immunohistochemistry for Fos and Fra-2 in the rat brain, and found that central autonomic cell groups, especially visceral sensory cell groups in the brain, which are in primary, secondary or tertiary connections with renal afferents, were activated in response to ARF [9].

Most information about deep brain stimulation-induced renal diseases has been derived from clinical reports. Guimaraes et al. reported acute renal failure in patients with bilateral deep brain stimulation to subthalamic nucleus (**Figure 1**) [10], and indicated that effect of deep brain stimulation- subthalamic nucleus (DBS-STN) in hypothalamic centers remained a valid hypothesis which could explain an altered kidney function immediately after DBS-STN [11]. The study of Aviles-Olmos et al. showed the urinary incontinence following deep brain stimulation of the pedunculopontine tegmental nucleus (PPTg) (**Figure 1**) [12], and stated that a possible explanation for the detrusor overactivity that developed immediately after right PPTg DBS is the proximity between the caudal PPTg and brain-



**Figure 1.** Schematic drawing showed that deep brain or spinal cord stimulation might induce renal diseases. Deep brain stimulation for STN (shown in Brown) may induce acute renal failure via acting hypothalamic center. Deep brain stimulation for the PPTg (shown in Blue) may induce urinary incontinence. Spinal cord stimulation for thoracic 9 segment (shown in Green) may induce acute renal failure via sympathetic innervation of the kidneys. IML, the intermediolateral cell column of spinal cord; PPTg, pedunculo-pontine tegmentum; STN, subthalamic nucleus.

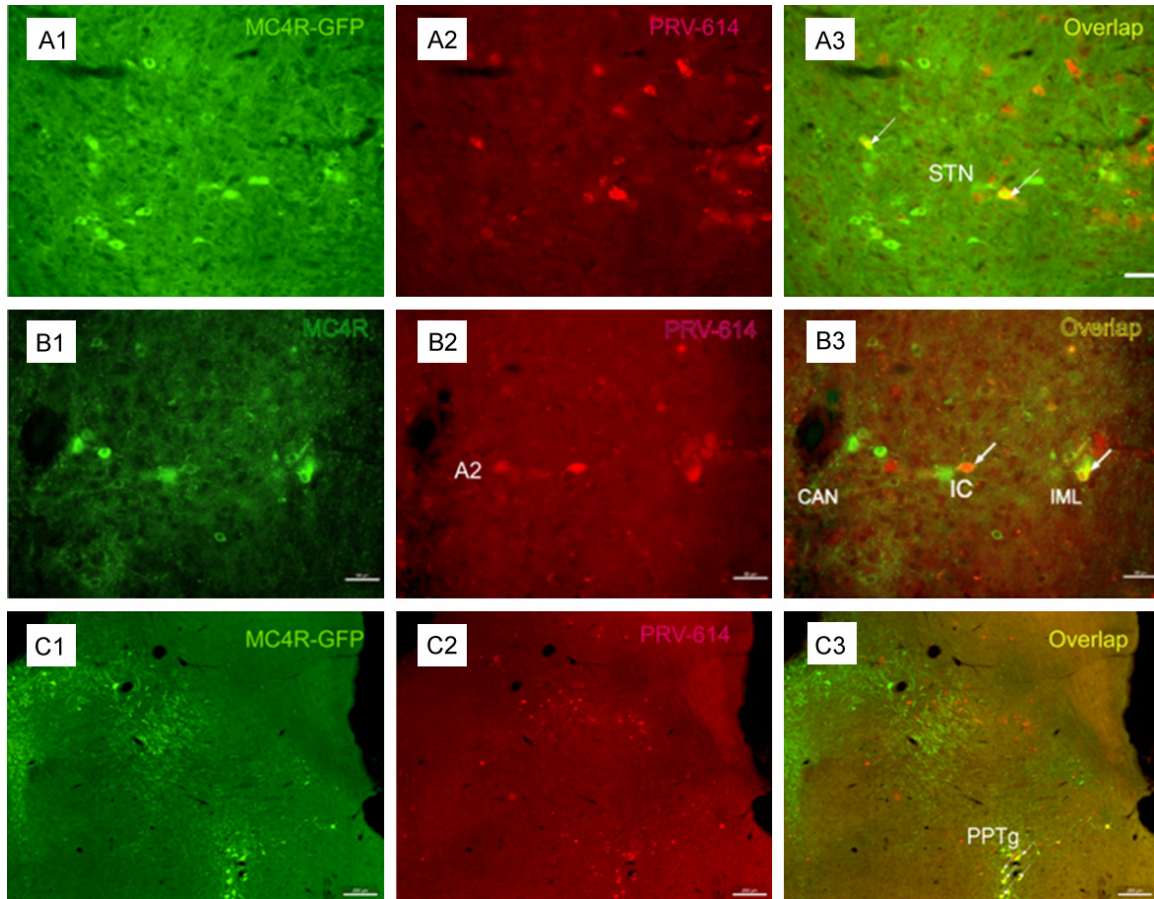
stem structures, which is implicated in the control of micturition. Fritsche et al. reported acute urinary retention in two patients after subthalamic nucleus deep brain stimulation for the treatment of advanced Parkinson's disease [13], and its possible mechanism was that STN-DBS influenced the integration of renal and afferent bladder information within the basal ganglia circuits [14].

Otherwise, Larkin TM et al. also reported a case of acute renal failure in a patient with failed back surgery syndrome and hypertension following a trial of spinal T9 stimulation (**Figure 1**) [15], and they postulated that the decreased sympathetic input induced by spinal cord stimulation could potentially lead to diminished renal blood flow via several mechanisms including peripheral vasodilatory effects, decreased renal perfusion pressure, and an attenuated cardiovascular response to the ensuing hypotension, and resulted in acute renal failure [16].

On the basis of above consideration, we indicated that understanding of the mechanisms of deep brain stimulation is urgently needed to clarify their role in the management of renal diseases and to aid the development of new, safer therapies.

#### Kidney and neural circuits in spinal cord

It is widely acknowledged that renal sympathetic innervations have an important role in the regulation of hydroelectrolytic and acid-base balance, reabsorption of small solutes and hormone production, and the maintenance of fluid homeostasis and renal hemodynamics [6, 17, 18]. Most information about the renal sympathetic preganglionic neurons (second order neurons) within the spinal cord has been derived from animal models (e.g. the mouse, rat, cat and rabbit) used in pseudorabies virus tracing research [1, 3, 6]. Developments in retrograde tracing technique research over the



**Figure 2.** Renal cell groups target MC4R-GFP positive neurons of the STN, spinal cord and PPTg. Injection of PRV-614 into the kidney resulted in retrograde infection of neurons in the IML (B2), PPTg (C2) and STN (A2) by sympathetic pathway. PRV-614/MC4R-GFP dual-labeled neurons were detected in the IML (B3), PPTg (C3) and STN (A3). (A1, B1, C1) showed MC4R-GFP-positive cells; (A2, B2, C2) showed PRV-614-labeled cells; and (A3, B3, C3) showed overlaid images of (A1, B1, C1) plus (A2, B2, C2). IML, the intermediolateral cell column of spinal cord; PPTg, pedunculo-pontine tegmental nucleus; STN, subthalamic nucleus. Arrows indicate double-labeled neurons. Some drawings were taken from Hong-Bing Xiang (Movement Disorders, 2013; Pain Physician, 2013).

past 2 decades have given us remarkable insight to characterize neuroanatomic circuits from spinal cord to the kidney [1, 6, 19]. We investigated spinal cord connections with the kidney by identifying sympathetic preganglionic neurons through the retrograde trans-synaptic transport of pseudorabies virus (PRV)-614 inoculated into the left kidney in combination with epifluorescence immunohistochemistry, and our data showed that the vast majority of spinal neurons infected by PRV-614 from the left kidney expressed red reporters (**Figure 2**), and neurons that participated sympathetic neural regulation of the kidney existed in ipsilateral spinal regions but were mainly located in the intermediolateral cell column (IML) of ipsilateral spinal T9 segment (**Figure 2**) [3].

Several studies have indicated the spinal labeling after PRV injection into the kidney by viral transneuronal tracing using isogenic recombinant strains (PRV-BaBlu, PRV-614 and PRV-152). Weiss, et al. reported that infected neurons were detected within laminae I and II of the dorsal horn of the caudal thoracic and upper lumbar spinal cord segments after four days PRV injection into the kidney, and the labeling patterns in the spinal cord are consistent with previous work, indicating the location of renal sympathetic sensory pathways [20]. The study of Zermann et al. reported that injection of PRV-Bartha into the rat kidney resulted in retrograde infection of neurons in the IML at the T6 to T13 spinal cord regions, and most PRV-positive neurons were found in T10 [6],



whereas the findings of Ye et al. suggested that PRV-614 labeled neurons in IML of ipsilateral spinal cord segments T4 to L1, and most PRV-614-infected cells were found in T9 [3]. The differences of these data are probably due to the species changes of PRV or animal. The results from Ye et al. [3] were also consistent with the prior immunocytochemical localization of viral reporter proteins that PRV-152 infection was restricted to the spinal IML of T3-T12 at different postinoculation times after PRV-152 injection into the rat kidney [1]. It is a strikingly attractive that the spinal IML included sympathetic preganglionic neurons and related interneurons, which are implicated in balance of excitatory and inhibitory influences to the kidney [4, 21]. A considerable amount of literature had demonstrated that neurons in IML display the intrinsic autorhythmicity and spontaneous discharge [22], and their neuronal activity and neural network strongly correlate with sympathetic activity [23], and the IML [1, 6, 24] and sympathetic nervous system played an important role in the regulation of the kidney [25, 26]. The study of Cano et al. using an anatomical symmetrical system expanded on current understanding of the neural control of renal function, which was exerted by the central nervous system via sympathetic innervations of the kidneys [1]. Collectively, these data further suggested that the spinal IML neuronal circuits strongly implicated in the regulation of renal functions.

It is reported that spinal melanocortineric pathways have an important in the control of the kidney. A considerable amount of literature has demonstrated that the melanocortin-4 receptor (MC4R) is expressed in numerous spinal cord regions known for their implication in sympathetic signaling [27, 28]. Xiang et al. reported that there existed MC4R-green fluorescent protein (GFP) positive neurons in the IML, the intercalates nucleus (IC), and the central autonomic nucleus (CAN) of ipsilateral spinal cord by using adult male transgenic mouse line expressing green fluorescent protein (GFP) under the control of the MC4R promoter [16]. After injections of PRV-614 into the kidney, PRV-614/MC4R-GFP dual labeled neurons were detected in the IML and IC of ipsilateral spinal cord, and most PRV-614/MC4R-GFP labeled cells were found in the T9 segment (**Figure 2**) [16], suggesting that the spinal T9 PRV-614/MC4R-GFP neuronal circuits involved

in the regulation of renal functions. Some reports had demonstrated that the IML [1, 6, 24] and sympathetic nervous system played an important role in the regulation of the kidney [25, 26]. Cano et al had reported that the central circuitry involved in the innervations of both kidneys was characterized in individual rats by dual viral transneuronal tracing, and the neural control of renal function was exerted by the central nervous system via sympathetic innervations of the kidneys by using an anatomical symmetrical system [1]. Otherwise, a growing body of literature supports that sympathetic nervous system activity are tightly interconnected via central melanocortineric circuits involving the MC4R [29-32]. Collectively, these studies further indicate that the MC4R-expressing neurons of spinal IML may influence renal function.

### Kidney and neural circuits in brain

The last decade has witnessed the identification of neural circuits from the brain to the kidney. The understanding of central innervations and neuronal connections is important for studying renal physiology, the consequences of renal disease and neurosurgical interventions compromising renal nerves [6]. Previous studies have proved that PRV has become a very powerful tool for studying multisynaptic neuronal connections, due to its ability to function as a self-replicating marker and to propagate exclusively between connected neurons by transneuronal transfer, which is strictly time-dependent, and the high and specific value of PRV tracing for describing neuroanatomical pathways to study central neural networks [33-38], including the central control of the kidney [1, 6, 19, 37, 39-41]. The study by Zermann et al indicated that at the supraspinal level PRV-positive cells were found within certain brain regions, namely the nuclei raphes, rostral ventromedial and ventrolateral medulla, A5 noradrenergic cell region, locus coeruleus and nucleus paraventricularis of the hypothalamus 120 hours after PRV injection into the left kidney [6]. Weiss et al reported that infected neurons were found in the nucleus tractus solitaries (NTS) five days after PRV injection into the kidney, suggesting that renal afferents travel in sympathetic and parasympathetic nerves and that this information may converge at the NTS [20].

Central melanocortinergetic circuits have an important in the control of the kidney [42-49]. The melanocortin-4 receptor (MC4R) is an important regulator of energy homeostasis, and evidence suggests that MC4Rs are broadly expressed in the central nervous system, including many regions classically associated with the autonomic nervous system, e.g. the nuclei raphes, rostral ventromedial and ventrolateral medulla, and nucleus paraventricularis of the hypothalamus [27, 29, 50]. The study by Rahmouni et al expanded on current understanding of the physiologic role for the MC4R in the regulation of renal sympathetic traffic [51]. Using the heterozygous and homozygous MC4R knock-out mice, they found that the RSNA response to MC-3/4R agonist (MTII) was attenuated and abolished, respectively. Haynes et al reported that intracerebroventricular (ICV) administration of the MC-3/4R antagonist SHU9119 blocked the sympathoexcitatory effects of leptin to the rat kidney but not to brown adipose tissue, suggesting that the effects of leptin on renal sympathetic nerve activity (RSNA) are mediated by the melanocortin receptors [52]. Rahmouni et al reported that ICV administration of leptin and MC-3/4R agonist (MTII) caused a significant and dose-dependent increase in RSNA in mice, and the sympathoexcitatory effects of melanocortin system stimulation are attenuated in the absence of leptin receptors, demonstrating an important role for the MC4R in the regulation of renal sympathetic nerve outflow [51]. Taken together, these results demonstrated a potential for the central melanocortin system in elevating sympathetic outflow in some renal diseases.

It is known that renal nerves are crosstalk focus between the CNS and the kidney. We had provided morphological and neuroanatomical evidence of the neural circuitry between brain and kidney, and characterized projections from the brain to the kidney in the melanocortin-4 receptor-green fluorescence protein (MC4R-GFP) knock-in mouse, in which GFP is confirmed to be a good indicator of MC4R positive neurons, by using retrograde tracing techniques of PRV-614, expressing a novel monomeric red fluorescent protein (mRFP1) under control of the cytomegalovirus immediate early promoter, for direct visualization under fluorescence microscope [35-38, 53]. We found that

injections of PRV-614 into the kidney resulted in retrograde infection of neurons in the pedunculo-pontine tegmental nucleus (PPTg) and subthalamic nucleus (STN), and these results provided direct neuroanatomical evidence that supports the presence of autonomic projections from the PPTg and STN to the kidney, which were in agreement with a previous immunohistochemical study in which a subset of neurons in the PPTg, that are involved in the regulation of sympathetic outflow to kidney, was of catecholaminergic or serotonergic nature [8]. It was strikingly attractive that PRV-614/MC4R-GFP dual-labeled neurons were detected in the STN, which were in line with a previous immunohistochemical study [54]. Therefore, it was presumed that possible mechanism of the STN stimulation-induced acute renal failure involved melanocortinergetic signals in STN [11]. The report by Liu et al indicated that injections of PRV-614 into the kidney resulted in retrograde infection of neurons in the middle PPTg (mPPTg) and caudal PPTg (cPPTg), and PRV-614/MC4R double-labeled neurons were detected in the mPPTg and the cPPTg [42]. Such a role is supported by previous findings in which the PPTg exhibited moderate levels of GFP immunoreactivity using a mouse line in which GFP is expressed under control of MC4R gene promoter [29]. Recently, some studies have suggested that the PPTg may be divided into the dissipated parts (dp) and compact parts (cp) of the PPTg [42, 55, 56]. We also found that injection of PRV-614 into the kidney resulted in retrograde infection of neurons in the dpPPTg (**Figure 2**), and PRV-614/TPH and PRV-614/TH dual-labeled neurons were detected in the dpPPTg. In contrast to the dpPPTg, we did not detect dual-labeled neurons in the cpPPTg. These data also provided a better understanding of the PPTg and STN neural circuits innervating renal tissues, clearly demonstrating the rodent PPTg and STN regions that contain MC4R, and belonging to the descending pathways that involve in the control of the kidney. Altogether, these data may help provide further rationale for the potential development of MC4R agonists for the treatment of some renal diseases.

### Conclusion

Findings from recently published data in clinical studies during deep brain stimulation have

established that there is a close interaction between the renal disease and neural circuits in brain. Improved knowledge about neural regulation to the kidney opens new prospects for the potential use of deep brain stimulation. Further studies should be undertaken to elucidate the nature of deep brain stimulation so that we may more effectively apply deep brain neurostimulation to avoid these special complications related to kidney.

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#### Disclosure of conflict of interest

None.

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