

e Possible Mechanism of Spinal T9 Stimulation-Induced Acute Renal Failure: A Virally Mediated Transsynaptic Tracing Study in Transgenic Mouse Model

To THE EDITOR:

The case report titled "Acute renal failure during a trial of spinal cord stimulation: Theories as to a possible connection" by Larkin et al (1) addressed that spinal T9 stimulation could lead to diminished renal blood flow by the decreased sympathetic input. Renal sympathetic innervation is widely acknowledged to involve the maintenance of fluid homeostasis and modulation of renal hemodynamics. The understanding of spinal cord segments innervating the kidney, and spinal sympathetic innervations and neuronal connections to the kidney is important for studying the possible mechanism of decreased renal sympathetic input during a trial of spinal T9 stimulation. We would like to further complete the discussion of Larkin and colleagues by introducing a virally mediated transsynaptic tracing study in a transgenic mouse model.

The autonomic nervous system plays a prominent role in modulating carbohydrate metabolism (2). The kidneys respond to altered water and sodium availability with a set of homeostatic responses mediated by sympathetic outflow (3,4). The melanocortin-4 receptor (MC4R) is expressed in numerous spinal cord regions, and some findings indicated an important physiologic role for the MC4R in the regulation of renal sympathetic traffic by both leptin and insulin (5). We had characterized projections from the kidney to the spinal cord in adult male MC4R-green fluorescent protein (GFP) transgenic mice by using retrograde tracing techniques of pseudorabies virus (PRV)-614, expressing a novel monomeric red fluorescent protein (mRFP1) under control of the cytomegalovirus immediate early promoter, for direct visualization under a fluorescence microscope (6-10). We found that injections of PRV-614 into the kidney resulted in retrograde infection of neurons in the ipsilateral intermediolateral cell column (IML), the intercalates nucleus (IC), and

the central autonomic nucleus (CAN) of the spinal cord, and PRV-614-infecting cells were most heavily concentrated in the IML and were distributed sparsely in the IC and CAN of thoracic spinal cord segments T4 to L1, and most PRV-614 labeled cells specifically concentrated in the IML of T9 segment. Otherwise, PRV-614/MC4R-GFP dual labeled neurons were detected in the IML and IC of the spinal cord (Fig. 1), and most PRV-614/MC4R-GFP labeled cells were found in the T9 segment (Fig. 2).

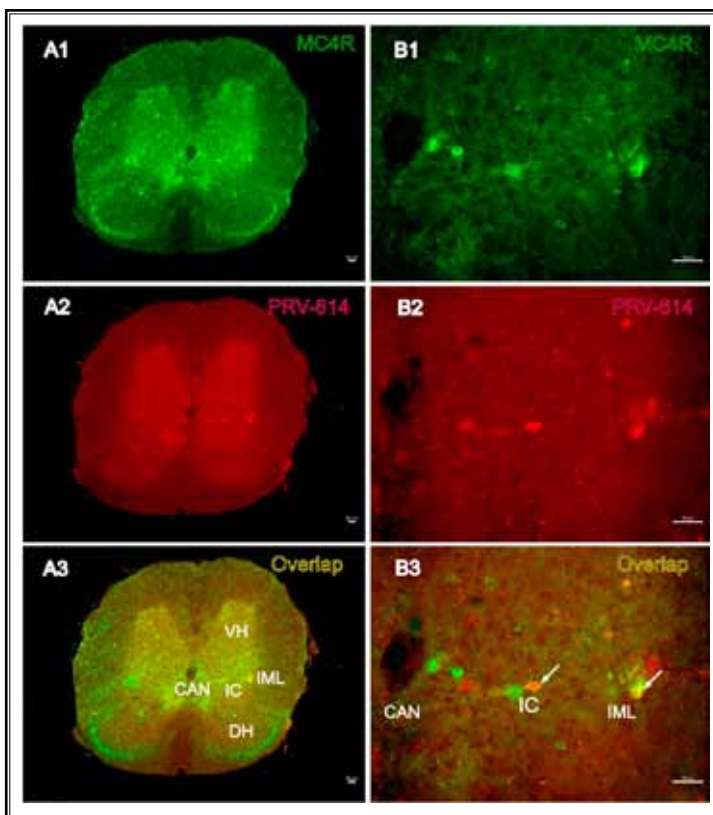
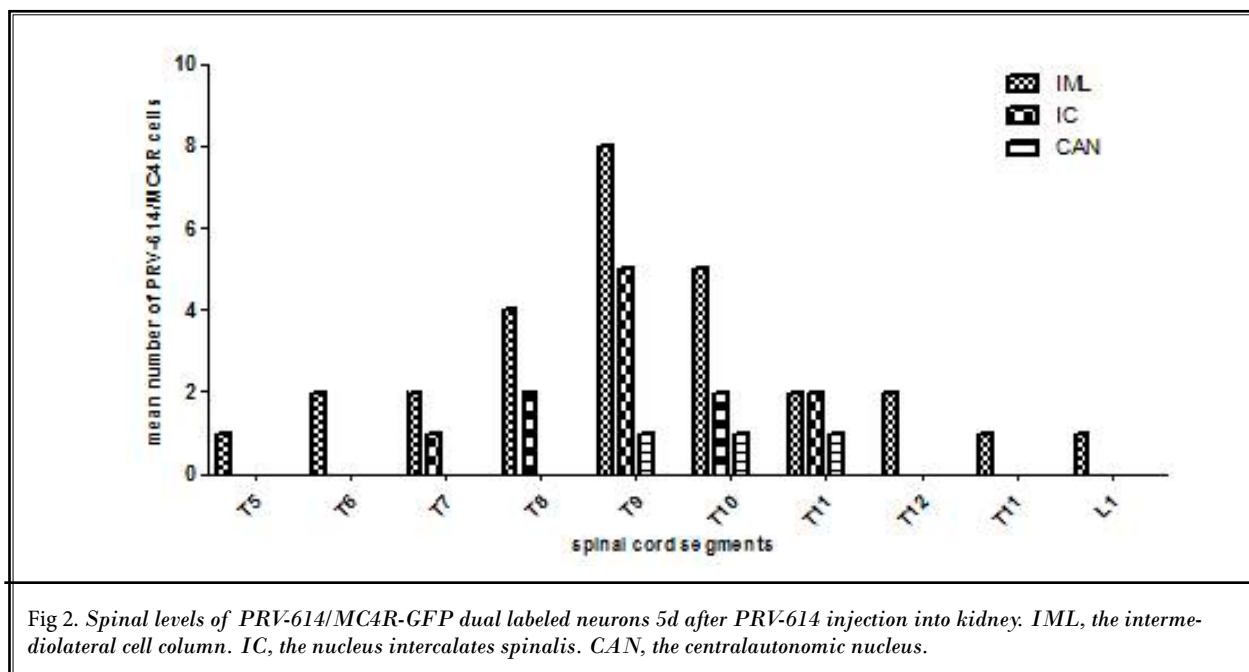


Fig. 1. Transverse section of the spinal cord, 5 days after PRV-614 injection. (A1) MC4R-GFP expressing neurons; (A2) PRV-614 expressing neurons in same section as (A1); (A3) overlap of (A1) and (B1), depicting distribution of MC4R-GFP-IR and PRV-614-bearing neurons. (B1, B2, and B3), amplified views of (A1, A2, and A3), respectively. IML, the intermediolateral cell column; IC intercalates nucleus; CAN, central autonomic nucleus; DH, Dorsal horn; VH, ventral horn. Scale bar: 50 μ m.



Based on all these findings, we speculate that the T9 spinal cord segment may be primarily involved in sympathetic regulation of renal functions, and spinal T9 stimulation may mainly blockade renal sympathetic innervations, thereby contributing to decreased renal blood flow. Animal studies have shown that the IML of the lower thoracic spinal cord segments (sympathetic kidney innervations T6 to T13) contained sympathetic preganglionic neurons (SPN) (11) and related interneurons, which are involved in processing excitatory and inhibitory influences to the kidney (12). A considerable amount of literature has demonstrated that the IML (13-15) and sympathetic nervous system (16,17) play an important role in the regulation of the kidney. Cano et al (15) demonstrated that the neural control of renal function was exerted by the central nervous system via sympathetic innervations of the kidneys. Otherwise, a growing body of literature supports that sympathetic activity is tightly interconnected via central melanocortinernergic pathways involving the MC4R (18-21). These studies indicate that the PRV-614/MC4R-GFP dual labeled neurons of the spinal cord may influence renal function. Our data further suggests that the spinal T9 PRV-614/MC4R-GFP neuronal circuits are involved in the regulation of renal functions.

In summary, the spinal T9 segment is considered a prominent neuronal circuit involved in the regulation

of renal functions. Thereby, spinal cord stimulation of T9 may induce diminished renal blood flow (e.g., secondary renal failure) by a reflex mechanism involving the sympathetic chain. Further investigation into the true incidence of secondary renal failure after SCS is warranted.

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