Molecular Mechanisms of Neuroplasticity in the Lower Urinary Tract: Contributions to Irritative Voiding and Chronic Visceral Pain

University of Virginia
William D. Steers

Interaction between a neuron and its target tissue is necessary for neuronal survival and synaptic organization during development, and probably throughout life. Evidence for alterations in neuronal morphology or function, termed neuroplasticity, in urologic disorders has been accumulating over the past decade. More recently, a detailed understanding has evolved built upon advancements in the areas of developmental neurobiology, long-term potentiation and nociception. Plasticity of nerves supplying the bladder occurs not only during embryonic development, but in response to denervation, obstruction, inflammation, and aging of the lower urinary tract. Mechanical stress to bladder tissues in response to urethral obstruction can serve as a stimulus for smooth muscle hypertrophy. Changes in smooth muscle, in turn, trigger changes in nerves. Obstructed bladders reveal a patchy decrease in innervation. Thus, a relative denervation exists. However, an increase in suburothelial sensory nerves has been seen in human specimens. In obstructed rats, enlargement of afferents within the dorsal root ganglia (DRG) develops as well as increased transport of retrograde tracers to the dorsal horn and sacral parasympathetic nucleus. Investigators have also noted an increased expression of nitric oxide synthase (NOS) in DRG cells supplying the bladder following outlet obstruction. Moreover, increased expression of GAP-43, a G-protein associated with axonal growth, is demonstrated using immunohistochemistry in the dorsal horn and around the sacral parasympathetic nucleus following bladder outlet obstruction. Obstructed experimental animals and humans develop unstable bladder contractions as well as the symptoms of urinary frequency, urgency, and nocturia. Electrophysiological studies reveal that obstruction of the lower urinary tract enhances a spinal micturition reflex. This reflex in the rat is triggered by Aδ-fiber afferents, whereas in the cat, C-fiber afferents mediate the spinal micturition reflex. These C-fibers are normally unresponsive, until a suprathreshold stimulus occurs such as injury or inflammation. Following spinal cord injury, this
nascent spinal reflex is responsible for voiding. Electrophysiologic studies reveal that changes also occur in sodium channel expression in bladder neurons in the DRG. Do similar alterations develop in humans? Patients with bladder outlet obstruction have been shown to have a positive ice-water test. This test is normally negative unless there is development of a C-fiber reflex, such as with spinal cord injury and neurologic disease. Intravesical capsaicin and resiniferatoxin dampen or abolish this reflex. Thus, bladder outlet obstruction triggers a wide range of neuroanatomical, biochemical, and electrophysiological changes in neural pathways supplying the urinary bladder.

What is the molecular trigger for these widespread changes following obstruction of the lower urinary tract? During embryonic development, nerve growth factor (NGF) is essential for the survival of DRG and in sympathetic neurons. NGF has also been shown to be important for maintenance of neurons in the adult. Exogenous administration of NGF to experimental animals and humans lowers cutaneous sensory thresholds. Likewise, intravesical administration causes bladder hyperactivity. Knockout models for the NGF receptor, tyrosine kinase-A (trkA), reveal that these animals have absent sensory nerve function. Urethral obstruction in animals triggers a rise in expression in NGF mRNA and protein. Stretch of cultured bladder smooth muscle cells also triggers increased NGF, mediated in part, by protein kinase C and the transcription factors AP-1 and NF κB. Furthermore, several clinical studies confirm that obstructed bladders from obstructed humans also contain increased levels of NGF compared to unobstructed subjects. In animals immune to NGF, obstruction fails to elicit changes in neural pathways and hyperactive voiding.

Changes in neural pathways and function of the urinary tract following inflammation of the bladder are amazingly similar to those seen with obstruction. Intravesical turpentine, mustard oil, acetic acid, or cyclophosphamide-induced cystitis trigger early intermediate gene expression (c-fos) within the dorsal horn of the spinal cord. Increased expression of GAP 43 within the dorsal horn and the sacral spinal cord has also been recently demonstrated with cyclophosphamide-induced cystitis. Similar to obstruction, inflamed
bladders contain transiently elevated levels of NGF, mRNA, and protein. Furthermore, administration of antibody against the NGF receptor, tyrosine kinase-A reduces bladder hyperactivity associated with inflammation. Thus, reminiscent of bladder outlet obstruction, inflammation is accompanied by neuroplasticity, which is NGF dependent and associated with hyperactive voiding. Thus, it is intriguing that patients with interstitial cystitis exhibit proliferation of suburothelial nerves, elevated NGF protein within bladder tissue, and increased NGF in their urine.

In addition to obstruction and inflammatory models, denervation or decentralization of the urinary bladder triggers a rise in NGF. Experimental studies on a variety of species reveal that transection of the pelvic nerve alters hypogastric nerve function. Normally, electrical stimulation of hypogastric nerve fails to alter bladder function. However, following bilateral pelvic nerve transection, hypogastric nerve stimulation then evokes a bladder contraction. This plasticity may be due to the rise in NGF.

Plasticity within the neural pathways supplying the lower urinary tract may one day be exploited with regard to either therapy or diagnostic tests. One can envision administration of antagonists to NGF receptors being useful in the treatment of hyperactive or voiding states such as the unstable bladder or urge, frequency, and bladder pain syndromes.