Model for chronic overexpression of NGF challenges old paradigms: focus on “Overexpression of NGF in mouse urothelium leads to neuronal hyperinnervation, pelvic sensitivity, and changes in urinary bladder function”

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Submitted 4 January 2010; accepted in final form 13 January 2010

NERVE GROWTH FACTOR (NGF) has been suggested to play a role in bladder pain by mediating inflammation (12) and functional changes in sensory and sympathetic neurons innervating the urinary bladder (5). Clinically, diseases such as interstitial cystitis/painful bladder syndrome (IC/PBS) have been associated with elevated urinary levels of NGF (10), and the urothelium of individuals with IC/PBS presents high expression of NGF (7). In addition, NGF is thought to play a predominant role in several lower urinary tract dysfunctions, including urinary incontinence and overactive bladder symptoms, such as urgency, frequency, and nocturia.

The majority of studies has focused on a central mechanism of NGF involvement in hyperalgesic states. However, as NGF is produced by peripherally located target cells, such as the bladder epithelium, a role for peripheral NGF in the physiopathology of the end organ has been proposed. Urothelium-secreted NGF binds to receptor complexes present on the nerve endings, is internalized, and provides trophic signals that support neuronal survival and function (Fig. 1). Although a consensus has been formed that NGF plays a fundamental role in lower urinary tract function and response to injury-induced referred hyperalgesia, the absence of an animal model with chronic NGF overexpression has hampered our understanding regarding the mechanisms underlying NGF activity in the lower urinary tract.

One of the difficulties involved in chronic overexpression of NGF is that systemic administration of this neurotrophin can cause allodynia that can last for several weeks and can complicate the interpretation of the results (4). Another confounding factor is that the proform of nerve growth factor (proNGF) is also secreted and is biologically active (6). ProNGF is synthesized from two alternatively spliced transcripts of 25- and 32-kDa isoforms (1). Posttranslational modification of ProNGF includes N-glycosylation that leads to a 40-kDa secreted protein. The 40-kDa form of proNGF is secreted in response to nerve stimulation, along with the proteases needed to generate the 13-kDa mature NGF (mNGF), or to degrade it (1).

In this issue of the American Journal of Physiology—Regulatory, Integrative and Comparative Physiology, Schnegelsberg and collaborators took advantage of a highly innovative model using the urothelium-specific uroplakin II (UPII) promoter (15) to drive the chronic expression of mouse NGF in a tissue-specific manner (13). The results show that urothelial NGF overexpression in transgenic mice resulted in neuronal proliferation, focal increases in bladder mast cells, increased urinary bladder reflex activity, and pelvic hypersensitivity (13). This model of stable NGF overexpression will open a new field of research by challenging old paradigms and will permit a better evaluation on the role of NGF in target organ development. In addition, this outstanding mouse model will contribute to a better understanding of how NGF contributes to inflammatory pain, angiogenesis, and wound healing. A difficulty in overexpressing NGF is that mNGF is seldom detected in tissues by immunoprecipitation or by immunohistochemical methods (1). This seems to be the case of the present work that presented sound evidence of NGF overexpression at the mRNA level but was unable to detect ectopic NGF immuno-
reactivity in apical urothelial cells of adult transgenic mice. It has been proposed that an antiserum directed against the predicted precursor protein sequence detects proNGF (1). Ideally, a better understanding on the role of NGF in bladder pathobiology should take into consideration the several steps involved in its synthesis and posttranslation modifications. The latter should be a natural progression of the present work.

Several laboratories have tried to access the consequences of NGF overexpression. Interestingly, ectopic expression of NGF in the cerebellum results in an increase in proNGF rather than mature NGF levels (2). Another study described transgenic mice that overexpress NGF in the skin and possess a greatly increased number of nociceptors (8). The latter is one more hypothesis that the present model will permit to be addressed. Specifically, what are the consequences of NGF overexpression on the density of bladder nociceptors? Surprisingly, mice overexpressing NGF in the skin display reduced hypersensitivity and recovered more rapidly in response to inflammation, suggesting a compensatory suppression of nociceptive transmission in these mice (8). It remains to be determined whether the urothelial specific expression of NGF would accelerate the healing from cyclophosphamide-induced cystitis. Another interesting study found that chronic administration of exogenous NGF to the detrusor smooth muscle of female rats provoked an increased bladder weight, reduced bladder capacity, reduced the intercontraction interval, and increased the amplitude of nonvoiding contractions (16). This is in agreement with the present work describing that urothelial overexpression of NGF also provokes trophic responses in the detrusor smooth muscle. Determination of the molecular pathway underlying such trophic alterations will shed light on the role of NGF in lower urinary tract disorders. It remains to be determined whether the effects of NGF overexpression are mediated by an increased survival of bladder nerves or a direct effect of this neurotrophin on nociceptors present in urothelial cells, blood vessels, and detrusor smooth muscle (Fig. 1). Finally, the recognition of a pathologic role of NGF and its receptor system has provided an attractive opportunity to develop a novel class of therapeutics for bladder inflammatory diseases and chronic pain syndromes (11), and the present work opens the proper avenue to evaluate this system.

REFERENCES


