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Editorial

Tachykinins: Role in Detrusor Overactivity?

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The nerves of the lower urinary tract synthesize, store, and release many neuropeptides, including tachykinins, i.e., substance P (SP), neurokinin A (NKA), and neurokinin B (NKB) [1]. It is generally accepted that tachykinins have an important role in afferent signaling from the bladder, and that they may be involved in different pathologies in the lower urinary tract. A pathophysiologic role in detrusor overactivity (DO) and the overactive bladder (OAB) syndrome has been suggested [2], but has not been established. Recently, Sellers et al. [3] found NKA-induced responses to be impaired in detrusor muscle from patients with idiopathic DO, but not from patients with neurogenic DO, in whom the response did not differ from that observed in detrusor tissue from normal controls. Even if the observation of Sellers et al. [3] supports their conclusion that idiopathic and neurogenic DO may have different pathophysiology (which does not seem unreasonable), it does not clarify the potential role of tachykinins in the pathogenesis of DO/OAB. If these peptides have such a role, where is the site of action: the detrusor muscle, afferent nerves, or other structures within the bladder? Or is their main site of action not in the bladder, but in the central nervous system (CNS)?

1. Tachykinins and tachykinin receptors

Tachykinins act on specific, G-protein-coupled neurokinin (NK) receptors, and SP, NKA, and NKB

possess the highest affinity for NK1, NK2, and NK3 receptors, respectively. All receptor subtypes have been identified in urinary bladders of various mammals, both in vitro and in vivo [4]. In the rat detrusor, NK1, NK2, and NK3 receptors have been demonstrated, as evidenced by radioligand binding, autoradiographs, and functional experiments, whereas, in hamster, mouse, dog, and human detrusor, NK2 receptors predominate [4]. The nerves containing the tachykinins are localized mainly suburothelially, but also can be found within the detrusor muscle. Binding sites for the peptides are localized mainly to the detrusor muscle, but also can be demonstrated either directly or functionally on blood vessels and on the urothelium/suburothelium [1].

2. Afferent signaling and “efferent” functions

Tachykinins are believed to serve not only as mediators of afferent functions, but they may also have a local effector or efferent function [4]. Thus, they may act as neurotransmitters and/or neuromodulators in the bladder ganglia and at the neuromuscular junctions. As a result, these peptides can be involved in the mediation of various effects, including smooth muscle contraction, potentiation of efferent neurotransmission, changes in vascular tone and permeability (“neurogenic inflammation”), and micturition reflex activation [4]. Evidence for their role is based mainly on experiments in animals.

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3. Detrusor contraction

In the human detrusor, the presence of tachykinins, their receptors, and their contractile effects have been well documented [5]. The predominant tachykinin receptor mediating contraction of the human detrusor is of the NK2 type.

The NK2 receptor-mediated contraction in the detrusor is dependent largely on the activation of L-type Ca^{2+} channels and is sensitive to nifedipine [6]. However, a role of intracellular Ca^{2+} cannot be excluded, since NK2-receptor stimulation also activates phospholipase C [6]. Prostanoids generated after NK2 receptor activation may amplify the direct contractile effect of NK2-receptor stimulation [4]. Additional mechanisms may be involved. Thus, possible attenuation of NKA-induced contractions of the rat detrusor by the Rho-kinase inhibitor Y-27632 suggests involvement of the Rho-kinase pathway [5,6].

Contractions of the detrusor may involve both cholinergic and noncholinergic components [5]. Even if the noncholinergic component seems to be mediated mainly by ATP, involvement of other mediators has not been completely excluded [5]. Whether tachykinins can contribute to the atropine-resistant contraction has been unclear. However, no involvement of tachykinins has been demonstrated either in contraction of normal human detrusor tissue, where the atropine-resistant component of responses to electrical stimulation of nerves is small, or in detrusor tissue from patients with e.g., idiopathic DO [7], where the atropine-resistant component can amount to 50% [5]. This finding, together with the observation of Sellers et al. [3] that the sensitivity to NKA is decreased in idiopathic DO, does not favour the view that a direct contractile effect of tachykinins on the detrusor muscle is involved in the generation of DO/OAB.

4. Central control

SP, NKA, NKB, and their preferred receptors, NK1, NK2, and NK3, respectively, have been demonstrated in various CNS regions, including those involved in micturition control [4]. NK1 receptor-expressing neurons in the dorsal horn of the spinal cord may play an important role in DO/OAB. Thus, at the spinal level, there was a tachykinin involvement via NK1 receptors in the micturition reflex induced by bladder filling. This was demonstrated in normal rats, and more clearly, in rats with bladder hypertrophy secondary to bladder outflow obstruction [5].

Seki et al. [8] demonstrated that NK1 receptor-expressing neurons in the spinal cord could be

eliminated by using intrathecal substance P-sapoin conjugate (SSP-SAP). They found that SSP-SAP reduced capsaicin-induced DO and suggested that SSP-SAP could be effective in treating DO induced by bladder irritation without affecting normal bladder function. In conscious rats undergoing continuous cystometry, antagonists of both NK1 and NK2 receptors inhibited micturition, decreasing micturition pressure and increasing bladder capacity at low doses, and inducing dribbling incontinence at high doses. This effect was most conspicuous in animals with outflow obstruction [5].

5. Tachykinins and detrusor overactivity

A significant increase in the density of suburothelial, SP-containing nerves was found in patients with idiopathic DO, compared with stable controls [9,10]. Since capsaicin-sensitive afferents (containing tachykinins) may be a part of a spinal, vesicovesical excitatory (short-loop) reflex providing a neurogenic mechanism for overactive detrusor contractions, both idiopathic and neurogenic [5], it cannot be excluded that peripheral tachykinins may be involved in pathophysiologic afferent signaling associated with DO/OAB. However, despite promising effects in animal models [5], there seem to be no published proof of concept studies showing that any of the selective NK-receptor antagonists available has a therapeutic effect in patients with DO/OAB.

6. Conclusions

Even if it has been suggested that the lower urinary tract is a primary site of action of the tachykinergic system, the roles of tachykinins in different types of bladder dysfunction still remain to be established. The investigation of Sellers et al. [3] shows that their effects on the detrusor muscle in different types of DO may not be the same. We do not know whether the authors' findings reflect whether the reaction to the peptides is changed as a consequence of other factors related to the disorder, or whether the bladder tachykinins are involved directly in the generation of some types of DO. A role of tachykinins within the CNS in the pathogenesis of DO cannot be excluded and should be further explored.

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