ATP and Spinal Cord Injury-related Neurogenic Bladder

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The urinary bladder is built to perform its functions of accommodating and emptying urine in a controlled and coordinated way. These performances rely on sophisticated regulation by the central and peripheral nervous systems. When after neurogenic insults, e.g. trauma, spinal cord injury, or systemic disease likes multiple sclerosis, the urinary bladder presents a malfunction in its functions, it is called neurogenic bladder.

Symptoms of neurogenic bladder vary from detrusor hypoactivity to overactivity, depending on the site of neurologic insult. The sphincter at the bladder outlet may also be involved, resulting in sphincter hypoactivity or overactivity and loss of coordination with bladder activity.

Injuries of the spinal cord between the pons and the sacral segment contribute to spastic bladder or overactive bladder. The bladder usually empties too quickly and too frequently. Patients with this lesion may experience urge incontinence. When both the urinary bladder and external sphincter contract simultaneously, the affected individual will feel an extreme desire to void but only a small amount of urine may dribble out, and this is described as detrusor-sphincter dyssynergia.

Voiding dysfunction with urinary incontinence is one of the most challenging consequences of spinal cord injury. Among the different types of complication in the neurogenic bladder, uncontrollable increase in intravesical pressure is the major cause of injury to the upper urinary tracts, which usually results in reflux uropathy and deterioration of renal function.[1] Both detrusor hyperreflexia and detrusor-sphincter dyssynergia may result in the elevation of intravesical pressure. For decades, efforts have been made to explore new medical treatments for neurogenic bladder based on new understandings in pharmacology.

The relationship of adenosine triphosphate (ATP) and bladder function can be traced back to 1972, when Burnstock et al first postulated that ATP could act as an excitatory co-transmitter with acetylcholine in parasympathetic nerves supplying the urinary bladder.[2] ATP could be produced and released from the urothelium in response to mechanical stretch, and stimulation in interstitial cystitis and bladder outlet obstruction.[3,4] These findings precipitated the discovery of purinergic receptors on the bladder mucosa. It was later shown that ATP response is mediated via ligand-gated cation channels, P2X receptors.[5] So far, there have been 7 subtypes of P2X receptors cloned and characterized in the P2X receptor family.[6] The bladder afferent cells in the L6–S1 dorsal root ganglion express chiefly $P2X_{2/3}$ heteromeric receptors.[7] Increased expressions of these purinergic receptors in the urothelium have been found in several bladder conditions such as idiopathic detrusor instability,[8] neurogenic detrusor overactivity, interstitial cystitis[9] and bladder outlet obstruction. Evidence suggests that P2X receptors serve a combined function in sensory and motor activity of the human bladder. P2X receptors mediate excitation of sensory neurons and evoke muscle contraction in response to ATP release. The purinergic receptors have also been proven to activate the afferent C-fibers. Many studies have aimed at better understanding these unique receptors and have helped to explore many newer purinergic receptor antagonists in the treatment of overactive bladder and non-voiding contraction, and the results seem promising in terms of more efficiency and less irritation to the bladder compared to intravesical treatment with conventional agents. Therefore, treatment with purinergic antagonist in these bladder conditions might provide a novel therapy for patients refractory to conventional antimuscarinic therapy.

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Spinal cord injury results in changes in pharmacologic and morphologic properties of urothelium and bladder afferent neurons. In this situation, ATP is released from the urothelium upon both mechanical and chemical stimulations. Through the purinergic receptors present in the C-fiber afferents, ATP can trigger a reflex bladder activity.

In this issue of the *Journal of the Chinese Medical Association*, Lu and colleagues[10] evaluate the effects of a selective non-nucleotide $P2X_3$ and $P2X_{2/3}$ purinergic receptor antagonist A-317491 (5-((3-phenoxybenzyl) [(1*S*)-1,2,3,4-tetrahydro-1-naphthalenyl] amino carbonyl)-1,2,4-benzenetricarboxylic acid) on the non-voiding contraction and voiding detrusor contractility of bladder in a rat model of spinal cord transection at the T8–T9 segmental level. A-317491 has been shown to be a good blocker of peripheral P2X receptors due to its ability to completely block the afferent activation and mechanical sensitization induced by P2X agonists.[11,12] In Lu et al's study, A-317491 was given intravesically in a series of escalating doses to rats 14–16 weeks after spinal transection, and cystometrograms were recorded before and after each drug administration. The investigators found that A-317491 at doses between 1 and 30 μmol/kg significantly prolonged the interval between voids and reduced the number of non-voiding contractions, and increased the pressure threshold for voiding. The effects appeared within 10 minutes of drug administration. However, they found that this drug failed to change the amplitude or the duration of the voiding contractions. These findings indicate that the mechanism via purinergic receptors $P2X_3$ or $P2X_{2/3}$ may contribute to the detrusor hyperreflexia that occurs after spinal cord injury. Therefore, A-317491 may be considered a promising option to treat detrusor overactivity in neurogenic bladder disorders if efficacy and safety issues are validated in further clinical trials.

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