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A Role for the P2X Receptor in Urinary Tract Physiology and in the Pathophysiology of Urinary Dysfunction

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Abstract

Objective: We provide a historical perspective of the P2X receptor class in bladder physiology and the pathophysiology of urinary dysfunction.

Methods: A literature search was performed using the MEDLINE database.

Results: Evidence suggests that P2X receptors serve a combined function in sensory and motor activity of human bladder. P2X receptors mediate excitation of sensory neurons and evoke muscle contraction in response to ATP release. Anatomical and functional defects in the P2X receptor signaling are associated with a variety of urologic diseases.

Conclusion: Current research underscores the importance of P2X receptors in urologic physiology. Potential applications exist in relation to the diagnosis and treatment of urinary dysfunction. However, the detailed mechanism of P2X receptor function in bladder physiology and in urinary tract disease remains unknown and warrants further investigation.

Keywords: P2X receptor; Sensory neuron; Overactive bladder; Urgency; Interstitial cystitis

1. Introduction

Modern research techniques have yielded better insight into the neurogenic factors that contribute to the pathophysiology of urinary dysfunction, including overactive bladder (OAB) and interstitial cystitis (IC). In addition to a large body of investigation that has better defined the role of motor neuron dysfunction in OAB, increasing evidence suggests that sensory neuron dysfunction may also be involved in the pathophysiology OAB and, in addition, IC. Upregulation of neuropeptide binding sites within the bladder and afferent nerve stimulation by nerve growth factor are examples of phenomena that can occur with urinary dysfunction and suggest sensory neuron involvement [1,2]. In addition, a class of ATP receptors, known as P2 receptors, may play critical roles in both sensory and motor functions in the bladder. Although these receptors function in normal bladder, they may be especially important in diseased bladder. As such, a basic understanding of P2 receptors and their involvement in the physiology of micturition, urinary dysfunction, and as a possible target of pharmacotherapy, is useful to the urologic community.

2. History of purinergic neurotransmission and the P2 receptor class

The early history of the P2X receptor in nerve signaling was based on investigation demonstrating that ATP was released from sensory nerves following antidromic stimulation. This raised the possibility that

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ATP might be involved in sensory neurotransmission [3]. Subsequently, a non-adrenergic, non-cholinergic (NANC) nervous supply to various viscera, including the urinary bladder, was identified [4]. These findings served as the foundation for subsequent research investigating the potential role of ATP in NANC neurotransmission. Accordingly, the concept of purinergic neurotransmission was introduced.

In 1978, Burnstock et al. [5] proposed that purinergic transmission could be classified as that mediated by P1 or P2 receptors, based on their differential activation by adenosine versus ATP/ADP, respectively. The P2 receptor family was subsequently subdivided into P2X and P2Y receptor subclasses based on separable physiologic actions in various tissues and agonist specificity [4]. The P2X receptor is an ATP-gated ion channel that likely consists of three protein subunits with each subunit containing two transmembrane domains [6,7]. The $P2X_1$ and $P2X_2$ subtypes were cloned in 1994, with cloning of the $P2X_3$ subtype one year later [8–10]. A total of seven mammalian P2X genes have been identified that encode receptor subtypes $P2X_1$-$P2X_7$.

In the last two decades, the role of P2X receptors in bladder physiology has been explored through several experimental techniques. These techniques include electrophysiology of isolated urothelial and detrusor preparations, immunohistochemistry, in situ hybridization, and pharmacology using P2X agonists and antagonists. Based on these experiments, anatomical and functional data suggest that the P2X receptor class is involved in both afferent (sensory) and efferent (muscle contraction) functions of the human bladder. Despite finding receptor protein for all seven subtypes in the rat and human bladder, it appears that the $P2X_1$ and $P2X_3$ subtypes play the most integral role in bladder function [11,12]. More specifically, evidence suggests that the $P2X_1$ subtype mediates excitation of bladder efferents, whereas the $P2X_3$ subtype mediates excitation of bladder sensory afferents.

3. The P2X receptor: sensory function

Experiments conducted over 25 years ago suggested a role for a P2 receptor in sensation. ATP induced pain in humans when injected subcutaneously [13]. At that time, the target receptor for ATP, and its location, were unknown. In the ensuing decades, evidence has accumulated suggesting $P2X_3$ receptors on sensory neurons mediate much of this response. During the initial $P2X_3$ gene cloning experiments, $P2X_3$ mRNA was found exclusively within sensory neurons [10]. This finding renewed interest in $P2X_3$ as a molecular detector for pain. This association was confirmed by Cockyane et al. [14] and Souslova et al. [15], who demonstrated through knockout experimentation that mice lacking the $P2X_3$ receptor exhibited reduced pain-related behavior following subcutaneous injection of formalin.

In addition to $P2X_3$ as a pain receptor, the knockout data suggested a role for $P2X_3$ in bladder sensation. Cockayne et al. [15] used cystometry to analyze voiding reflexes in wild-type and $P2X_3$-knockout animals. Mice lacking the $P2X_3$ receptor demonstrated significantly decreased micturition frequencies and increased bladder capacity. No accompanying change in baseline and voiding bladder pressures or density of sensory neuron innervation was observed. This functional evidence lead investigators to propose a generalized role for $P2X_3$ receptors in sensing internal organ distention [16]. In this proposal, ATP, released by urothelial cells upon bladder distention, acts on $P2X_3$ receptors on suburothelial sensory afferents. This interaction triggers nerve activation and the sensation of bladder fullness (Fig. 1) [17]. Consistent with this hypothesis, Ferguson et al. [16] detected ATP release from urothelial cells in response to bladder distention. Urothelial ATP release was proportional to the degree of bladder distention and was associated with the level of sensory afferent nerve activity [18].

In addition to these functional data, anatomical studies support a role for the P2X receptor class in bladder sensation. Sensory neuron cell bodies contain high concentrations of $P2X_3$ mRNA [10,19]. Immunohistochemistry studies have identified $P2X_3$ protein on sensory neurons within the urothelium and detrusor

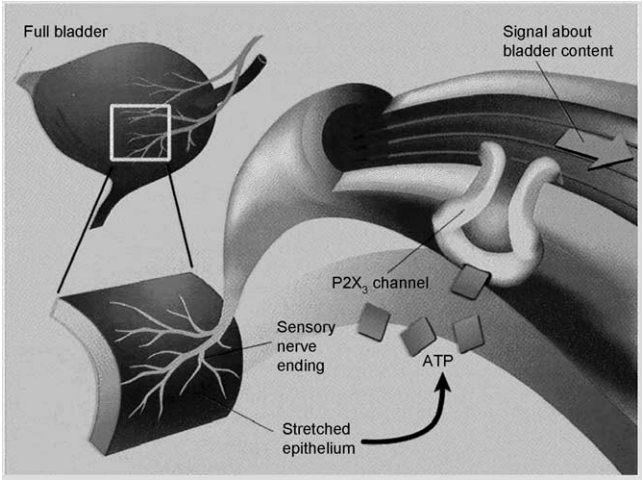

Fig. 1. Proposed mechanism of $P2X_3$ action in the sensation of bladder distention: ATP is released from urothelial cells in response to bladder distention. Released ATP binds to $P2X_3$ receptors on suburothelial afferent neurons. ATP binding activates an afferent neuronal pathway that leads to sensation of bladder fullness. (*Adapted with permission from* Cook SP, McCleskey EW. ATP, pain and a full bladder. Nature 2000;407:951–2.).