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Review article

ATP Signalling in the Urinary Bladder

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Abbreviations NANC: Non-Adrenergic Non-Cholinergic; Panx1: Pannexin 1 channels

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Abstract

ATP is involved in a number of physiological and pathological mechanisms in the urinary bladder. This review summarizes the main role of ATP and its metabolites, by acting on P1 and P2 purinoceptors present in the bladder wall. The ATP role in the urethra is not addressed. Prevalent mechanisms of modulation of ATP activity are also presented. Possible ATP release mechanisms from urothelium are presented and future directions proposed.

Introduction

Sources of ATP in the urinary bladder

The seminal work by Ferguson and collaborators in 1997 using electric filed stimulation and hydrostatic pressure changes in the urinary bladder have demonstrated that urothelial cells release a large amount of ATP, suggesting that these cells are the major source of ATP in the urinary bladder [1]. However, other bladder cells release this molecule. For instance, parasympathetic and sympathetic nerve fibres co-release ATP and acetylcholine, and ATP and noradrenaline, respectively [2,3]. Similarly to urothelial cells, suburothelial myofibroblasts release ATP when submitted to stretch [4].

ATP role in the urinary bladder

Exogenous administration of ATP induces immediate urinary bladder contractions [5,6]. In fact, experiments performed with different forms of purines and pyrimidines showed that ATP, ADP, GTP and CTP induce bladder contractions and the development of cross-tachyphylaxis [7]. The co-administration of ATP with cholinergic, adrenergic and/ orpurinergic blockers suggested that ATP is responsible for part of the Non-Adrenergic Non-Cholinergic (NANC) atropine-resistant bladder contractions [8-12]. By acting directly in P2X-purinoceptors (namely P2X3) in the detrusor smooth muscle cell, ATP promotes a calcium-dependent initial rapid, phasic contraction followed by a cholinergic-mediated tonic prolonged contraction [13-17]. As ATP mediates an increase in bladder pressure faster than the one induced by cholinergic stimulation, it is suggested that ATP has a role in the initiation of maturation [18].

ATP may also activate P2Y2/P2Y4 receptors expressed in urothelial cells promoting the release of additional modulators of maturation reflex (such as nitric oxide, and acetylcholine) [19]. Also, acting on urothelial P2X, ATP may further increase urothelial ATP release (autocrine mechanism), a mechanism thought to occur during bladder pathologies such as bladder pain syndrome/interstitial cystitis [20].

ATP can also act on P2Y receptors expressed in myofibroblasts, possible as part of the triggering mechanism regulating urge sensation [21]. This mechanism may be downstream of urothelial P2Y2/P2Y4 activation by ATP [19].

When ATP targets P2X3 expressed in non receptors coursing the suburothelial, it triggers non receptors pathways that lead to pain behavior [22-25]. In fact, experiments using P2X3 knockout mice demonstrated that these animals presented hypoalgesic behavior [24].

Modulation of ATP activity in the urinary bladder

The modulation of ATP activity is complex. It relies on the proximity of ATP releasing cells to the effectors cells and on several different mechanisms [26]. For instance, AMP and adenosine, formed upon ATP degradation, act on pre-synaptic P1-purinoceptors and induce of a slow hyper polarization of parasympathetic neurons which significantly contributes to the reduction of bladder contractions [7, 27-31]. Adenosine may also inhibit contractions by acting on P1-purinoceptors present in detrusor smooth muscle cells [32,33]. ATP itself may exert bladder relaxation by acting

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on P2Y receptors [34]. Curiously, P2 receptors are more effective upon decrease of temperature [35], showing that ATP responses are also modulated by temperature. Acetylcholine also influences ATP response as muscarinic M2 receptors exert a modulatory effect on purine-evoked relaxations [36]. On the other hand, ADP resulting from ATP breakdown stimulates prostaglandins synthesis, namely prostaglandin E2, which is thought to cooperate with ATP to modulate the tonic contraction [14,37,38]. Bradykinin also induces prostaglandin E2 synthesis [39] and may be accounted as a modulator of ATP-induced contractions. In fact, bradykinin acts on bradykinin-B2 receptor potentiating ATP-induced contractions [40]. Serotonin modulates both acetylcholine-induced contractions, by acting on 5-HT3-receptor, and ATP-induced contractions, by acting on5-HT2A and 5-HT4 receptors present in parasympathetic pre-synaptic terminals [41,42]. Conversely, histamines influence ATP-induced contractions without affecting the cholinergic-mediated contractions [43].

Mechanisms of ATP release in the urinary bladder

The mechanisms that induce ATP release are multi modal and are dependent of stimulus intensity (recently reviewed in [44]), suggesting the existence of more than one mechanism of ATP release (reviewed in [45]). Our ATP release mechanistic snapshot highlights on the activation of mechanosensitive Piezo 1 channel as well as TRPV1 and TRPV4 as high profile candidates for an initial physiological urothelial cell response to mild stretch stimulus or direct activation with agonists [46-49]. Pharmacological inhibition or genetic knock-out of these channels showed additive effects on the decrease of ATP release under mild stimulation and approximately 50% reduction of ATP release by removal of extracellular calcium. However, strong stretch stimulus induced ATP release that was not dependent on these channels [48], implying the activation of an independent pathway. After an initial (mild) stimulus there seems to be an ATP release amplification system operated by Pannexin 1 channels (Panx1) in concert with low-affinity P2X7 purinoceptors as evidenced by a reduction in ATP release by knocking-out either Panx1 or P2X7 channels and complemented by an approximately 4-fold increase in ATP release in low extracellular calcium and substantial reduction of ATP release by rapid extracellular ATP breakdown with apyrase [50]. The initial mechanical trigger of ATP release followed by ATP-induced ATP release amplification might serve to coordinate a synchronized urothelium syncytium response that depends on the extension of bladder wall distension and provide the brain with the appropriate input for the management of adequate maturation reflex.

The actual urothelial ATP efflux mechanism, or mechanisms, for the mild stimulus or the self-amplification is still a matter of debate. While extracellular calcium does not seem to be an absolute requirement for urothelial ATP release it is not clear if recruitment of intracellular Ca2+ occurs and suffices to activate Ca2+-dependent ATP release through the canonical exocytotic vesicular release mechanism or through Ca2+-activation of ATP efflux from the cytoplasm through mediatophores [51-55]. If a Ca2+-dependent mechanism is found, it will be advised to look for vesicular ATP accumulation that is not displaced by vesicular Ca2+-entry to feed the cytoplasm pool of ATP [56-58]. Alternatively, Ca2+-independent ATP efflux from the cytoplasmic pool might occur simply by activation of channels permeable to small molecules like Panx1 or TRP channels self-controlled by an ATP binding pocket and membrane inositides, respectively [59,60]. Evidences that multiple activators and/or ATP release effectors are involved in ATP secretion from the urothelium highlight the need for simultaneous targeting of multiple proteins to reach complete ATP release blockade. The acute inactivation of secretory proteins [61] instead of permanent blockade of proteins might also prevent compensatory expression or off-target effects (such as drugs that block membrane trafficking [62,63]). It is also possible that alternative ATP release effectors might also be involved like the voltage-dependent anion channels, ATP-binding cassette transporters, bestrophins, cystic fibrosis transmembrane conductance regulator and the CALHM1 and connexin channels [44,51,64].

Concluding Remarks

The contribution of ATP signaling in the maturation responses is altered in different urological pathologies, such as bladder pain syndrome/interstitial cystitis. The characterization of the mechanisms of ATP release and its sites of action, under physiological and pathological conditions may provide new therapeutic targets representing an improvement in the quality of life of many patients suffering from bladder pathologies.

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References

1. Ferguson DR, Kennedy I, Burton TJ. ATP is released from rabbit urinary bladder epithelial cells by hydrostatic pressure changes--a possible sensory mechanism? J Physiol. 1997; 505: 503-511.
2. Parija SC, Raviprakash V, Mishra SK. Adenosine- and alpha,beta-methylene ATP-induced differential inhibition of cholinergic and non-cholinergic neurogenic responses in rat urinary bladder. Br J Pharmacol. 1991; 102: 396-400.
3. Theobald RJ Jr. Evidence against purinergic nerve fibres in the hypogastric nerves of the cat. J Auton Pharmacol. 1983; 3: 235-239.
4. Cheng Y, Mansfield KJ, Sandow SL, Sadananda P, Burcher E, Moore KH. Porcine bladder urothelial, myofibroblast, and detrusor muscle cells: characterization and ATP release. Front Pharmacol. 2011; 2: 27.
5. Ambache N, Zar MA. Non-cholinergic transmission by post-ganglionic motor neurones in the mammalian bladder. J Physiol. 1970; 210: 761-783.
6. Burnstock G, Dumsday B, Smythe A. Atropine resistant excitation of the urinary bladder: the possibility of transmission via nerves releasing a purine nucleotide. Br J Pharmacol. 1972; 44: 451-461.
7. Lukacsko P, Krell RD. Response of the guinea-pig urinary bladder to purine and pyrimidine nucleotides. Eur J Pharmacol. 1982; 80: 401-406.
8. Burnstock G, Cocks T, Kasakov L, Wong HK. Direct evidence for ATP release from non-adrenergic, non-cholinergic ("purinergic") nerves in the guinea-pig taenia coli and bladder. Eur J Pharmacol. 1978; 49: 145-149.
9. Burnstock G, Cocks T, Crowe R, Kasakov L. Purinergic innervation of the guinea-pig urinary bladder. Br J Pharmacol. 1978; 63: 125-138.
10. Choo LK, Mitchelson F. The effect of indomethacin and adenosine 5'-triphosphate on the excitatory innervation of the rate urinary bladder. Can J Physiol Pharmacol. 1980; 58: 1042-1048.
11. Acevedo CG, Contreras E. Possible involvement of adenine nucleotides in

the neurotransmission of the mouse urinary bladder. Comp Biochem Physiol C. 1985; 82: 357-361.

12. Kura H, Obara K, Yabu H. Contractile responses to electrical field stimulation and ATP in guinea-pig urinary bladder. Comp Biochem Physiol C. 1992; 102: 193-197.

13. Sjogren C, Andersson KE. Inhibition of ATP-induced contraction in the guinea-pig urinary bladder in vitro and in vivo. Acta Pharmacol Toxicol (Copenh). 1979; 44: 221-227.

14. Husted S, Sjogren C, Andersson KE. Direct effects of adenosine and adenine nucleotides on isolated human urinary bladder and their influence on electrically induced contractions. J Urol. 1983; 130: 392-398.

15. Khanna OP, Barbieri EJ, Moss M, Son D, McMichael RF. Effects of calcium and verapamil on vesicourethral smooth muscle of rabbits. Urology. 1983; 21: 284-290.

16. Hourani SM, Welford LA, Loizou GD, Cusak NJ. Adenosine 5'-(2-fluorodiphosphate) is a selective agonist at P2-purinoceptors mediating relaxation of smooth muscle. Eur J Pharmacol. 1988; 147: 131-136.

17. Hoyle CH, Chapple C, Burnstock G. Isolated human bladder: evidence for an adenine dinucleotide acting on P2X-purinoceptors and for purinergic transmission. Eur J Pharmacol. 1989; 174:115-118.

18. Chancellor MB, Kaplan SA, Blaivas JG. The cholinergic and purinergic components of detrusor contractility in a whole rabbit bladder model. J Urol. 1992; 148: 906-909.

19. Chopra B, Gever J, Barrick SR, Hanna-Mitchell AT, Beckel JM, Ford AP, et al. Expression and function of rat urothelial P2Y receptors. Am J Physiol Renal Physiol. 2008; 294: F821-829.

20. Sun Y, Chai TC. Augmented extracellular ATP signaling in bladder urothelial cells from patients with interstitial cystitis. Am J Physiol Cell Physiol. 2006; 290: C27-34.

21. Wu C, Sui GP, Fry CH. Purinergic regulation of guinea pig suburothelial myofibroblasts. J Physiol. 2004; 559: 231-243.

22. Pandita RK, Andersson KE. Intravesical adenosine triphosphate stimulates the micturition reflex in awake, freely moving rats. J Urol. 2002; 168: 1230-1234.

23. Cockayne DA, Hamilton SG, Zhu QM, Dunn PM, Zhong Y, Novakovic S, et al. Urinary bladder hyporeflexia and reduced pain-related behaviour in P2X3-deficient mice. Nature. 2000; 407: 1011-1015.

24. Vlaskovska M, Kasakov L, Rong W, Bodin P, Bardini M, Cockayne DA, Et al. P2X3 knock-out mice reveal a major sensory role for urothelially released ATP. J Neurosci. 2001; 21: 5670-5677.

25. Rong W, Spyer KM, Burnstock G. Activation and sensitisation of low and high threshold afferent fibres mediated by P2X receptors in the mouse urinary bladder. J Physiol. 2002; 541: 591-600.

26. Inoue R, Brading AF. Human, pig and guinea-pig bladder smooth muscle cells generate similar inward currents in response to purinoceptor activation. Br J Pharmacol. 1991; 103: 1840-1841.

27. Andersson KE, Husted S, Sjögren C. Contribution of prostaglandins to the adenosine triphosphate-induced contraction of rabbit urinary bladder. Br J Pharmacol. 1980; 70: 443-452.

28. Akasu T, Shinnick-Gallagher P, Gallagher JP. Adenosine mediates a slow hyperpolarizing synaptic potential in autonomic neurones. Nature. 1984; 311: 62-65.

29. Katsuragi T, Kuratomi L, Furukawa T. Clonidine-evoked selective P1-purinoceptor antagonism of contraction of guinea-pig urinary bladder. Eur J Pharmacol. 1986; 121: 119-122.

30. Acevedo CG, Contreras E, Escalona J, Lewin J, Huidobro-Toro JP. Pharmacological characterization of adenosine A1 and A2 receptors in the bladder: evidence for a modulatory adenosine tone regulating non-adrenergic non-cholinergic neurotransmission. Br J Pharmacol. 1992; 107: 120-126.

31. Westfall TD, Kennedy C, Sneddon P. The ecto-ATPase inhibitor ARL 67156 enhances parasympathetic neurotransmission in the guinea-pig urinary bladder. Eur J Pharmacol. 1997; 329: 169-173.

32. King JA, Huddart H, Staff WG. Purinergic modulation of rat urinary bladder detrusor smooth muscle. Gen Pharmacol. 1997; 29: 597-604.

33. Gopalakrishnan SM, Buckner SA, Milicic I, Groebe DR, Whiteaker KL, Burns DJ, et al. Functional characterization of adenosine receptors and coupling to ATP-sensitive K+ channels in Guinea pig urinary bladder smooth muscle. J Pharmacol Exp Ther. 2002; 300: 910-917.

34. Boland B, Himpens B, Paques C, Casteels R, Gillis JM. ATP induced-relaxation in the mouse bladder smooth muscle. Br J Pharmacol. 1993; 108: 749-753.

35. Ziganshin AU, Rychkov AV, Ziganshina LE, Burnstock G. Temperature dependency of P2 receptor-mediated responses. Eur J Pharmacol. 2002; 456: 107-114.

36. Giglio D, Delbro DS, Tobin G. On the functional role of muscarinic M2 receptors in cholinergic and purinergic responses in the rat urinary bladder. Eur J Pharmacol. 2001; 428: 357-364.

37. Husted S, Sjögren C, Andersson KE. Mechanisms of the responses to non-cholinergic, non-adrenergic nerve stimulation and to ATP in isolated rabbit urinary bladder: evidence for ADP evoked prostaglandin release. Acta Pharmacol Toxicol (Copenh). 1980; 47: 84-92.

38. Kasakov LN, Vlaskovska MV. Profile of prostaglandins generated in the detrusor muscle of rat urinary bladder: effects of adenosine triphosphate and adenosine. Eur J Pharmacol. 1985; 113: 431-436.

39. Nakahata N, Ono T, Nakanishi H. Contribution of prostaglandin E2 to bradykinin-induced contraction in rabbit urinary detrusor. Jpn J Pharmacol. 1987; 43: 351-359.

40. Acevedo CG, Lewin J, Contreras E, Huidobro-Toro JP. Bradykinin facilitates the purinergic motor component of the rat bladder neurotransmission. Neurosci Lett. 1990; 113: 227-232.

41. Chen HI. Evidence for the presynaptic action of 5-hydroxytryptamine and the involvement of purinergic innervation in the rabbit lower urinary tract. Br J Pharmacol. 1990; 101: 212-216.

42. Messori E, Rizzi CA, Candura SM, Lucchelli A, Balestra B, Tonini M. 5-Hydroxytryptamine receptors that facilitate excitatory neuromuscular transmission in the guinea-pig isolated detrusor muscle. Br J Pharmacol. 1995; 115: 677-683.

43. Patra PB, Westfall DP. Potentiation of purinergic neurotransmission in guinea pig urinary bladder by histamine. J Urol. 1994; 151: 787-790.

44. Andersson KE. Purinergic signalling in the urinary bladder. Auton Neurosci. 2015; 191: 78-81.

45. Burnstock G, Verkhratsky A. Mechanisms of ATP Release and Inactivation, in Purinergic Signalling and the Nervous System. 2012; 79-118.

46. Birder LA, Nakamura Y, Kiss S, Nealen ML, Barrick S, Kanai AJ, et al. Altered urinary bladder function in mice lacking the vanilloid receptor TRPV1. Nat Neurosci. 2002; 5: 856-860.

47. Charrua A, Reguenga C, Cordeiro JM, Correiade-Sá P, Paule C, Nagy I, et al. Functional transient receptor potential vanilloid 1 is expressed in human urothelial cells. J Urol. 2009; 182: 2944-2950.

48. Miyamoto T, Mochizuki T, Nakagomi H, Kira S, Watanabe M, Takayama Y, et al. Functional role for Piezo1 in stretch-evoked Ca^{2+} influx and ATP release in urothelial cell cultures. J Biol Chem. 2014; 289: 16565-16575.

49. Calvert RC, Thompson CS, Burnstock G. ATP release from the human ureter on distension and P2X (3) receptor expression on suburothelial sensory nerves. Purinergic Signal. 2008; 4: 377-381.

50. Negoro H, Urban-Maldonado M, Liou LS, Spray DC, Thi MM, Suadicani SO. Pannexin 1 channels play essential roles in urothelial mechanotransduction and intercellular signaling. PLoS One. 2014; 9: e106269.

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https://dx.doi.org/10.36876/smju.1011

51. Burnstock G. Purinergic signalling in the urinary tract in health and disease. Purinergic Signal. 2014; 10: 103-155.

52. Dunant Y, Cordeiro JM, Gonçalves PP. Exocytosis, mediatophore, and vesicular Ca2+/H+ antiport in rapid neurotransmission. Ann N Y Acad Sci. 2009; 1152: 100-112.

53. Knight GE, Bodin P, De Groat WC, Burnstock G. ATP is released from guinea pig ureter epithelium on distension. Am J Physiol Renal Physiol. 2002; 282: F281-288.

54. Birder LA, Barrick SR, Roppolo JR, Kanai AJ, de Groat WC, Kiss S, et al. Feline interstitial cystitis results in mechanical hypersensitivity and altered ATP release from bladder urothelium. Am J Physiol Renal Physiol. 2003; 285: F423-429.

55. Sui G, Fry CH, Montgomery B, Roberts M, Wu R, Wu C. Purinergic and muscarinic modulation of ATP release from the urothelium and its paracrine actions. Am J Physiol Renal Physiol. 2014; 306: F286-298.

56. Reigada D, Díez-Pérez I, Gorostiza P, Verdaguer A, Gómez de Aranda I, Pineda O, et al. Control of neurotransmitter release by an internal gel matrix in synaptic vesicles. Proc Natl Acad Sci USA. 2003; 100: 3485-3490.

57. Cordeiro J, Goncalves PP, Dunant Y. Synaptic vesicles control the time course of neurotransmitter secretion via a Ca(2)+/H+ antiport. J Physiol. 2011; 589: 149-167.

58. Wang EC, Lee JM, Ruiz WG, Balestreire EM, von Bodungen M, Barrick S, et al. ATP and purinergic receptor-dependent membrane traffic in bladder umbrella cells. J Clin Invest. 2005; 115: 2412-2422.

59. Chiu YH, Ravichandran KS, Bayliss DA. Intrinsic properties and regulation of Pannexin 1 channel. Channels (Austin). 2014; 8: 103-109.

60. Borbiro I, Badheka D, Rohacs T. Activation of TRPV1 channels inhibits mechanosensitive Piezo channel activity by depleting membrane phosphoinositides. Sci Signal. 2015; 8: 15.

61. Cordeiro JM, Boda B, Gonçalves PP, Dunant Y. Synaptotagmin 1 is required for vesicular CaÂ²âº/Hâº-antiport activity. J Neurochem. 2013; 126: 37-46.

62. Khera M, Somogyi GT, Kiss S, Boone TB, Smith CP. Botulinum toxin A inhibits ATP release from bladder urothelium after chronic spinal cord injury. Neurochem Int. 2004; 45: 987-993.

63. Cruz F. Targets for botulinum toxin in the lower urinary tract. Neurourol Urodyn. 2014; 33: 31-38.

64. Taruno A, Vingtdeux V, Ohmoto M, Ma Z, Dvoryanchikov G, Li A, et al. CALHM1 ion channel mediates purinergic neurotransmission of sweet, bitter and umami tastes. Nature. 2013; 495: 223-226.

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