Loss of Purinergic P2X3 and P2X5 Receptor Innervation in Human Detrusor from Adults with Urge Incontinence

Kate H. Moore,1 Fiona R. Ray,2 and Julian A. Barden2

1The Detrusor Muscle Laboratory, Department of Urogynaecology, St. George Hospital, The University of New South Wales, New South Wales 2217, Australia and 2Protein Structure Laboratory, The Institute for Biomedical Research and Department of Anatomy and Histology, The University of Sydney, New South Wales 2006, Australia

Activation of purinergic P2X receptors associated with the parasympathetic nerves that supply the human bladder smooth muscle (detrusor) is implicated in control of detrusor contractility. The relative abundance of all seven subtypes colocalized with synaptic vesicles on parasympathetic nerves was examined in specimens from normal adult bladder, infants, and in adults with overactive detrusor contractility and a diagnosis of idiopathic detrusor instability (IDI) to determine whether receptor distribution varied with age or in patients with incontinence. Alteration in control of detrusor innervation was examined with P2X subtype-specific antibodies and an antibody against synaptic vesicles, using immunofluorescence and confocal microscopy. Detrusor samples were taken from: controls, at cystectomy for cancer or cystoscopic biopsy for hematuria (n = 22; age 33–88), child bladder, at surgical correction of vesicoureteric reflux (n = 21; age 4 months to 2 years), and adults with detrusor instability at cystoscopy–cystodistension (n = 18; age 30–81). Adult specimens contained muscle with large varicosities (1.2 μm) along parasympathetic nerves with colocalized patches of all P2X1–7 subtypes. Infant bladder revealed little evidence of P2X at age <9 months but approached adult levels at 2 years. Detrusor from IDI patients revealed selective absence of P2X3 and P2X5 beneath all the varicosities. This specific lack of P2X3 and P2X5 may impair control of detrusor contractility and contribute to the pathophysiology of urge incontinence.

Key words: purinergic P2X receptors; hypertonia; human urinary incontinence; detrusor instability; innervation; IDI bladder

In the last two decades, the innervation of the smooth muscle of the human bladder (the detrusor) has received considerable attention, because increased detrusor muscle contractility is associated with urge incontinence (also known as detrusor instability). This type of urinary incontinence affects men and women across the life-span (Bower et al., 1996; Hunskar et al., 2000) and affects 25–40% of all those who seek help for incontinence (Moore, 1999), or ~5–20% of the population. Despite recent efforts, the pathophysiology of detrusor instability remains incompletely understood.

The efferent limb of the human micturition reflex is predominantly governed by the muscarinic receptor, which mediates detrusor contractility, with a minor contribution from adrenergic receptors in facilitating bladder relaxation. Increasing attention has also been paid to the subepithelial innervation (Moore et al., 1992) and the role of sensory neuropeptides in regulating afferent input (Smet et al., 1997), because patients with urge incontinence also experience a frequent strong need to micturate, both when awake and when asleep (nocturia), in association with a small bladder capacity.

Studies from lower-order mammals and from human detrusor have suggested that purines such as ATP may also be important in regulating detrusor contractility (Burnstock et al., 1979; Brading and Inoue, 1991; Bolego et al., 1995; Theobald, 1995). Changes in P2X receptor distribution that occur in pregnant, adult, and neonatal rats have been characterized (Hansen et al., 1998; Dutton et al., 1999; Yunaev et al., 2000). Recently, knock-out mice that lack the P2X3 subtype were found to have markedly enlarged bladder capacity and reduced frequency of micturition (Cockayne et al., 2000). To date, the distribution of purinergic receptor subtypes has not been characterized in humans who have an increased frequency of micturition with a small-capacity, overly contractile bladder, nor has the morphology of P2X receptors been characterized in children of varying ages.

The aim of the present study was to examine human detrusor taken from control adults, neonates, infants, and adults with detrusor instability, to search for alterations in P2X receptor subtypes that may vary with age and/or have a bearing on the etiology of urge incontinence.

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MATERIALS AND METHODS

Tissue. Control detrusor samples were taken at cystectomy for nonin- 
tradiated bladder cancer or at cystoscopy for surveillance of previous 
low-grade malignancy or investigation of hematuria. Cystectomy speci-
mens were selected from macroscopically normal areas of bladder. Biopsies 
were taken from the bladder base just lateral to the trigone in view of its 
distinct innervation pattern (Gosling and Dixon, 1975). Infant bladder 
biopsies were taken at cystotomy during surgical correction of vesi-
coueretic reflux that was detected by antenatal ultrasonography with 
neonatal follow-up, or by sibling tracing. All subjects demonstrated 
radiological grade III reflux (Lebowitz et al., 1985) and had failed to 
resolve spontaneously with antibiotic prophylaxis, as previously reported 
(Werkstrom et al., 2000); urine culture was sterile before surgery. Cys-
tosopic biopsies were taken from patients with proven idiopathic detru-
stor instability (as per urodynamic testing) who had failed to respond to 
antimuscarnic drugs for $>12$ months (Moore et al., 1992). Diagnostic 
urodynamic features (Abrams et al., 1990) were spontaneous detrusor 
contractions provoking an urgent desire to micturate during filling with 
warm sterile water, which the patient was unable to inhibit, accompanied 
by either an early first desire to void ($<250$ ml) or a reduced bladder 
capacity ($<450$ ml). Detrusor instability was characterized as idiopathic 
by virtue of the patients having no neurologic abnormality and no 
obstructive features, i.e., normal flow rate with no evidence of residual 
urine (Abrams et al., 1990). Because of failure to respond to standard 
anti-muscarnic therapy, patients underwent cystoscopy at which stan-
ton cold cup biopsy was taken for routine pathological examination to 
exclude carcinoma in situ that might account for refractory irritative 
symptoms. A deeper sample was then taken from the side wall of the 
small crater created by the first specimen, providing tissue $3 \times 4$ mm that 
contained detrusor muscle. All tissue collection was undertaken after 
informed consent in accordance with protocols approved by the local 
hospital ethical committee.

Materials. Antibodies specific to the extracellular domains of individ-
ual human P2X receptor subunits were produced in rabbits using similar 
etiopes to those used in the rat specific antibodies, as previously re-
ported (Dutton et al., 1999). The small and nonhomologous sequences 
68–84 (P2X1), 209–226 (P2X7), 185–303 (P2X2), 270–285 (P2X1), 272-
288 (P2X2), 200–218 (P2X4), and 65–81 (P2X5) were used with those 
from P2X2 and P2X4, each having an N-terminal Cys added for conjuga-
tion via diphtheria toxin using maleimidocaproyl-N-hydroxysuccinimide 
(Dutton et al., 1999). No cross-reactivity between subtypes was encour-
dered when cRNA from the particular receptor was transfected into 
human embryonic kidney 293 cells and Xenopus oocytes. Further stan-
dard testing for specificity with adsorption controls showed that binding 
of each antibody was blocked in the presence of $10 \muM$ of the individual 
cognate blocking peptide. SV2 monoclonal antibody was specific for the 
synaptic vesicle proteoglycan SV2 (Dutton et al., 1999). Cyamine2 and 
Cyamine5 conjugates of donkey anti-rabbit and donkey anti-mouse 
fluorescent secondary antibodies, adsorbed against conspecific IgGs were 
purchased from Jackson ImmunoResearch (West Grove, PA). All other re-
Agents were purchased from Sigma (St. Louis, MO).

Immunohistochemical methods. Human bladder tissue was fixed in $4\%$
paraformaldehyde in PBS buffer, pH 7.2, for 6 hr. The tissue was then 
cryoprotected in immersion in $30\%$ sucrose for $24$ hr before sections (30 
$\muM$) were cut on a freezing microtome, and sections were labeled as 
described (Hansen et al., 1998; Dutton et al., 1999; Yao et al., 2000; 
Yunaev et al., 2000). Three tissue sections from each patient, including at 
least 10 high-power fields from each section, were viewed on a Leica 
(Nussloch, Germany) TCS NT UV laser confocal microscope system, 
with the pinhole set at 1.0 as a compromise between focal depth and 
background fluorescence. The monoclonal antibody to the proteoglycan 
SV2 was used to immunolocalize nerve varicocities. These were only 
variably able to be labeled with an antibody to tyrosine hydroxylase and 
thus are identified as being the parasympathetic nerves in the body of the 
bladder detrusor, rather than sympathetic (Theobald, 1995). SV2 immu-
noreactivity manifested as spheroidal puncta of $1.2 \muM$ in diameter. 
The varicocities, labeled with SV2 and the mouse Cy5 scurry were then 
used as reference points to determine the relationship of the labeled P2X 
receptors to the parasympathetic detrusor nerves. By using confocal 
microscopy, each P2X receptor subtype that was labeled with the rabbit 
Cy2 secary and was colocalized with SV2 varicosity was counted individ-
ually. Controls in which only one primary and/or one secondary antibody 
was used revealed no breakthrough of fluorescence between the two 
widely separated channels at 525 nm (Cy2) and 665 nm (Cy5). Not all 
SV2/Cy5-labeled varicocities were labeled with a corresponding P2X/ 
Cy2 antibody. Each SV2/Cy5-labeled varicocity in each field of view 
was counted, and the corresponding varicocities labeled with each of the 
P2X/Cy2 labels was then recorded from the separate channel, and the 
number of coincident labels was tabulated. Relative intensities of the 
different P2X labels were compared with the intensity of the SV2 labels 
from different slides, and results were quantitated using NIH Image 
software. Comparisons between populations of specific receptor types 
from adult controls and IDI tissue were made using the unpaired $t$ test with 
$95\%$ confidence limits. Values of $p < 0.05$ were considered 
significant.

RESULTS

P2X receptors in neonates, infants, and control adults

All seven P2X receptor subunits (P2X1 $\rightarrow$ P2X7) exhibited specific im-
munoreactivity in older children ($>2$ years) and adults. Large 
P2X puncta, $1.2 \muM$ in diameter were found closely apposition-
ted to presynaptic vesicles labeled with SV2. In young infants of 
$<9$ months, no P2X receptor labeling was found in relation to 
the clearly apparent strings of varicocities on the nerves. Figure 
1A shows an abundance of clearly resolved varicocities in strings 
outlining nerves in the detrusor from an 8-month-old infant. None of these varicocities were colocalized with P2X2 (Fig. 1B) 
or indeed any other P2X subtype. These are shown at higher 
resolution in Figure 1, C and D.

At 2 years, most infants exhibited clearly colocalized P2X 
subtypes adjacent to the SV2-labeled varicocities. A representa-
tive example is shown of SV2 and P2X1 in Figure 1, E and F. It 
should however be noted that the relative abundance of the 
P2X receptor subtypes found colocalized with the varicocities 
was low. The size of the SV2 puncta were generally much larger 
than the corresponding size of the P2X puncta, indicating that the 
varicocities were not completely apposed with P2X receptor at 
this age.

In control adult bladder, the varicocities that are identified by SV2 
labeling are routinely colocalized with P2X1,2,3 and P2X4, 
but the abundances of P2X5, P2X6, and especially P2X7 are much 
lower, with many varicocities appearing entirely devoid of these 
receptors with other varicocities exhibiting sparse receptor label-
ing. A representative example labeled with P2X7 is shown in 
Figure 1, G and H, in which SV2-labeled varicocities exhibit an 
abundance of colocalized P2X7 receptor. The size of the P2X7 
puncta in adult tissue is commensurate with the size of the SV2 
puncta, indicating a more extensive association of the P2X recep-
tors with the varicocities on the parasympathetic nerves.

Table 1 summarizes results of measurements of varicocity co-
localization with the P2X subtypes in the different tissues. A total 
of eight young infants aged 4–9 months, eight infants aged 10–18 
months, and five children aged 2 years were examined together 
with 22 adult controls and 18 IDI patients. In the case of the 
young infants aged 4–9 months, no P2X subtypes were found 
co localized with the varicocities on the nerves in the detrusor. In 
the 10–18 month age group, individual labeling of varicocities with 
P2X subtypes commenced, but levels were quite variable, 
and thus averages in this category have not been presented. By 2 
years, the degree of colocalization had reached an equilibrium 
with the majority of varicocities appearing to be labeled with all 
subtypes of P2X receptor, with only P2X5 and P2X7 not being 
associated with all varicocities. The size of the P2X puncta was 
still somewhat smaller than the size of puncta from adult tissue.

Alterations of P2X distribution in adults with urge incontinence

The results in 22 adult control bladders (8 female and 14 male) 
tested revealed a consistent pattern of receptor colocalization.
Tissue samples collected from either males or females at cystoscopy or cystectomy exhibited similar patterns of colocalization between P2X receptors and the SV2-labeled varicosities. Almost all varicosities were colocalized with P2X1–3 and P2X5. In contrast, very few varicosities were observed to be colocalized with P2X4, P2X6, and P2X7 receptor subtypes. When present at all, the intensity of receptor labeling on these varicosities appeared to be much lower than P2X1,2,3,5 (Table 1).

The 18 patients with IDI were women aged 30–81 years. Urodynamic testing of these patients revealed the first desire to void occurred at an average 173 ml (range, 50–340 ml), and the average maximum bladder capacity was 340 ml (range, 150–570 ml). The average maximum detrusor pressure was 48 cm H2O (range, 18–100 cm H2O). At microscopy, we were unable to observe any SV2-labeled varicosities that were colocalized with either of the subtypes P2X3 or P2X5 (Fig. 1I,J). The expression or synthesis of these two subtypes appeared markedly reduced in the detrusor from IDI patients. In the unstable muscle, P2X4 and P2X6 subtypes were more commonly associated with SV2-staining varicosities than in control bladders (36 and 33% vs 16% for P2X4 and P2X6, respectively).

Figure 1. A and B show a representative image pair of bladder detrusor muscle from an 8-month-old labeled for SV2 and P2X2, respectively. The vesicles in the long strings of varicosities on the parasympathetic nerves are labeled, but there is no corresponding P2X2 label, nor is there any other P2X subtype present at this age. Scale bar, 5 μm. C and D show an enlargement of A and B. Scale bar, 2 μm. E and F show detrusor taken from a 2-year-old labeled for SV2 and P2X3, respectively. Like other subtypes, the P2X3 is found colocalized with the large varicosities to various extent. Scale bar, 2 μm. G and H show a string of varicosities from adult control bladder labeled with P2X3. This is representative of subtypes P2X1, P2X2, and P2X5, with other subtypes appearing at much lower levels in the adult. Scale bar, 1 μm. I and J show an example taken from a patient with IDI labeled with SV2 and P2X3. Like P2X5, P2X3 is completely downregulated in these patients, whereas other subtypes remain essentially unaltered. Scale bar, 2 μm. SV2 primary antibody was labeled with Cy5 secondary, whereas all P2X antibodies were labeled with Cy2 secondary.
and 18% respectively, but like the control bladders, image analysis showed that the intensity of the Cy2 fluorescence with these subtypes was low compared with P2X1 and P2X2 (<10%). The majority of SV2-labeled varicosities from IDI patients were immunolocalized with trace amounts of P2X3, whereas control bladder exhibited far fewer varicosities with any detectable P2X7, immunofluorescence, although these were brighter. The levels observed were typically <10% of the levels observed in varicosities colocalized with P2X1 and P2X2.

**DISCUSSION**

Immunohistochemical studies have demonstrated the existence of P2X1-7 subtypes in rat bladder detrusor (Hansen et al., 1998; Dutton et al., 1999; Yunaev et al., 2000) but, until recently, evidence for the existence of P2X receptors in human bladder has been limited (Bo and Burnstock, 1995; Evans et al., 1996; Longhurst et al., 1996; Bayliss et al., 1999).

The adult rat bladder detrusor receives a dense innervation from parasympathetic nerve terminals (Hoyes et al., 1975) but very little sympathtic innervation, with most of this restricted to the trigone (Gosling and Dixon, 1975). During development of the rat bladder, the miicturition reflex, including a mature spinobulbospinal element, is not established before 2-3 postnatal weeks (Araki and de Groat, 1997). During this time there is considerable increase in the extent of purinergic transmission to the smooth muscle cells (Dutton et al., 1999). The rich purinergic supply to the urinary bladder found in many other species, including humans, suggests that purinergic transmission may be involved in initiating contraction and urine flow from the bladder (Theobald, 1995). The response of the bladder in many species such as guinea pig to single intramural nerve impulses however is biphasic, with the fast phasic contraction caused by ATP followed by a slower tonic contraction induced by acetylcholine (Brading and Inoue, 1991). The relative contributions of these two phases of the response to single pulses differs between species, but approximately half the contractile response can be attributed to purinergic transmission and the remainder to cholinergic transmission (Levin et al., 1991). The latter is probably responsible for the maintenance of bladder contraction and urine flow after this has been initiated by purinergic transmission (Theobald, 1995). In humans however, the purinergic control is less clear (Inoue and Brading, 1991). Normal human bladder strips were found to elicit very little purinergic nerve-mediated response, although direct application of ATP agonist elicited very large responses. It has been suggested that the closeness of innervation and extent of cell–cell coupling in humans may explain these results (Inoue and Brading, 1991). In contrast, strips taken from IDI bladders did show direct purinergic responses to stimulation of the intrinsic nerves (Bayliss et al., 1999).

In this study we have established that P2X receptor subtypes found subsynaptically in rat (Dutton et al., 1999) are similarly found to be closely associated with the parasympathetic varicosities in human detrusor muscle and that, like the young rat pup bladder, infants of <10 months appear to lack purinergic innervation and thus lack effective bladder control. Only after 2 years of age are the varicosities consistently colocalized with the P2X receptors. It is only at this stage of child development that more effective bladder control becomes established, and this can vary with the individual. It should be noted that the proportion of varicosities colocalized with the subtypes P2X3, P2X5, and P2X7 in the 2 year olds (Table 1) is similar to the levels in the IDI patients in that they are localized under more varicosities than in normal adults, and this may suggest a similar immature control of contractility in the IDI bladders. By adulthood, the normal pattern of expression is closely similar to that we have previously found in adult rats (Dutton et al., 1999; Yunaev et al., 2000). This consistent pattern of expression provides the basis for an examination of the role of P2X receptors in the pathophysiology of dysfunctional bladders in humans.

The identification of subsynaptic P2X receptors in normal bladder is consistent with observations that normal and idiopathic unstable human detrusor contracts in response to ATP (Tagliani et al., 1997; Bayliss et al., 1999). However, any additional purinergic component in the unstable detrusor appears not to be attributable to stimulation of extrajunctional receptors that may be more accessible to ATP from disrupted nerves because such junctional receptors are found in both tissues.

The question arising is why IDI bladders exhibit a purinergic current from direct nerve stimulation whereas normal bladders apparently do not. Of particular interest is the altered pattern of expression of receptors in the condition IDI, with P2X3 and P2X5

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**Table 1. The percentage of colocalization of SV2-labeled parasympathetic nerve varicosities in the body of the detrusor with P2X subtypes in the groups 4-9 months, 2 years, control, adult, and IDI**

<table>
<thead>
<tr>
<th>Group</th>
<th>P2X1</th>
<th>P2X2</th>
<th>P2X3</th>
<th>P2X4</th>
<th>P2X5</th>
<th>P2X6</th>
<th>P2X7</th>
</tr>
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<tbody>
<tr>
<td>Neonate (8)</td>
<td>0/230</td>
<td>0/243</td>
<td>0/222</td>
<td>0/219</td>
<td>0/238</td>
<td>0/229</td>
<td>0/208</td>
</tr>
<tr>
<td>4 - 9 month</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Infant (5)</td>
<td>146/153</td>
<td>141/143</td>
<td>109/110</td>
<td>145/201</td>
<td>193/210</td>
<td>93/223</td>
<td>121/140</td>
</tr>
<tr>
<td>2 year</td>
<td>95</td>
<td>99</td>
<td>99</td>
<td>72</td>
<td>92</td>
<td>42</td>
<td>86</td>
</tr>
<tr>
<td>Adult (22)</td>
<td>806/827</td>
<td>836/844</td>
<td>763/809</td>
<td>139/892</td>
<td>715/783</td>
<td>156/892</td>
<td>36/591</td>
</tr>
<tr>
<td>33 - 88 year</td>
<td>97</td>
<td>99</td>
<td>94</td>
<td>16</td>
<td>91</td>
<td>18</td>
<td>6</td>
</tr>
<tr>
<td>IDI (18)</td>
<td>518/538</td>
<td>548/556</td>
<td>0/555</td>
<td>194/532</td>
<td>0/511</td>
<td>178/544</td>
<td>156/232</td>
</tr>
<tr>
<td>30 – 81 year</td>
<td>96</td>
<td>99</td>
<td>0</td>
<td>36</td>
<td>0</td>
<td>33</td>
<td>67</td>
</tr>
<tr>
<td>Adult/IDI</td>
<td>p = 0.32</td>
<td>p = 0.16</td>
<td>p &lt; 0.000</td>
<td>p &lt; 0.0001</td>
<td>p &lt; 0.0001</td>
<td>p &lt; 0.0001</td>
<td>p &lt; 0.0001</td>
</tr>
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Twenty to forty SV2-labeled varicosities were counted for each P2X receptor subtype for each patient sample. Immunohistochemical analysis showed that the intensity of the Cy2 fluorescence with these subtypes was low compared with P2X1 and P2X2 (<10%). The majority of SV2-labeled varicosities from IDI patients were immunolocalized with trace amounts of P2X3, whereas control bladders, image analysis showed, indicative of much lower expression levels of these receptors. The extreme differences between P2X3 and P2X5 in normal adult and IDI patients are clearly evident. Comparison between P2X1 expression in these two cohorts also showed highly significant differences (p < 0.0001; unpaired two-tailed t test).
no longer being observed beneath the varicosities. Cystometry studies in the P2X3 knockout mouse (Cockayne et al., 2000) revealed that a marked increase in bladder capacity occurred in the absence of P2X3. Because the converse is found in IDI patients, i.e., all displayed marked urge incontinence, with reduced bladder capacity, we expect that P2X3 is similarly essential for full control of the micturition initiation signal, if not through direct nerve stimulation, then certainly through an alteration in cell–cell coupling in the detrusor muscle. Further studies of the micturition reflex in the P2X3 knockout mouse will be needed to confirm this hypothesis. Nevertheless, the striking absence of P2X3 and P2X6 labeling in relation to parasympathetic nerve varicosities that we observed for the first time in patients with urge incontinence (in sharp contrast with the pattern seen in control adult specimens and the older infants) suggests that the absence of these two receptor subtypes is related to the pathophysiology of detrusor instability. Partial loss of purinergic control observed in IDI may cause loss of inhibition of micturition initiation signals. This may manifest as a loss of inhibition of acetylcholine release at the varicosities. Certainly young infants lacking P2X2 receptors have no effective bladder control, so the urge resulting from progressive bladder filling cannot be suppressed. Subsynaptic P2X receptors may fulfill this role. In serial examination of the superior cervical ganglia of the rat pup, there is a progressively greater appearance of P2X receptors at this location (Li et al., 2000) and in peripheral sites such as bladder sequentially after day 1 (Dutton et al., 1999). Thus, with increasing maturity, there is increasing central and peripheral evidence of P2X distribution in the rat pup. Other observations indicate that P2X receptors are progressively delivered to the parasympathetic nerves of the bladder, with P2X2 being the first subtype to arrive in the axons in the detrusor of day 1 rats with others like P2X6 also arriving postsynaptically (Dutton et al., 1999).

Adults with urge incontinence often have difficulty focusing the frontal lobe of their cerebral cortex on the inhibition of the desire to void. This activity, called “bladder training” is an essential part of continence treatment for patients with IDI. The process requires them to ignore afferent stimuli from progressive bladder filling. Theoretically, adults with IDI may be suffering from a lack of purinergic receptor maturity in the periphery, perhaps in association with poor coordination and integration of the incoming stimuli at the locus of the cerebral cortex. Thus, there may be a mismatch between the normal inhibitory actions of the P2X3- and/or P2X6 receptors and the excitatory effects of the other P2X subtypes. Very early observations of the purinergic innervation of the subepithelial layers of patients with IDI indicate that both these subtypes are present in the lamina propria, suggesting a selective deficit in the detrusor, but further collection of subepithelial specimens is awaited. The overall mechanism may be that the purinergic inhibitory control of the parasympathetic release of acetylcholine is disrupted in IDI.

Aside from the total loss of expression of these two normally abundant subtypes in IDI, the minor subtypes P2X4, P2X5, and P2X7 all exhibit increased subsynaptic distribution (p < 0.0001), albeit at lower densities than found in normal adult tissue. It may be a combination of the total loss of the rapid desensitizing subtypes P2X3 and P2X6 that are expected to internalize in response to ATP application (Li et al., 2000) in combination with a small increase in overall distribution of the non-desensitizing subtypes P2X4 and P2X7, that leads to an overall prolongation of purinergic response seen in the IDI detrusor after application of agonist. Thus, previous emphasis on research into new antimuscarinic agents for the treatment of urge incontinence may now be modified to encourage a search for agents that affect regulation of the purinergic (P2X) system in the human detrusor.

REFERENCES


