Diabetes Induced Changes in Rat Urinary Bladder and Urethral Epithelium

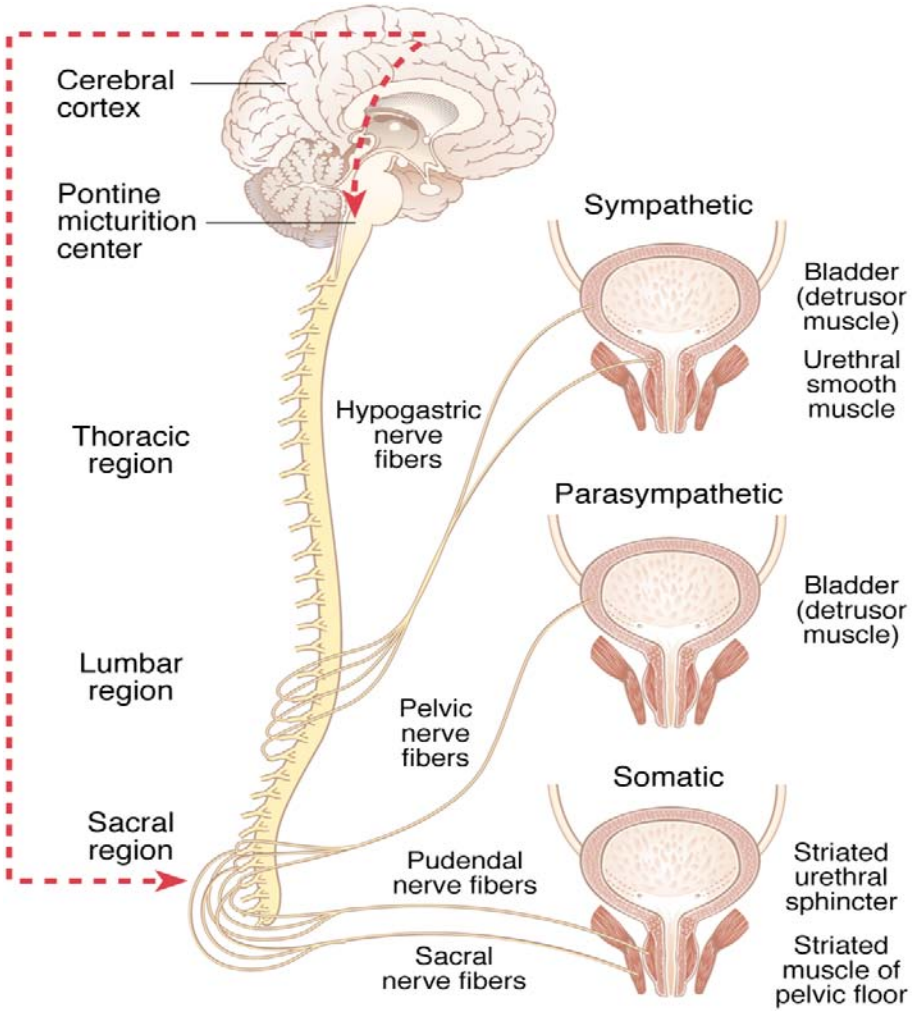
Lori A. Birder, Ph.D.

Departments of Medicine and Pharmacology

University of Pittsburgh School of Medicine

The biology of DM-associated bladder complications is multi-factorial

These can be the result of alteration in smooth muscle, innervation / function of bladder nerves or changes in the bladder urothelium



Evidence suggests that diabetes alters the urothelium

(increased bladder weight & increased urothelial 'remodeling', altered release of mediators)

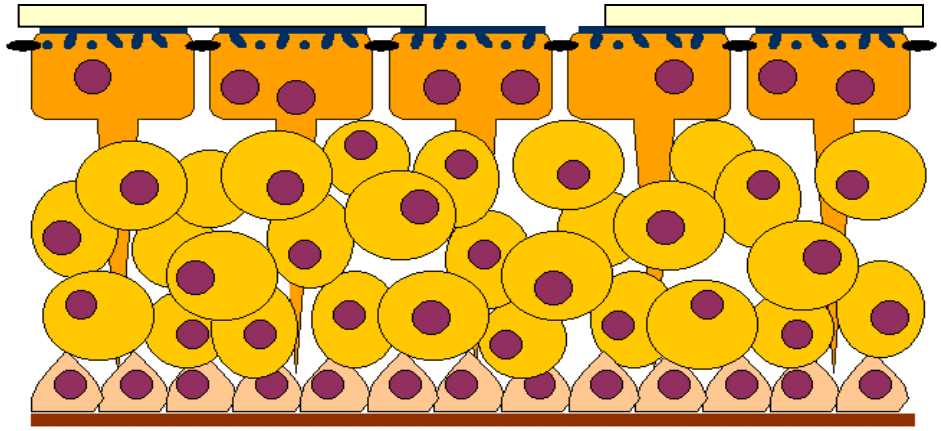
Does the urothelium play a role in diabetes-associated bladder complications?

(retention of urine, loss of sensation and a greater incidence of lower urinary tract infection)

How does the urothelium respond to changes in 'sensory inputs' (i.e. increased polyuria, hyperglycemia and ischemia)----and how do these cells communicate to underlying tissues

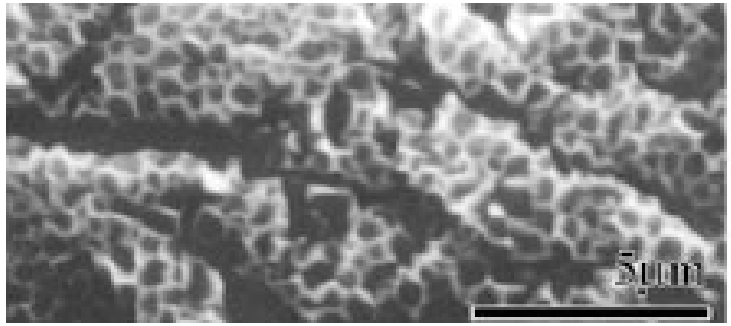
Urothelium (UT):

Multilayered structure (transitional epithelium) consisting of apical (which act as a 'barrier'), intermediate and basal cells.

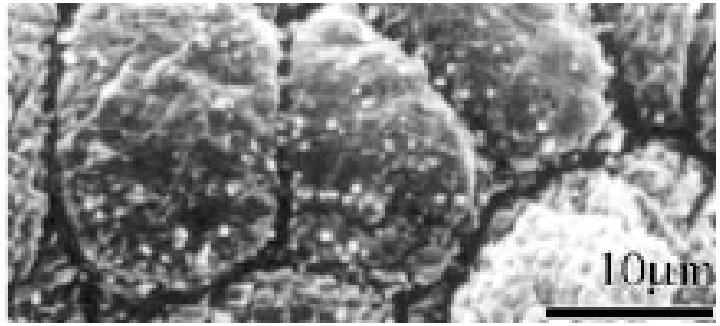


The major part of the urinary tract is covered with a fully differentiated 'urothelium', regions in which a complete barrier is unnecessary (i.e. urethra) have a 'simple epithelium' *Romih et al Cell Tissue Res 2005*

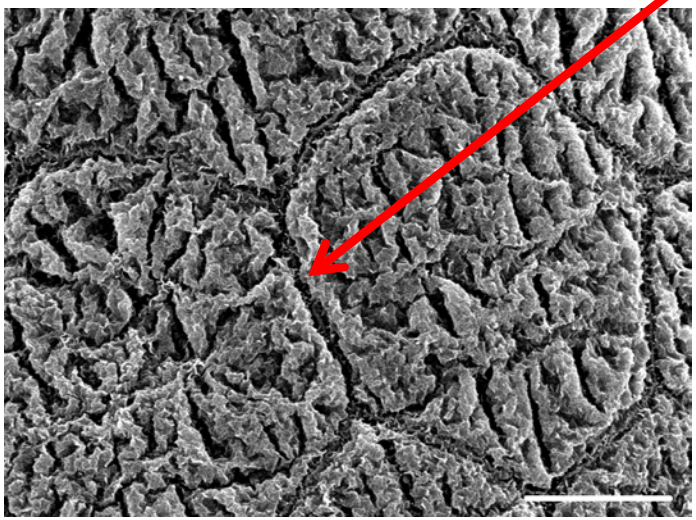
Umbrella cells (rigid-appearance)

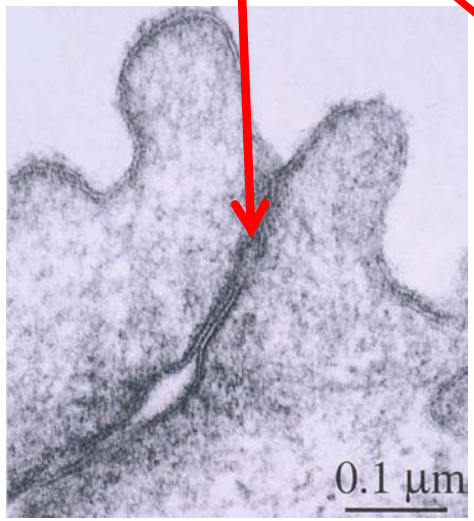


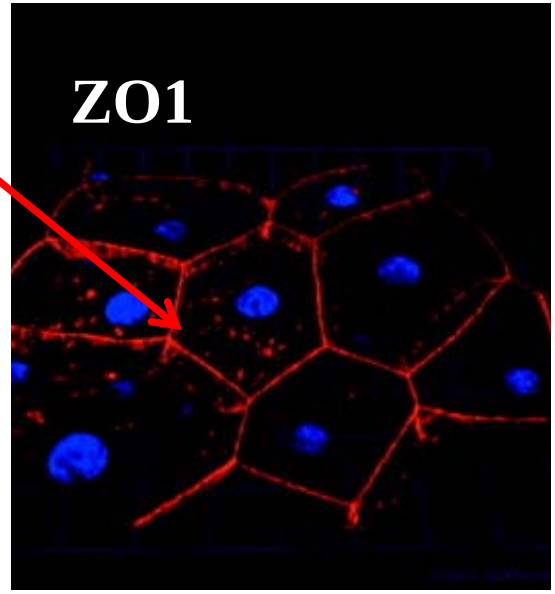
Urethra is covered with a stratified epithelium



The barrier function is dependent on special membrane domains between apical cells (tight junctions)---







Apodaca, AJP, 282:F179-80, 2002 and Truschel et al., J Biol Chemistry 274:15020-9, 1999.

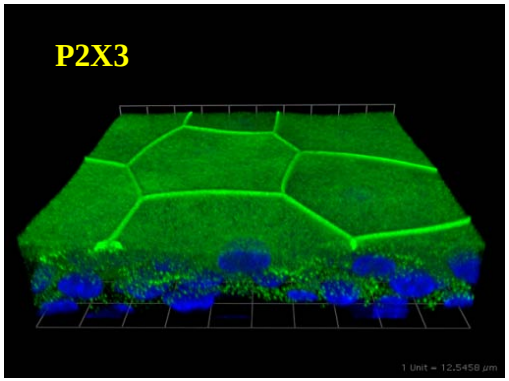
Mucosal Barrier may be disrupted in various diseases such as Painful Bladder Syndrome / Interstitial Cystitis (Bladder Pain Syndrome) and Spinal Cord Injury

When the barrier is compromised, it can result in passage of toxic substances into the underlying tissue resulting in urgency, frequency and pain during distension

More than just a barrier: The Urothelium Functions as a Primary Transducer of Physical and Chemical Stimuli

4 Lines of evidence lend support for involvement of the urothelium in visceral sensation

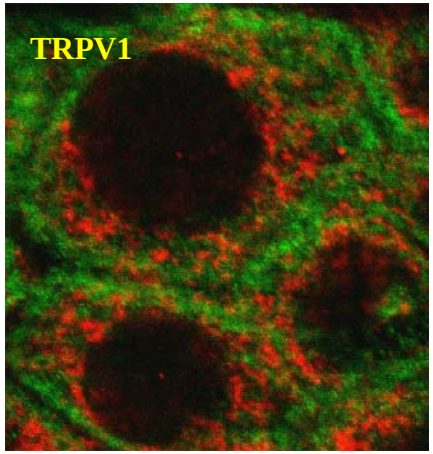
#1 Urothelial cells express receptors/ion channels similar to mechanoreceptive & nociceptive afferent nerves



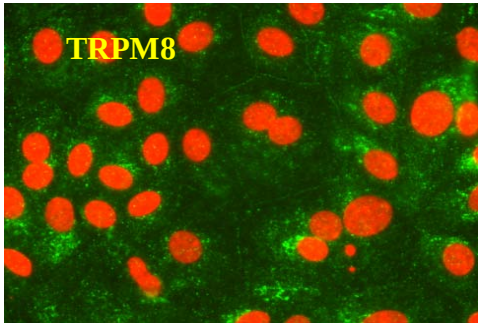
Wang et al JCI 115:2412-22,2005

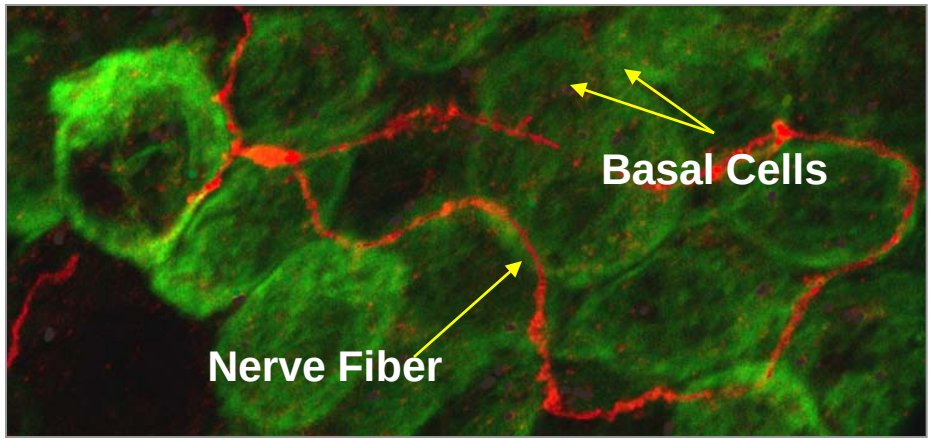
Polymodal Properties of Urinary Bladder Urothelial Cells

Sensor Function/Stimuli	Urothelial Sensor Molecules	Neuronal Sensor Molecules
ATP	P2X/P2Y	P2X/P2Y
Capsaicin/Resiniferatoxin	TRPV1	TRPV1
Heat	TRPV1; TRPV2; TRPV4	TRPV1; TRPV2; TRPV3; TRPV4
Cold	TRPM8; TRPA1	TRPM8; TRPA1
H^+	TRPV1; ?	TRPV1; ASIC; DRASIC
Osmolarity	In part TRPV4	In part TRPV4
Bradykinin	B1; B2	B1; B2
Acetylcholine	Nicotinic/muscarinic	Nicotinic/muscarinic
Norepinephrine	α/β subtypes	α/β subtypes
Nerve Growth Factor	p75/trkA	p75/trkA
Mechanosensitivity	Amiloride Sensitive Na^+ Channels	Amiloride Sensitive Na^+ Channels



Birder et al PNAS 98:13396-401, 2001





Birder et al., PNAS 98:13396-401, 2001.

#2

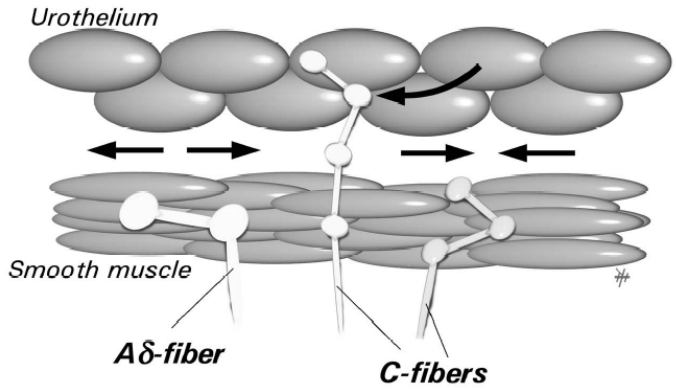
The location of bladder nerves (afferents and efferents) in close proximity to the epithelium.

This suggests the potential for a chemical dialogue

#3

Urothelium can release transmitters/mediators during bladder stretch or following chemical stimulation.

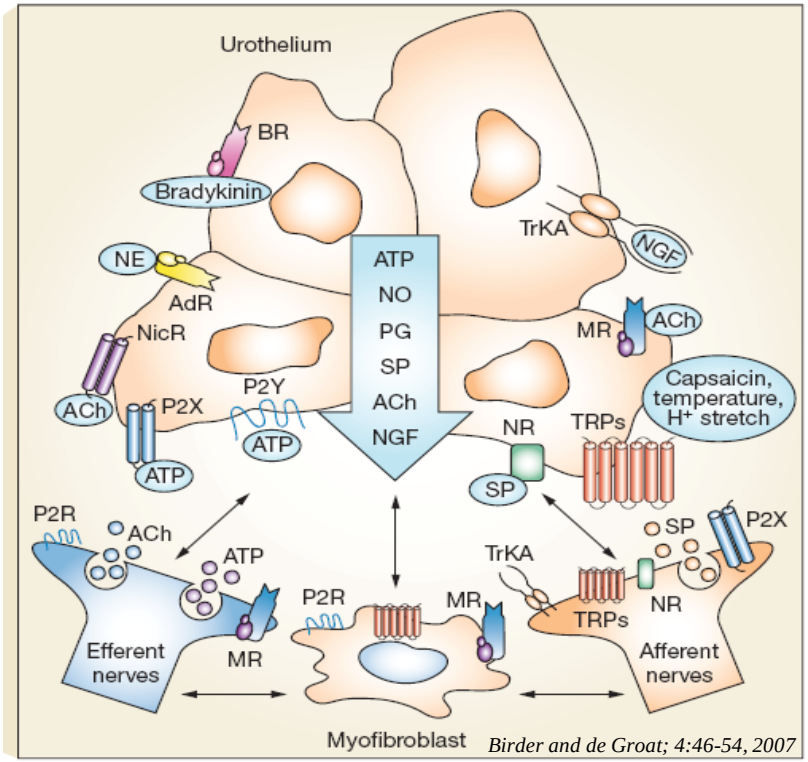
This could activate suburothelial nerves---and play a role in voiding



Andersson and Hedlund, Urology, 60:13-21, 2002

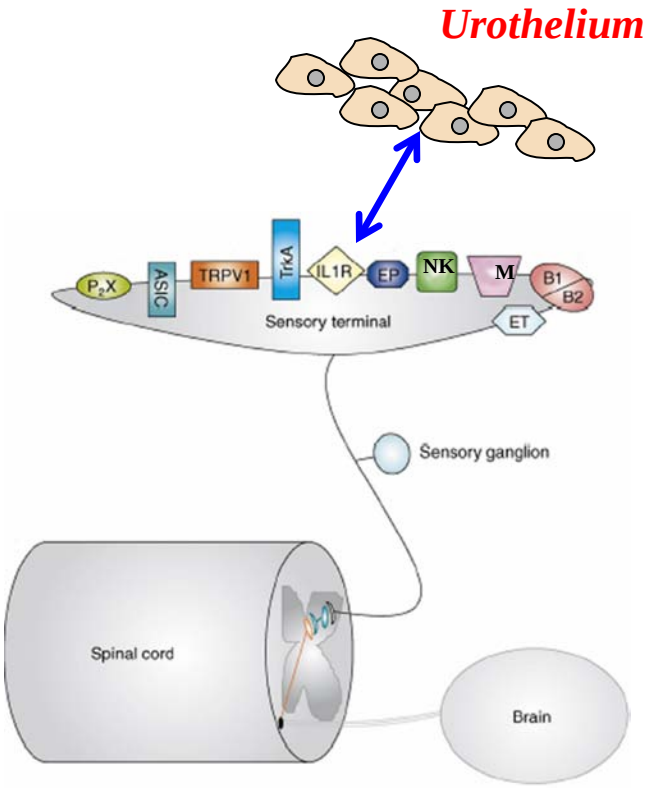
#4 Plasticity in signaling functions induced by pathological conditions

Alterations in *expression of targets* and/or *release of mediators* may also contribute to bladder instability, hyperactivity and altered bladder sensation



Changes in the urothelium appear now to be an important factor in a number of bladder syndromes

How does the urothelium respond to diabetes-induced changes & what are the sources of these 'sensory inputs'?



These could include alterations in:

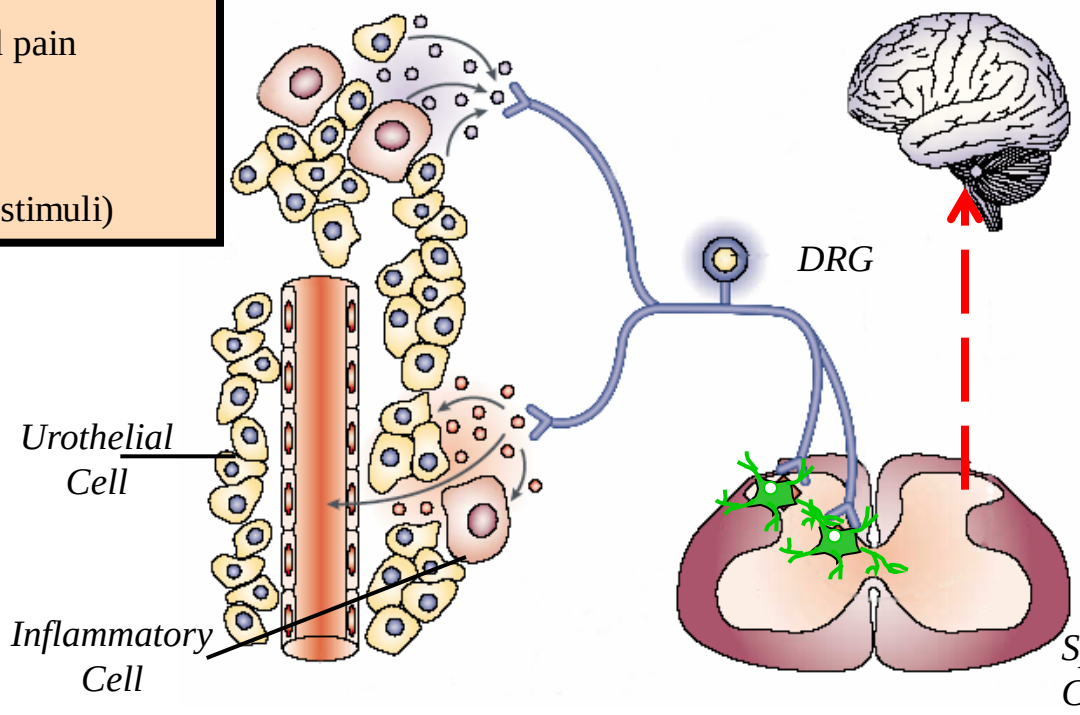
- ✓ **Autonomic, Neuroendocrine and Pain Modulatory Systems**
- ✓ **Osmolarity**
- ✓ **Glucose** (could alter urothelial junctional expression; affect urothelial targets that recognize bacteria thereby increasing susceptibility to infection)
- ✓ **Diuresis/polyuria** (alters bladder size/weight; likely to affect urothelial properties including size, permeability and signaling)

Our goals are to:

1. Evaluate bladder *(as well as urethra) epithelial* sensor targets following treatment with STZ
2. Evaluate changes in urothelial ultrastructure following treatment with STZ

Urothelial cells exhibit plasticity (changes in expression/sensitization of various targets) and react to alterations in the environment---

- autonomic, neuroendocrine and pain modulatory systems
- osmolarity / glucose
- increased diuresis (mechanical stimuli)



Defects in the urothelial expression of receptors or aberrant release of mediators may alter the *'chemical cross talk'* with a number of cell types in the bladder wall including bladder nerves---*and contribute to diabetes-associated bladder complications*

As changes in epithelial structure/function could alter neural signaling---we will also characterize localization of urethral epithelium and submucosal afferents