Using neurobiology to understand the origins of pelvic pain

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Outline of this presentation

1. Introduction to pelvic pain
2. Key neurobiological features of visceral pain
   - Contrast with somatic pain
   - Intersection with autonomic reflexes
3. Experimental approaches for studying neurobiology of pelvic visceral pain
   - Animal models
   - Plasticity of nociceptors
   - Actions of estrogens
Persistent pelvic pain

- endometriosis
- interstitial cystitis
- painful bladder syndrome
- irritable bowel syndrome
- pelvic inflammatory disease
- recurrent dysmenorrhoea
- pelvic floor pain
- vulvodynia

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painaustralia™

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FACULTY OF PAIN MEDICINE ANZCA
Persistent pelvic pain

interstitial cystitis / painful bladder syndrome
increased urinary frequency and urgency commonly accompanied by pelvic, perineal, or abdominal pain

co-morbidity
endometriosis, fibromyalgia, irritable bowel syndrome

Do we blame the organ, the nervous system or both?
Persistent pain as a disease entity

Symptoms, signs and primary pathology

Primary pain-related pathology becomes independent of initiating disease process

Persistent pain becomes a self-perpetuating condition, continuing beyond resolution of the initiating disease state

Michael Cousins
Key neurobiological features of visceral pain

diffuse localisation
unreliable pathology
often referred to other sites
common analgesics often ineffective
Where does visceral pain fit?

nociceptive
inflammatory
neuropathic
functional

cascade: peripheral and central amplification of signal

abnormal connections
abnormal excitability

noxious stimulus

Costigan & Woolf 2009
Features of visceral sensation

Most visceral sensory activity is not consciously perceived.

Visceral sensory activity can elicit **unique sensations**, e.g., bloating, nausea, dyspnea *cf.* cutting, touch, heat, vibration.

**Code sensation over wide range:** physiological to noxious

Many visceral nociceptors are **silent** and unresponsive to noxious stimuli until “awakened” by chemical sensitisers.

Specialised peripheral sensory endings are rare.

Extensive **branching** of peripheral and central processes.
Features of visceral sensation
peripheral terminals

CGRP, sensory nerves
Cryosection (left), whole mount, suburothelial plexus, right
Features of visceral sensation
central terminals

somatic

visceral

Sugiura et al. J Neurophysiol 1989
Features of visceral nociceptors

Unclear separation of nociceptors from sensory nerves involved in autonomic reflexes

Visceral pain commonly associated with exaggerated autonomic reflexes

L5 (somatic)  L6/S1 (somatic + visceral)
Features of visceral nociceptors

Unclear separation of nociceptors from sensory nerves involved in autonomic reflexes

Visceral pain commonly associated with exaggerated autonomic reflexes
Experimental approaches for studying neurobiology of pelvic visceral pain
Cystitis model of bladder pain

cyclophosphamide
(75 mg/kg, i.p., 24h-10d)

renal metabolism to acrolein

inflammation of lower urinary tract

altered voiding behaviour
increased frequency, decreased capacity
increased non-voiding contractions
referred mechanical hyperalgesia

plasticity of sacral DRG neurons
increased excitability
spontaneous activity
axonal sprouting in bladder
Understanding the abnormal sensory signals that initiate the cascade

1. Nociceptor axons in urinary bladder
2. Nociceptor neurons in dorsal root ganglia
3. Nociceptor terminals in sacral spinal cord
Understanding the abnormal sensory signals that initiate the cascade

1. Nociceptor axons in the urinary bladder
2. Nociceptor neurons in the dorsal root ganglia
3. Nociceptor terminals in the sacral spinal cord

Abnormal connections, abnormal excitability
1. nociceptor nerves in the bladder
Understanding the abnormal sensory signals that initiate the cascade

- Abnormal connections
- Abnormal excitability

- Damaged or inflamed urothelium may establish long-term change in nociceptor behavior

- Exposure of nociceptor axons to damaging environment

- Release of substances that sensitise nociceptors
recreating the connection between nociceptor neurons and urothelial cells
recreating the connection between nociceptor neurons and urothelial cells

O'Mullane et al 2013 J Urol
Presence of urothelial cells increases neuronal growth
Understanding the abnormal sensory signals that initiate the cascade

- Abnormal connections
- Abnormal excitability

1. Nociceptor axons in urinary bladder
2. Nociceptor neurons in dorsal root ganglia
3. Nociceptor terminals in sacral spinal cord
The intriguing issue of estrogens…..

IC/PBS are much more common in women than men.

Pain of IC and related comorbid conditions (IBS, fibromyalgia) can vary in intensity during the cycle.

Estrogens reduce pain symptoms of endometriosis.

It has been difficult to determine the effects of hormones on pain in experimental or clinical studies.
2. Nociceceptor neurons signalling bladder pain

finding bladder nociceptors

many bladder sensory neurons express estrogen receptors

bladder sensory neuron
estrogen receptor (ERα)
Analysing behavior of single nociceptor neurons
In vitro assay for nociceptor behavior

Responses to capsaicin (opens TRPV1 cation channels)

Tominaga 2006
Do estrogens affect nociceptor behavior?

Many bladder **nociceptors** express estrogen receptors

**TRPV1**

**ER**

Many bladder **nociceptors** express estrogen receptors

Estrogen has powerful **inhibitory** action on bladder nociceptors
Understanding the abnormal sensory signals that initiate the cascade

- Abnormal connections
- Abnormal excitability

1. Nociceptor axons in urinary bladder
2. Nociceptor neurons in dorsal root ganglia
3. Nociceptor terminals in sacral spinal cord
3. Communication between bladder nociceptor neurons and spinal cord
Visualising activation of **individual spinal neurons** following peripheral activation of a nociceptor

- Release of substance P at first synapse
- Substance P receptor (NK1R)
- NK1R+ endosomes
Visualising activation of individual spinal neurons following peripheral activation of a nociceptor

- Substance P
- NK1R

- Capsaicin (hindpaw)
- Saline (hindpaw)
Understanding the abnormal sensory signals that initiate the cascade

1. Nociceptor axons in urinary bladder
2. Nociceptor neurons in dorsal root ganglia
3. Nociceptor terminals in sacral spinal cord

Abnormal connections
Abnormal excitability
Using a similar strategy to understand endometriosis pain

Jane Girling, Martin Healy, Peter Rogers
University of Melbourne (O&G)

development of sympathetic and sensory innervation of cysts (lesions) closely parallels pelvic pain

Berkley et al 2005
implanted endometrial cyst

sensory and autonomic nerves innervating a cyst

sensory neurons innervating a cyst
Priorities

• to determine the site of the problem: the organ vs. the nervous system vs. both
• to define biological differences in visceral and somatic pain circuitry
• to understand interactions with autonomic reflex function (and dysfunction)
• to continue to refine animal models of visceral pain states
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