JARCA 2013

LES DOULEURS VISCERALES:
Actualités physiopathologiques et perspectives thérapeutiques

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DOULEURS D'ORIGINE DIGESTIVE

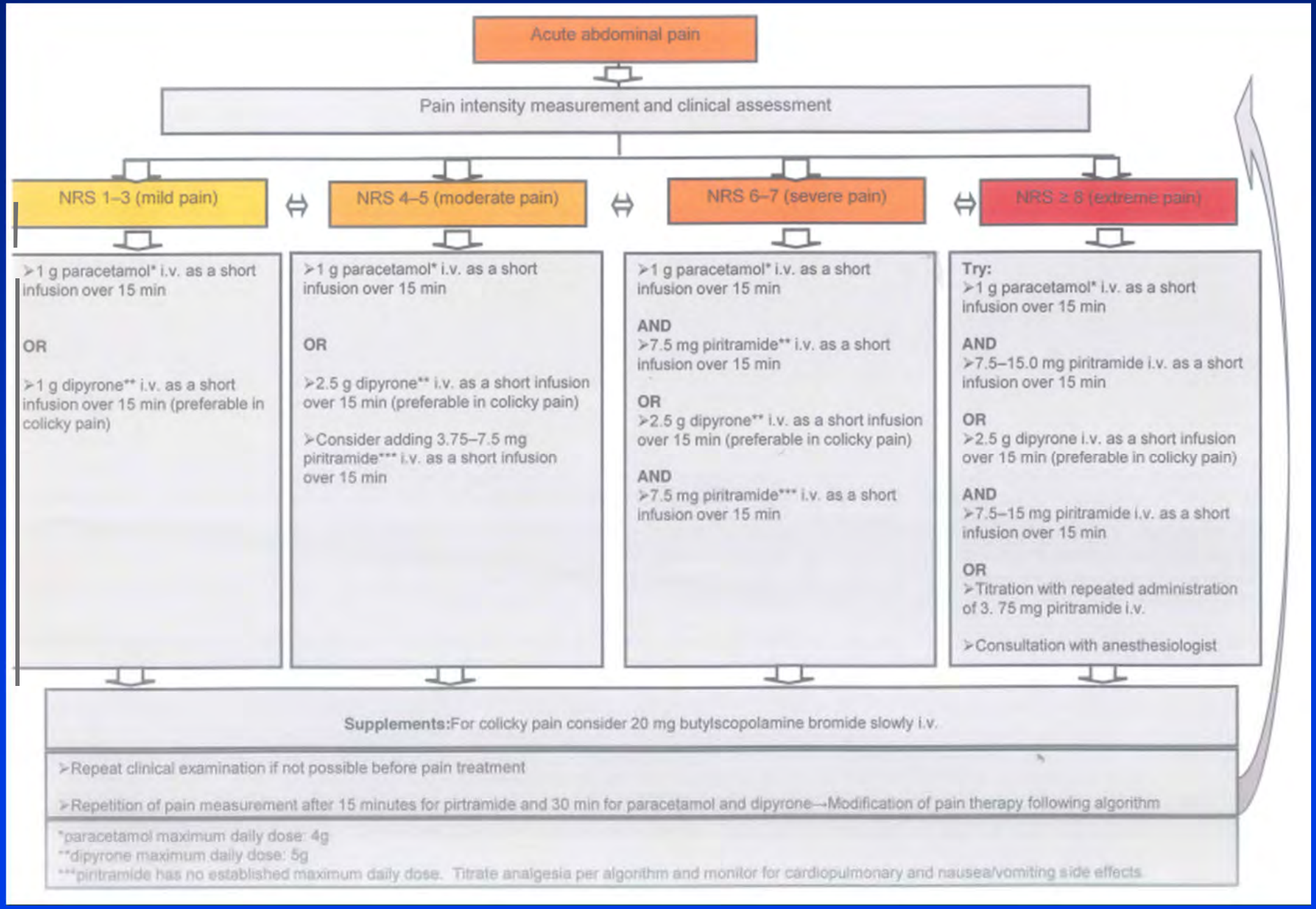
✓ Organiques et/ou inflammatoires:

- Pathologies cancéreuses (foie, pancréas, intestins…etc)
- Pathologies ischémiques (intestins…etc)
- MICI (Crohn, RCH)
- Obstructions, accident,

✓ Fonctionnelles et/ou non-inflammatoires

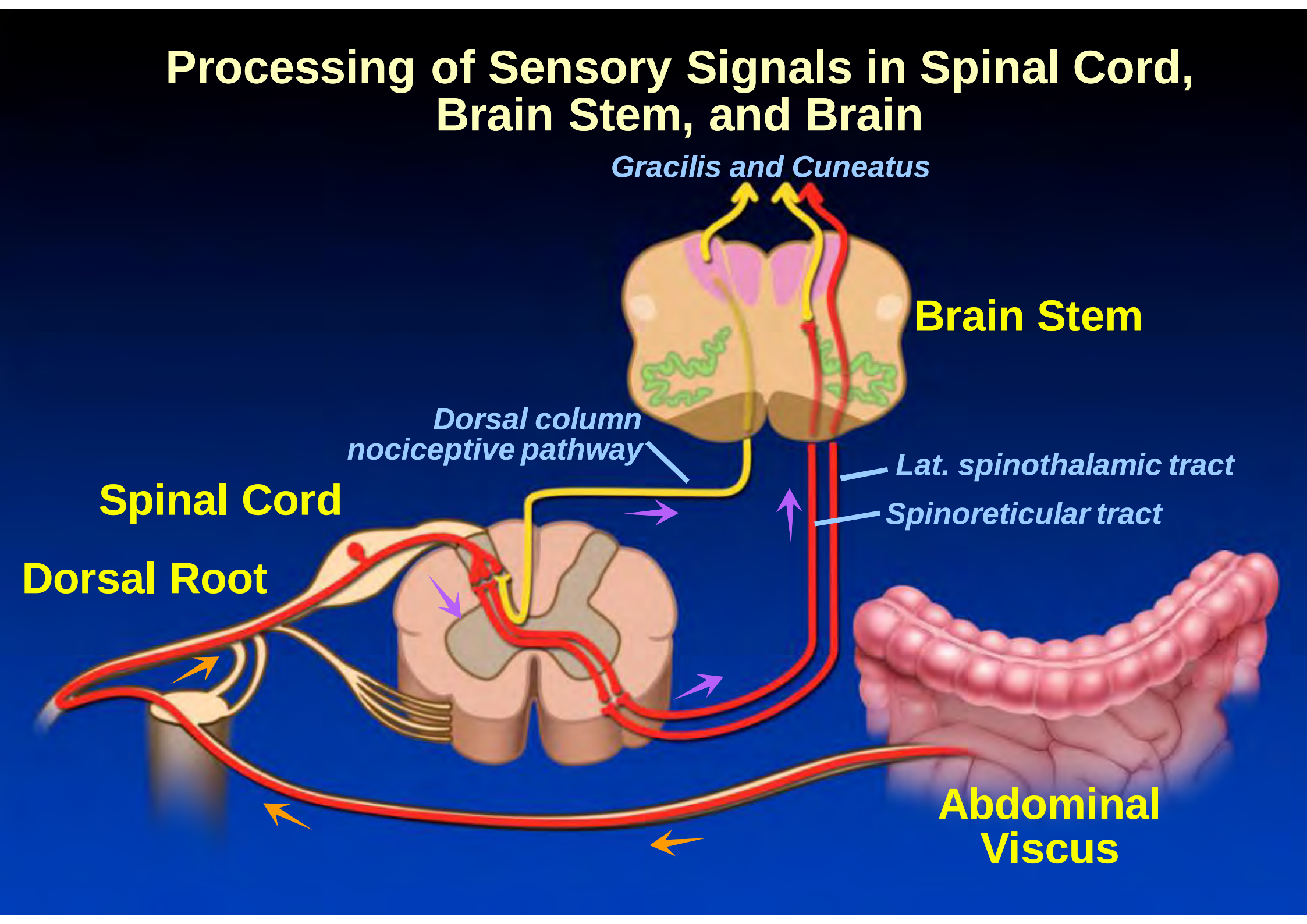
- RGO
- Dyspepsie
- TFI - SII
- FAPS

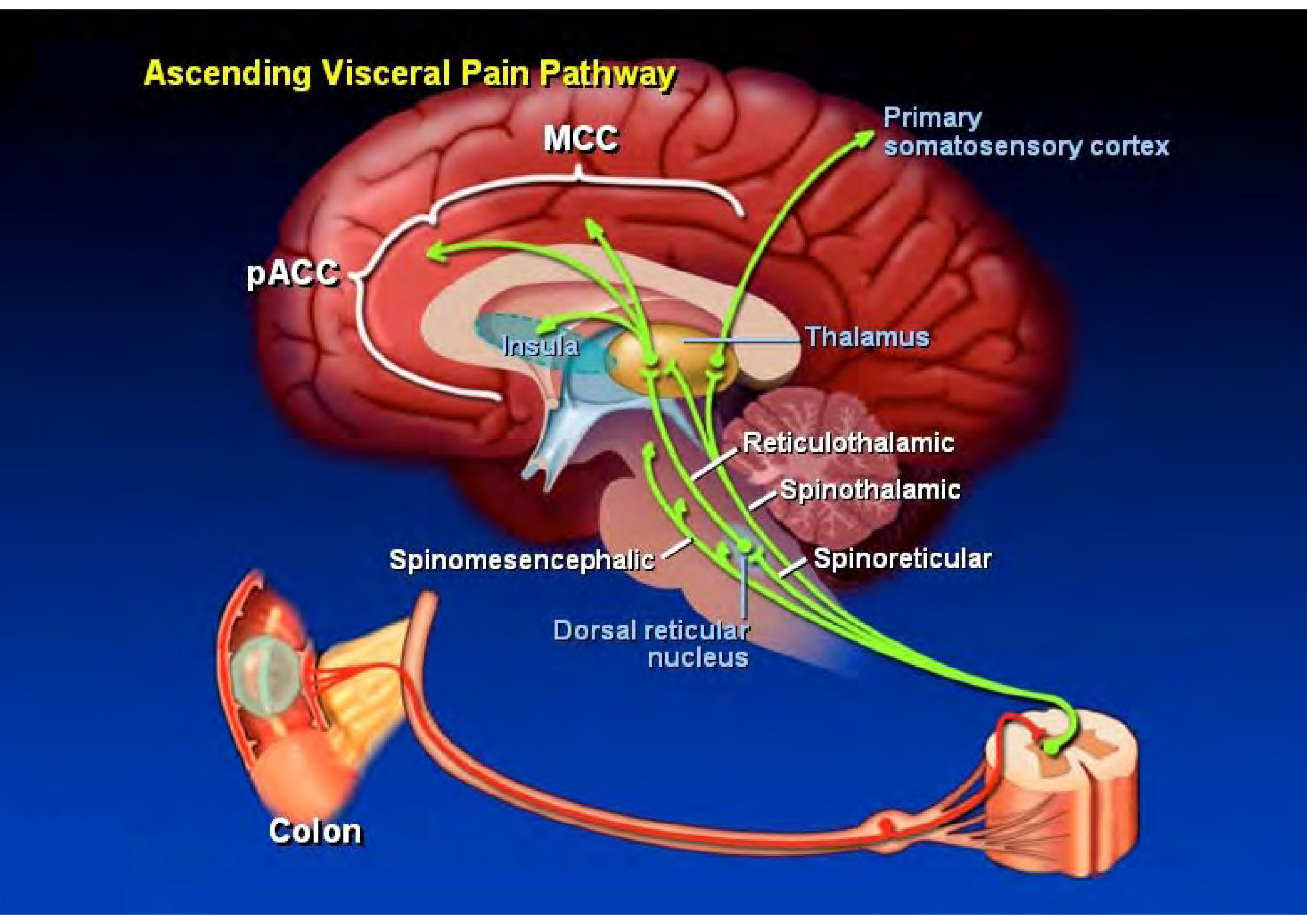
Algorithm for pre-diagnostic analgesia of acute abdominal pain in general adult population



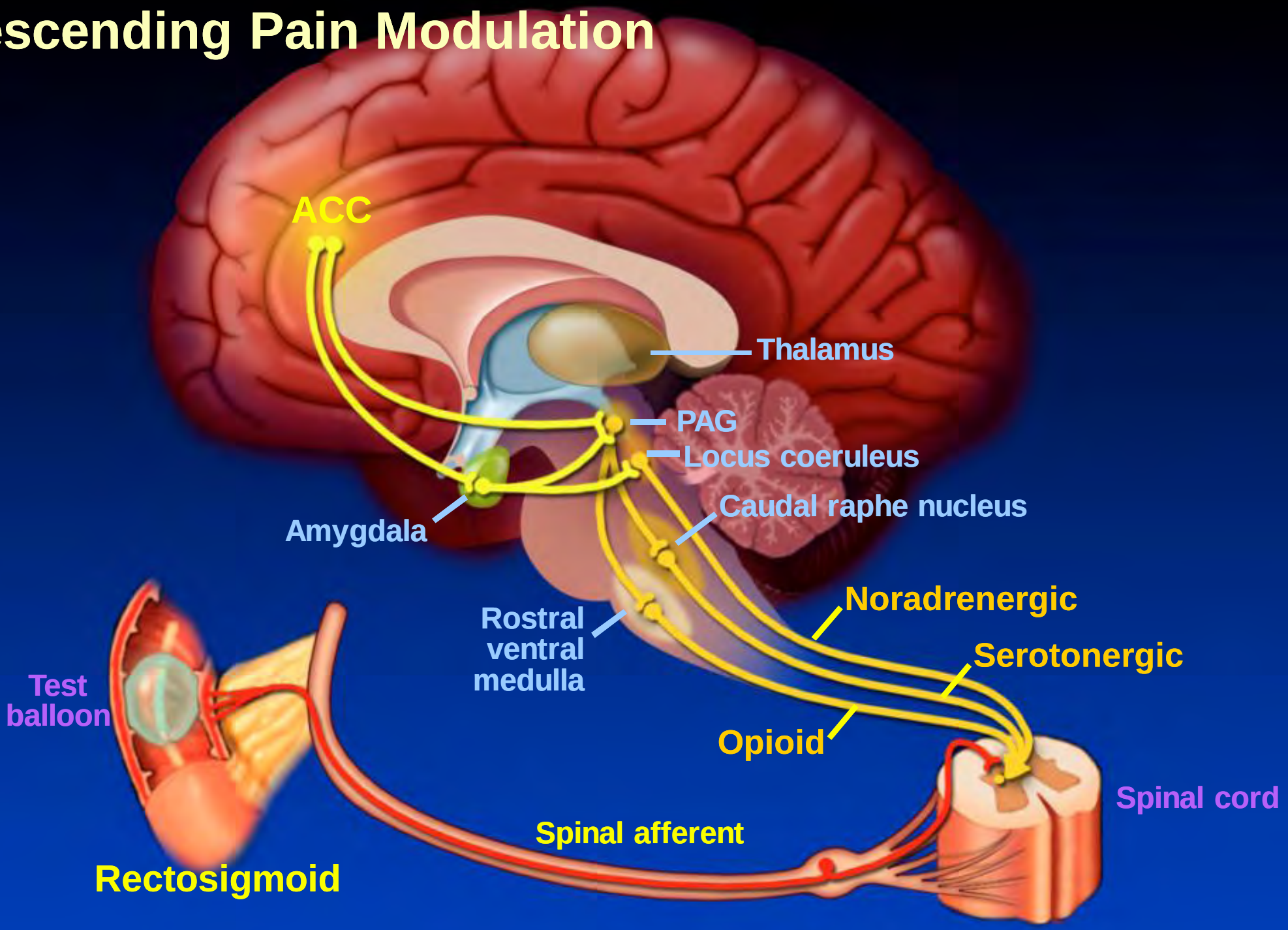
Manterola et al. Cochrane rev. 2011

Processing of Sensory Signals in Spinal Cord, Brain Stem, and Brain

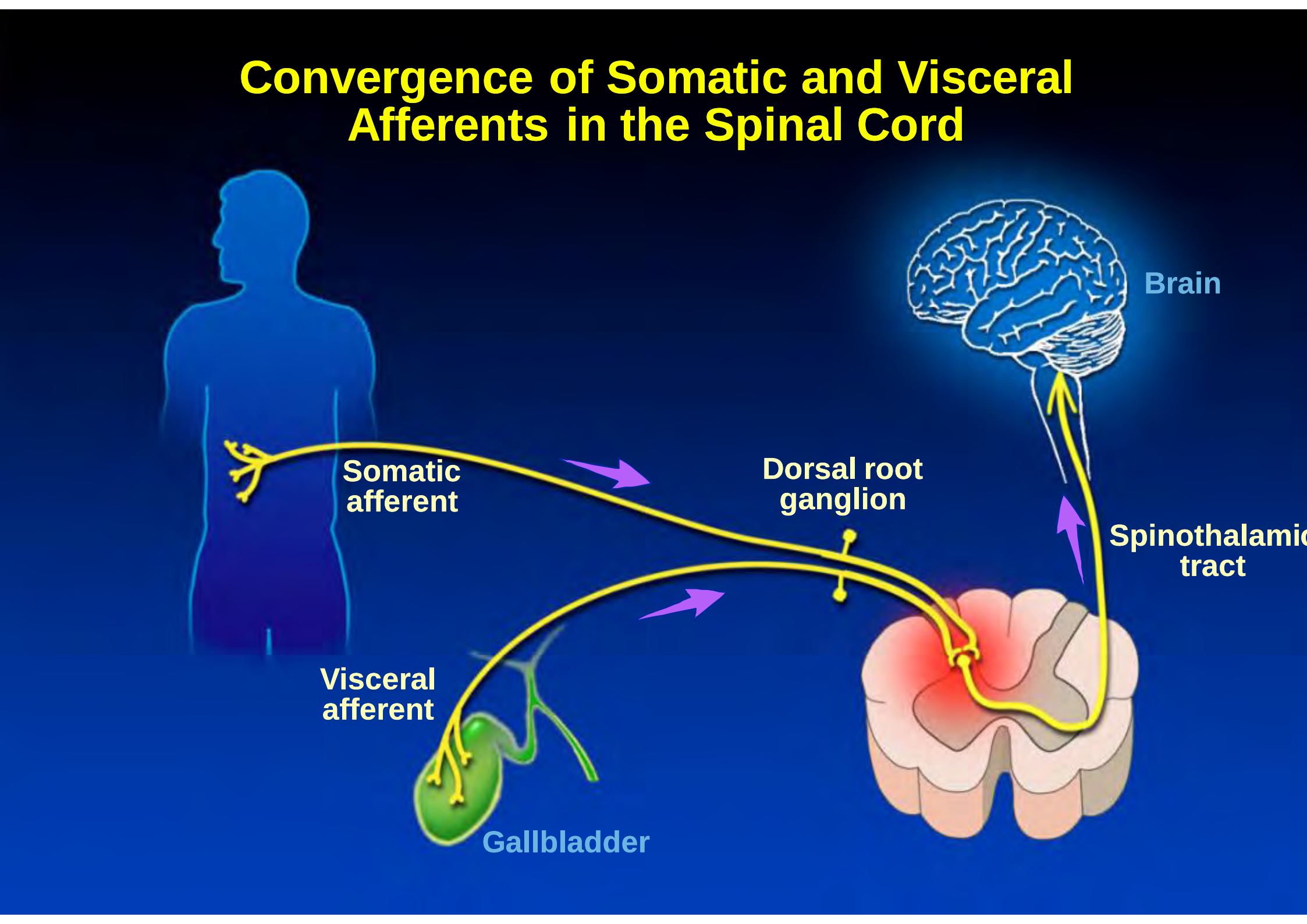



Ascending Visceral Pain Pathway
MCC
Primary somatosensory cortex
pACC
Insula
Thalamus
Reticulothalamic
Spinothalamic
Spinomesencephalic
Spinoreticular
Dorsal reticular nucleus
Colon

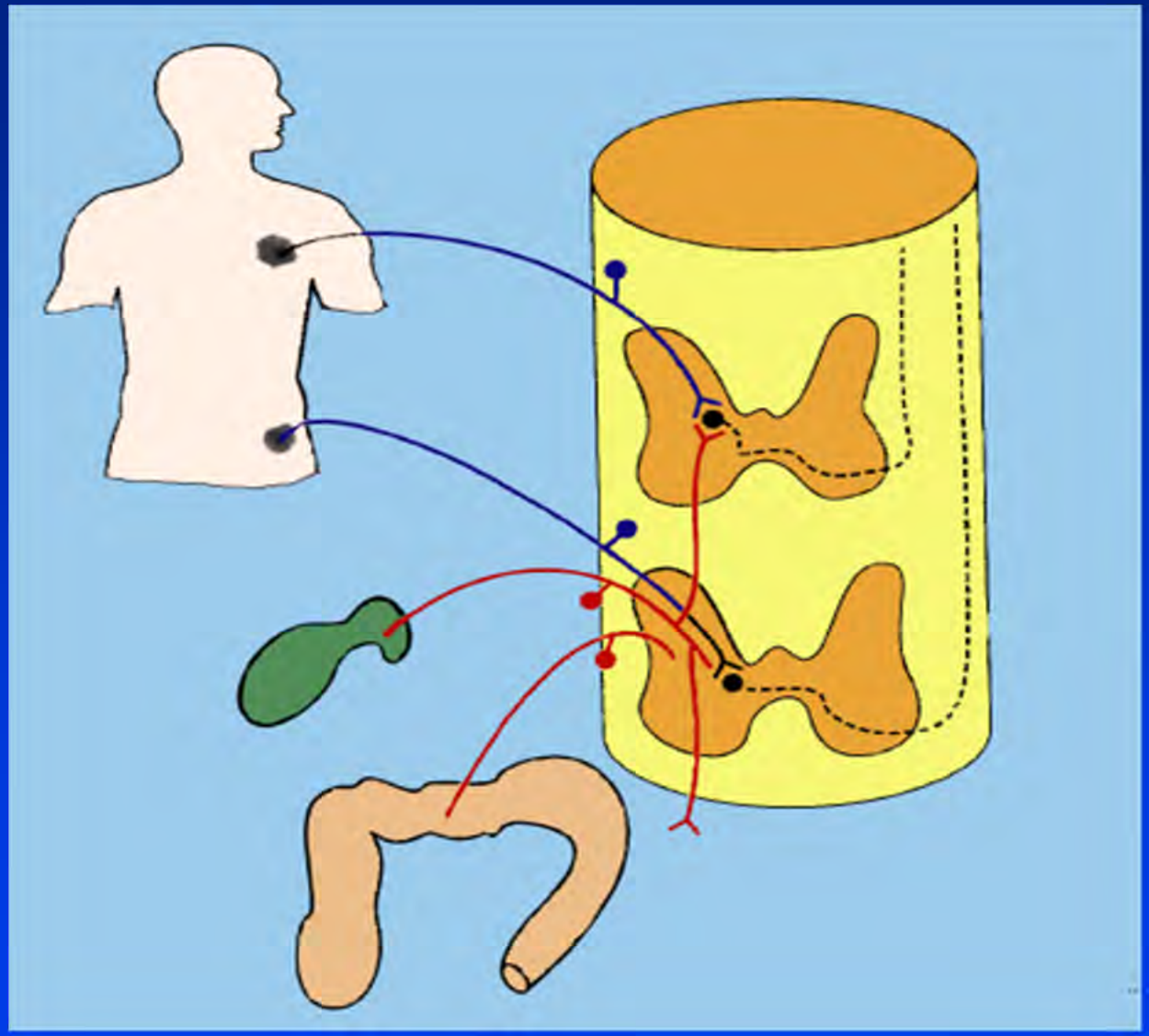
Descending Pain Modulation



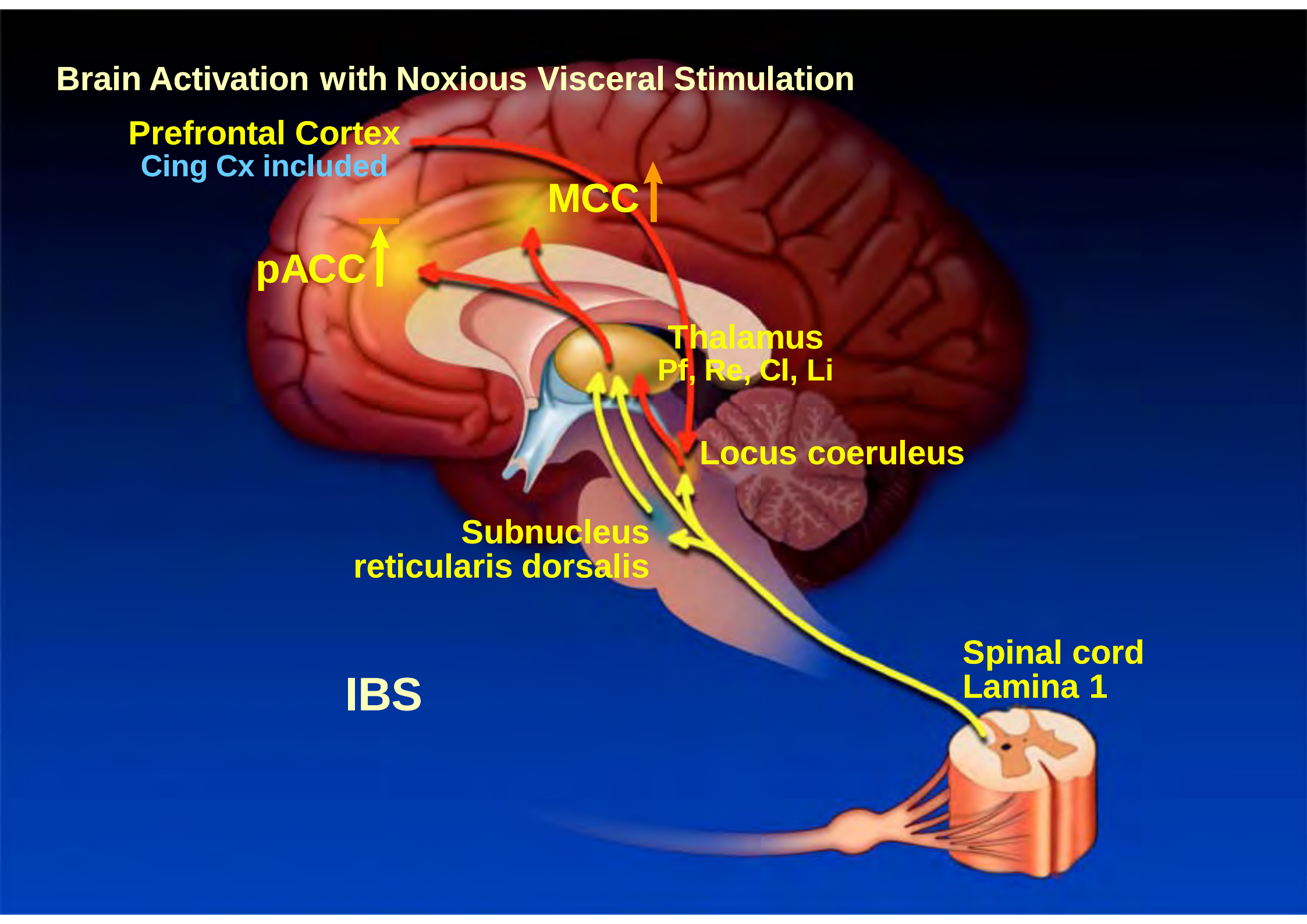
Convergence of Somatic and Visceral Afferents in the Spinal Cord



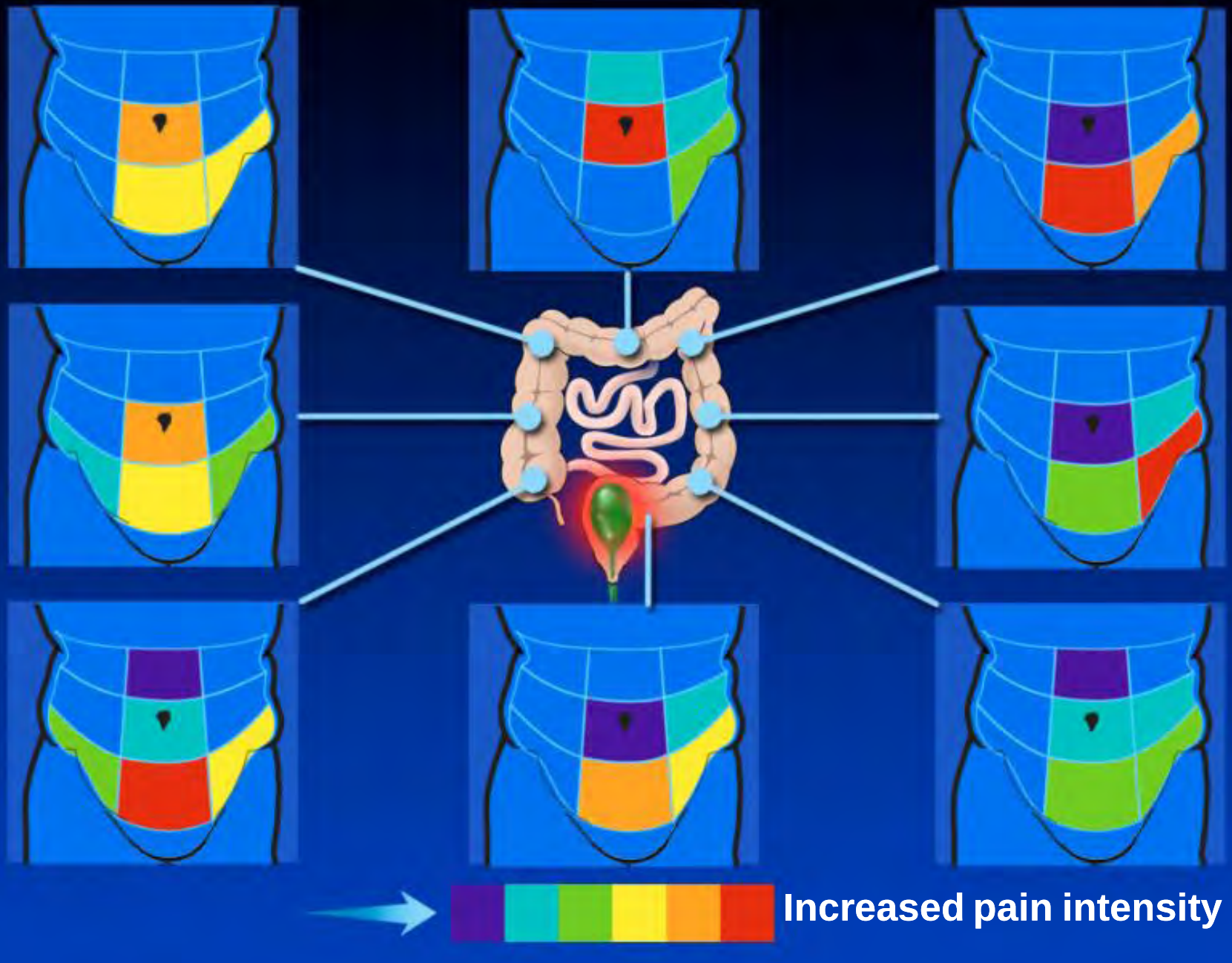
Divergence of Somatic and Visceral Afferents in the Spinal Cord



(Wolf et al. 1965)


Brain Activation with Noxious Visceral Stimulation
Prefrontal Cortex
Cing Cx included
MCC
pACC
Thalamus
Pf, Re, Cl, Li
Locus coeruleus
Subnucleus
reticularis dorsalis
Spinal cord
Lamina 1
IBS

Colonic Referred Pain
(mechanosensitivity)



PATHOLOGIES INTESTINALES DOULOUREUSES

Cancer

MICI: maladie de Crohn, RCH

Gastroentérites infectieuses

Reflux gastro-esophagien (EBO +/-)

Troubles fonctionnels intestinaux (TFI)
Dyspepsie
Syndrome de l'Intestin Irritable (SII-IBS)
Douleurs fonctionnelles abdominales (FAPS)

Dans les TFI: la douleur viscérale est-elle associée à une hypersensibilité de la paroi en particulier à celle des mécano-récepteurs?

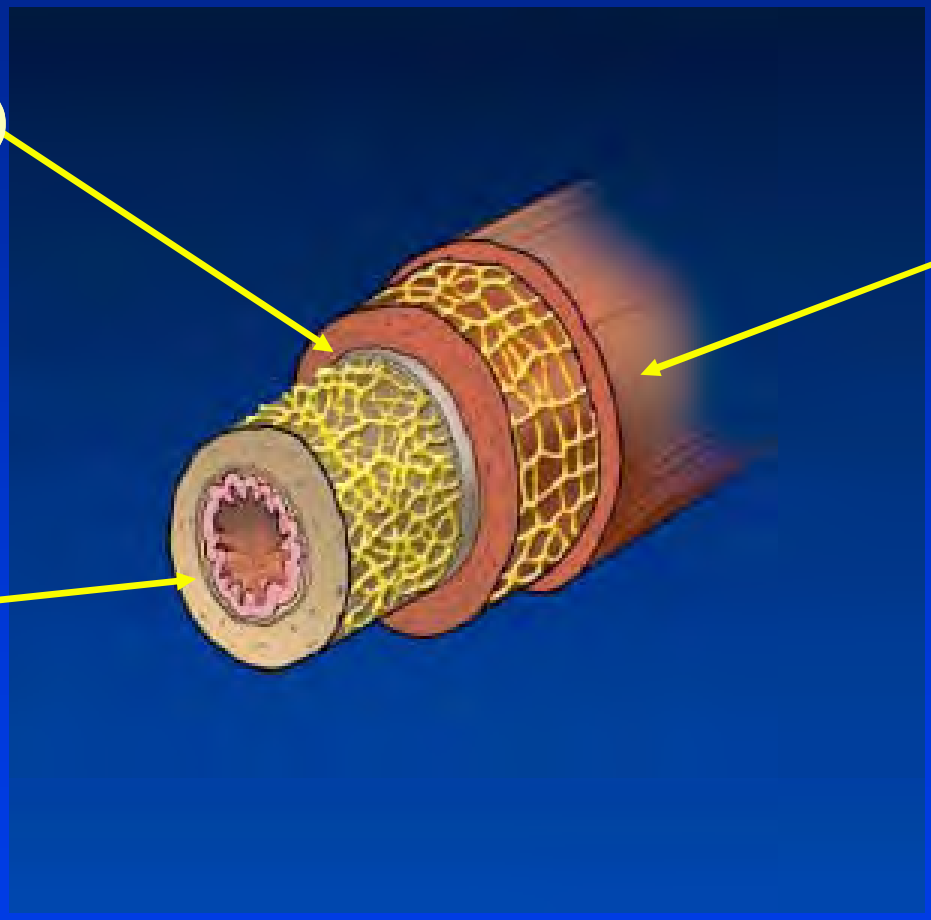
Mechanoreceptors of the Digestive tract - localisation

Vascular
(8/10 high threshold)

Tonic & Phasic distensions

Mucosal
(8/10 low threshold)

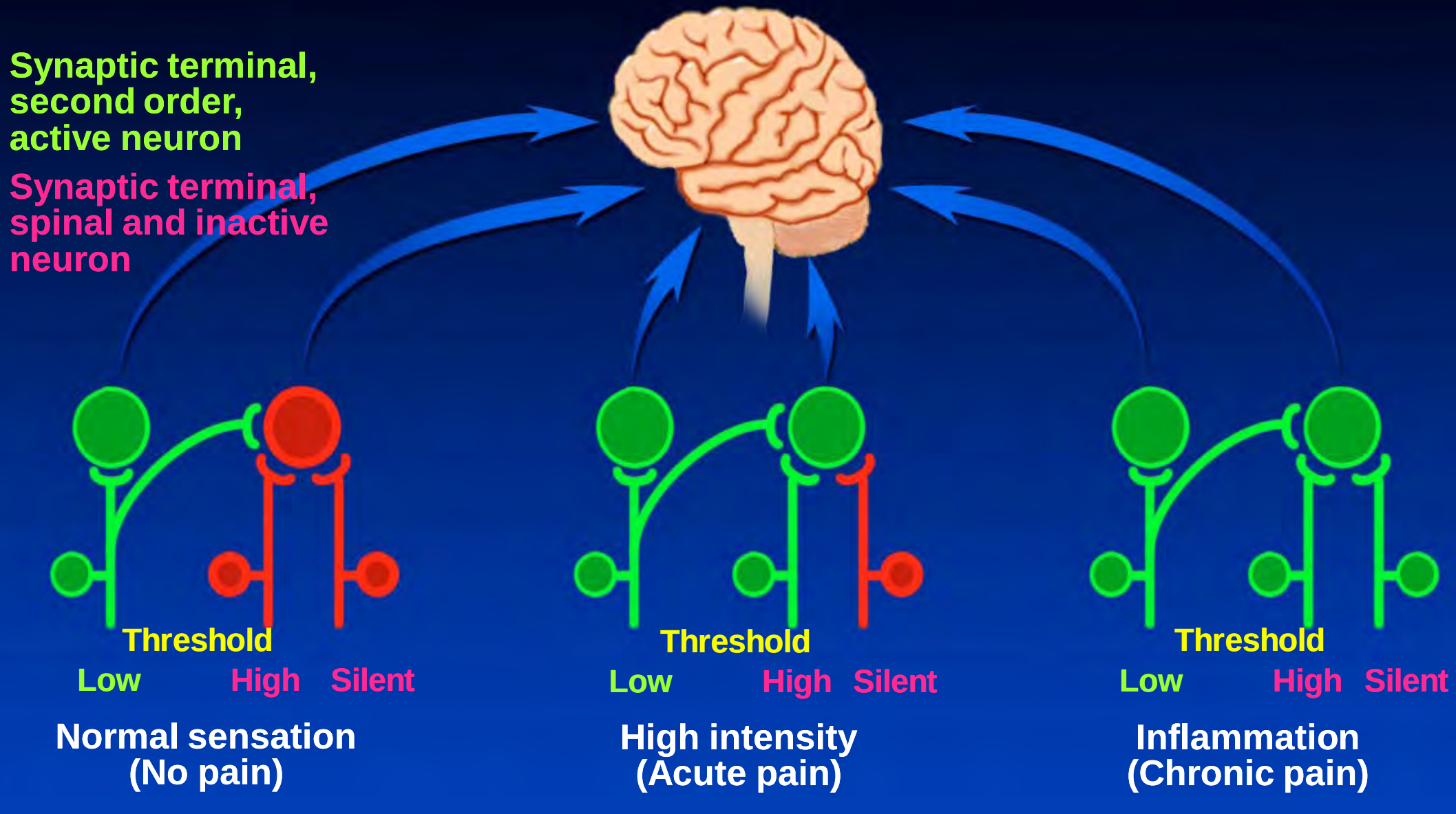
Phasic Distension (act in parallel)



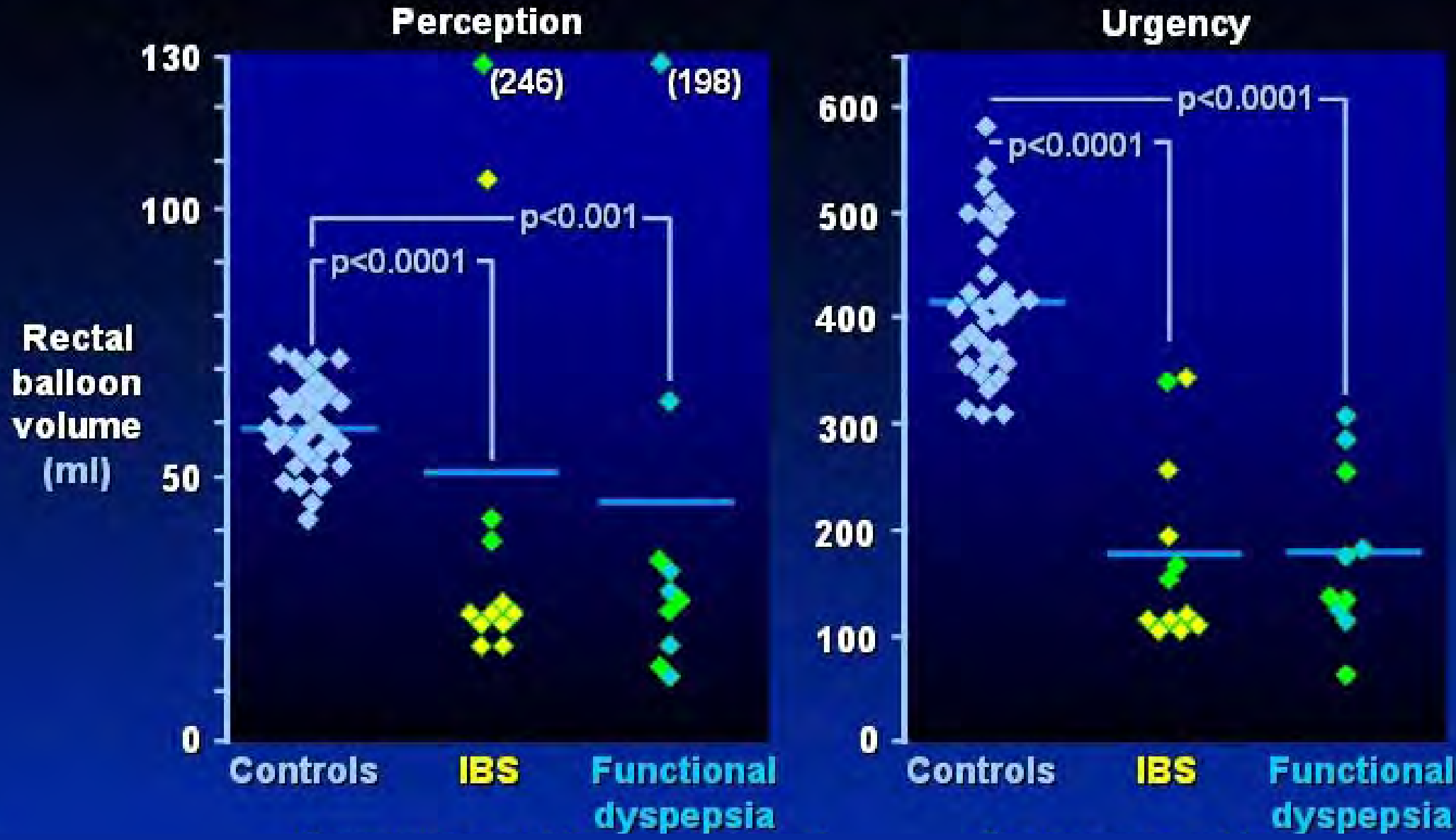
Serosal
(1/3 low threshold)

Tonic Distension (act in series)

Spinal Gating for Three Classes of Visceral Nociceptors (Low, High and Silent) Account for Normal Regulatory Functions, Acute and Chronic Pain

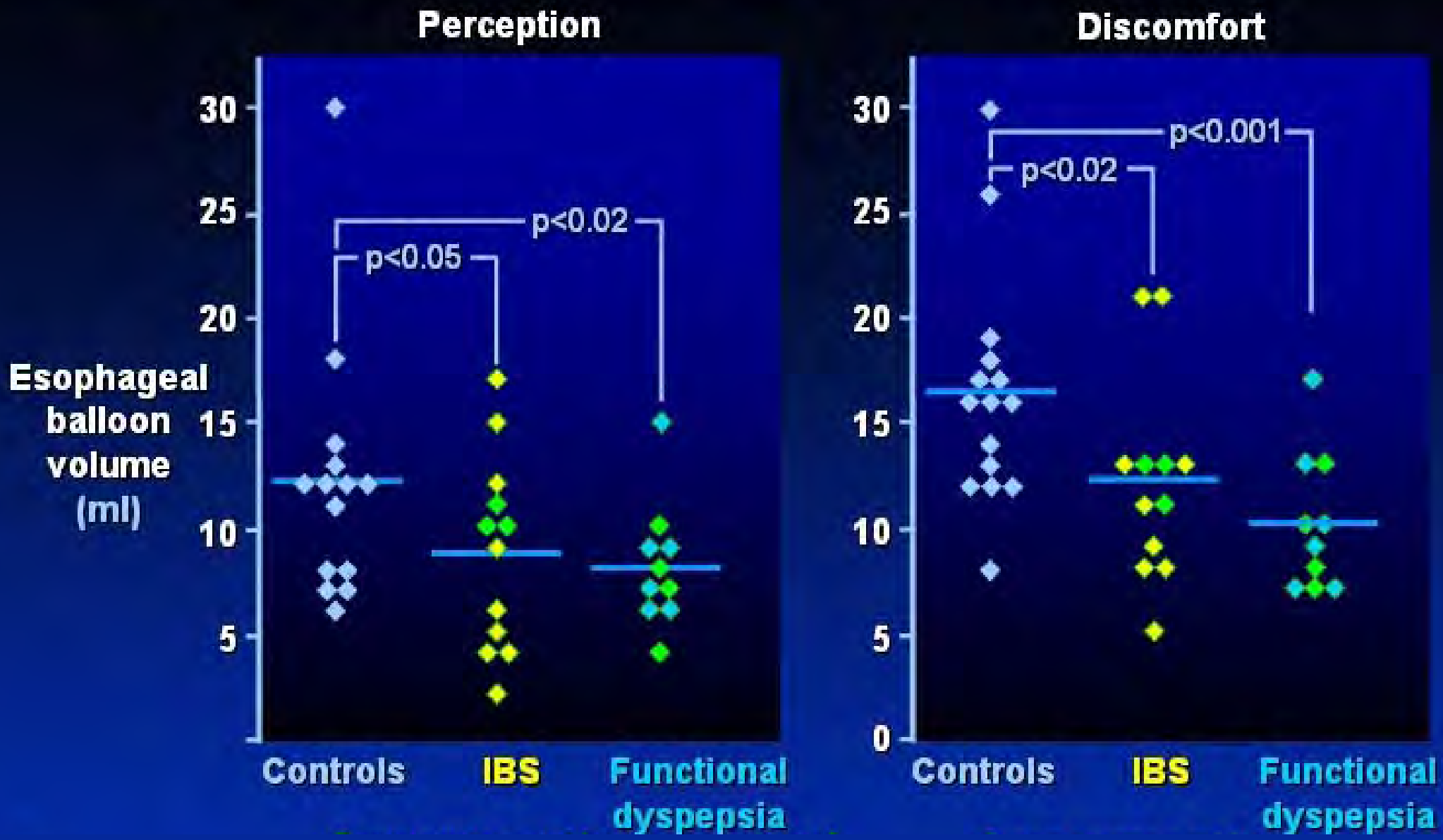


IBS Physiology - Visceral Hypersensitivity: Rectal Distention



Trimble et al.1995

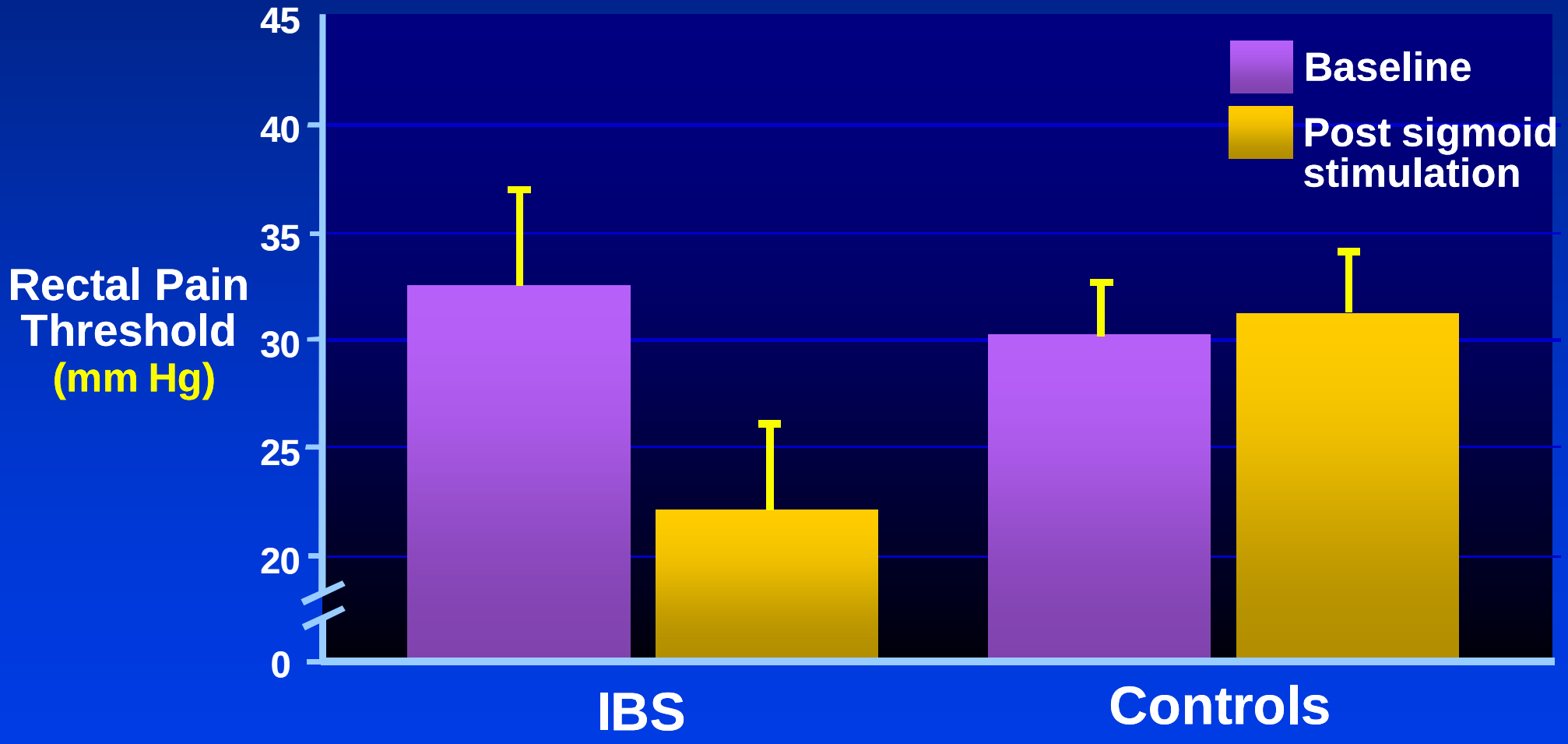
IBS Physiology – Visceral Hypersensitivity: Esophageal Distension



1995-2013: Evidence (27 articles) of allodynia in 60-70% of IBS patients

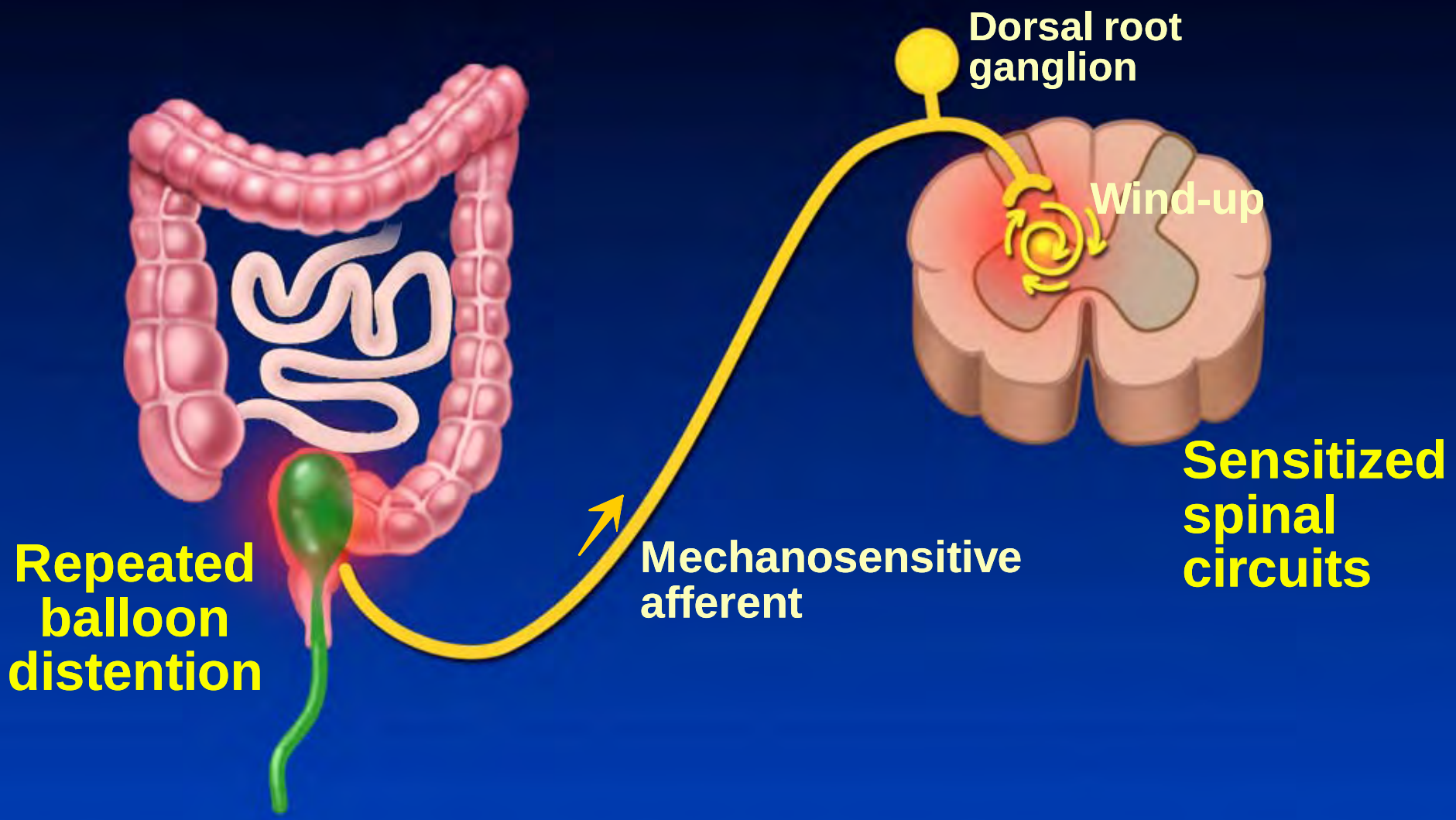
Trimble et al.1995

HYPERALGESIA IN IRRITABLE BOWEL SYNDROME
(Use of “barostatic” distensions)

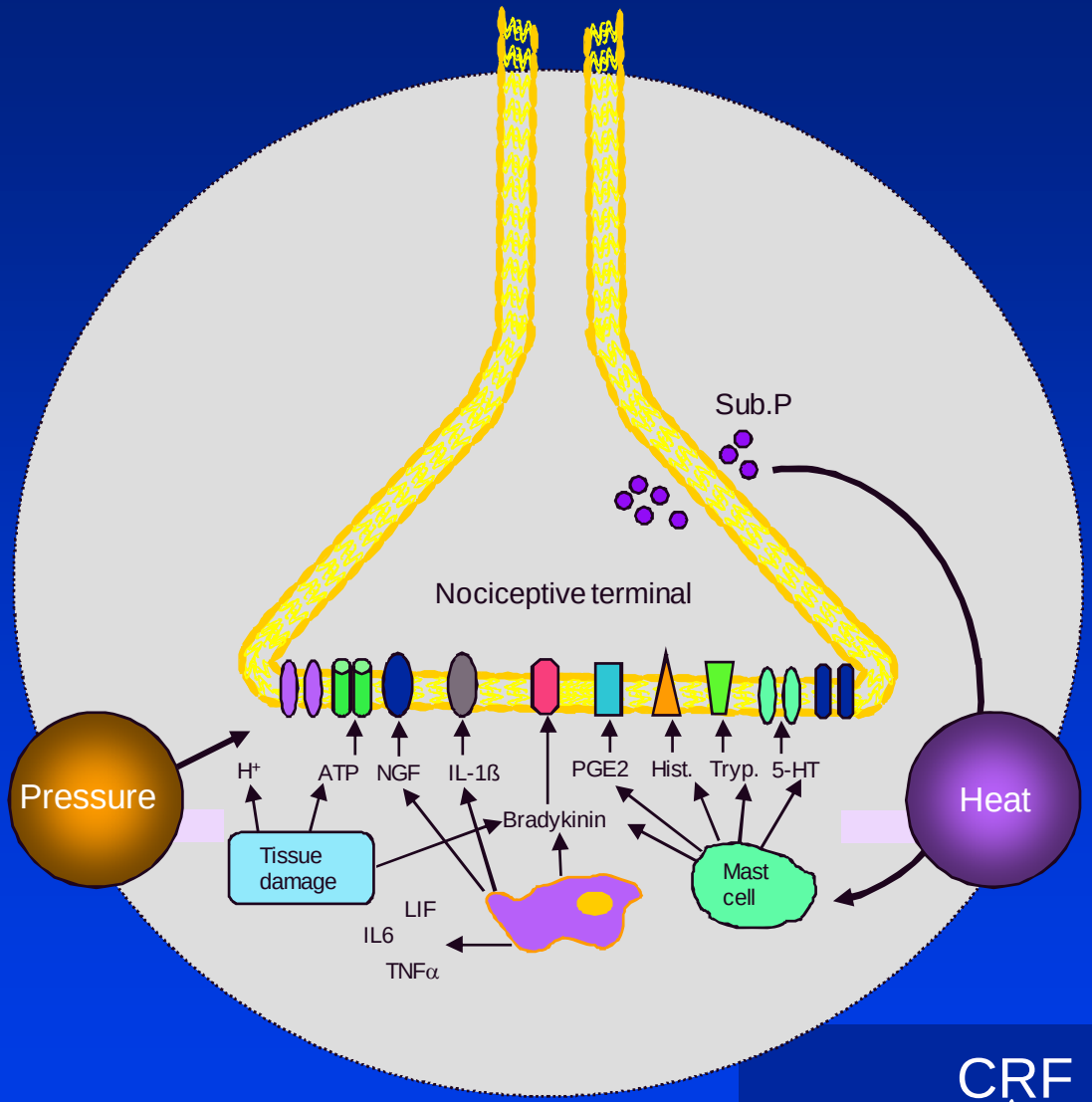


Munakata J, Gastroenterology 1997; 112:55

Repetitive Stimulation Sensitizes the Spinal Cord



Receptors at nerve terminals of nociceptive fibers as putative targets to reduce inflammation-induced hyperalgesia



(Bueno et al. 2005)

Other putative targets (spinal cord level)

$TRPV_{1....5}$
$mGluR_{1,5}$
CB_1, CB_2
$\alpha_2\delta$
κ opioid
$NK_{1,2,3}$
CCK_1
and….. others

Other putative targets (periphery)

CRF	NGF	Proteases
$CRF\text{-}R_1$, $CRF\text{-}R_2$	TrkA, p75	PAR_1, PAR_2

TRILOGY OF IBS PERIPHERAL PATHOPHYSIOLOGY

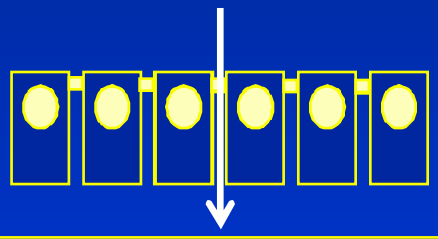
- **Altered gut sensitivity to Distension**
  - Lower threshold of sensitivity (pain) to distension evidenced in 60-70% of IBS patients
  - Increased perception of pain for a given visceral stimulus (Whitehead et al.1998, 20-25 ref.)
- **Colonic mucosal micro-inflammation**
  - Increased number of mast cells, immune cells (Weston et al.1993 and 10-12 ref.)
  - Presence of pro-inflammatory cytokines (Gwee et al. 2003)
  - Release of pro-inflammatory (eicosanoïds)(Jones et al.1982) and pronociceptive agents (Barbara et al. 2005)
- **Increased paracellular permeability**
  - colonic or intestinal level in PI-IBS (Dunlop,2000),
  - intestinal in all Rome I (Marschall et al.2004)
  - colonic in IBS-D patients (Gesce et al. 2008)

IS INCREASED GUT PERMEABILITY ABLE TO INITIATE MUCOSAL IMMUNE RESPONSE AND VISCERAL HYPERSENSITIVITY?

Increased paracellular permeability

=

Entry of pathogens, toxins, antigens, bacteria



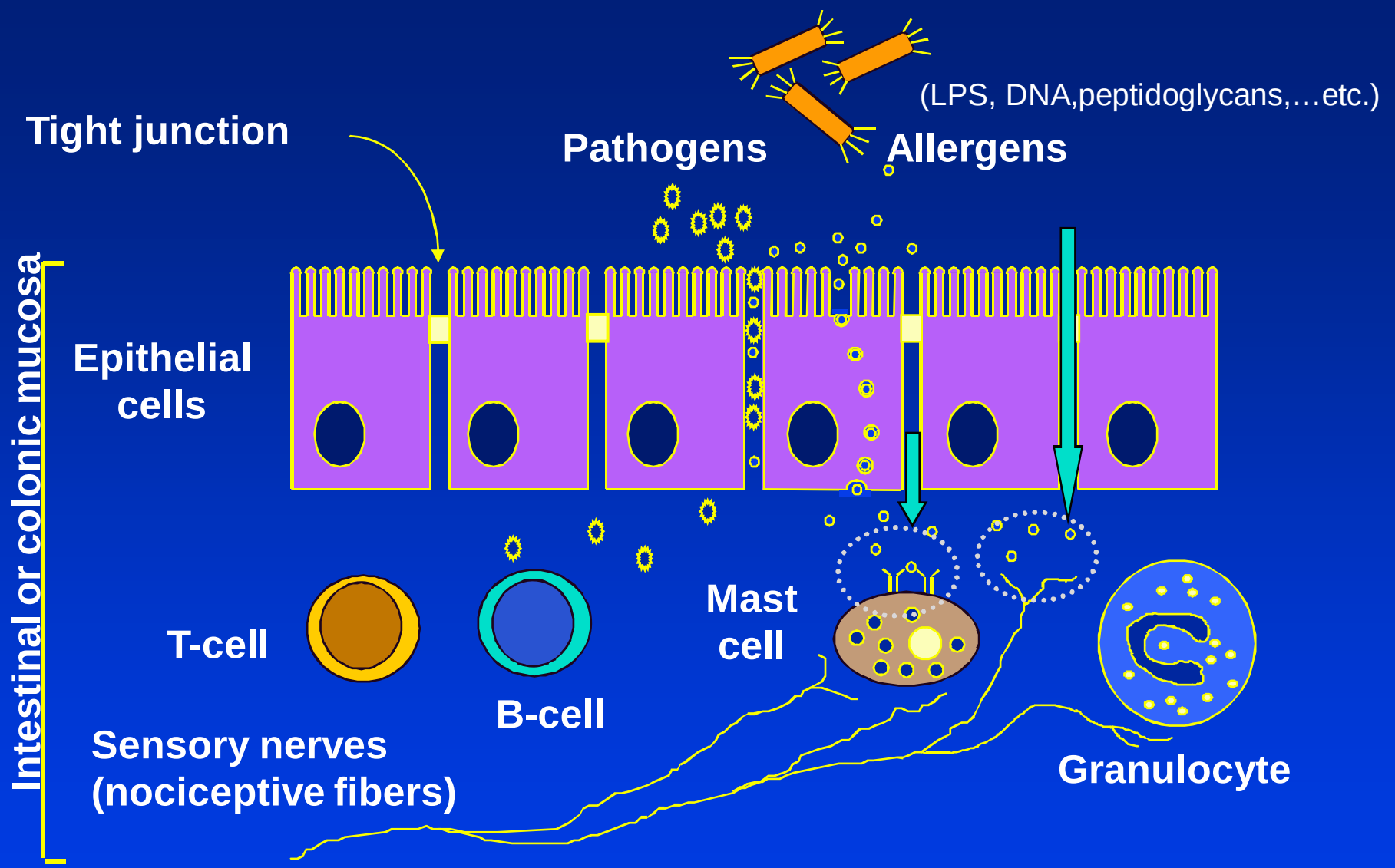
- activation of immunocytes
- cytokines release
- inflammatory mediators

Motility disorders

ENS disorders

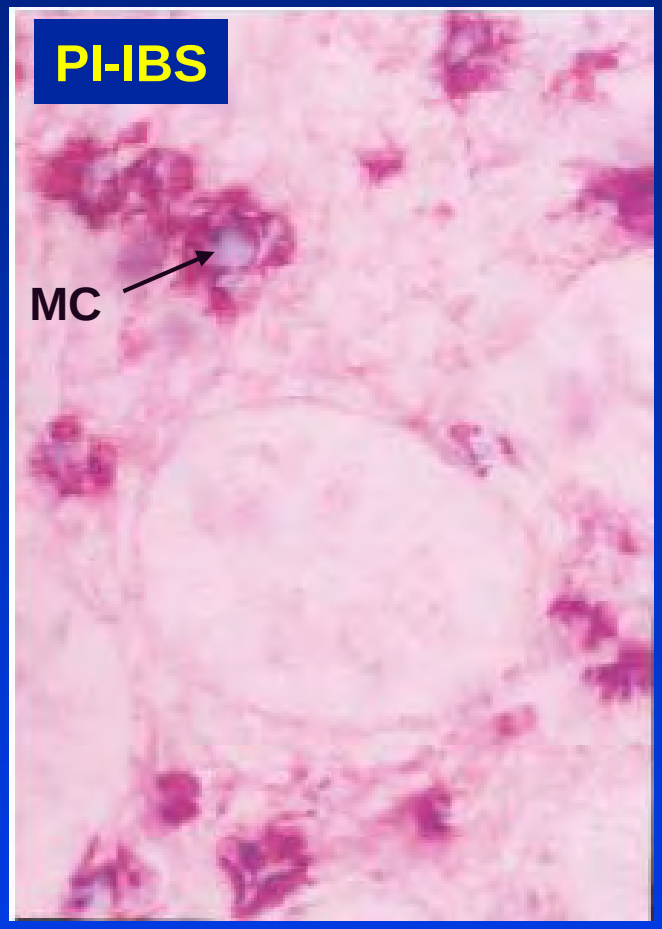
Nociceptive hypersensitivity

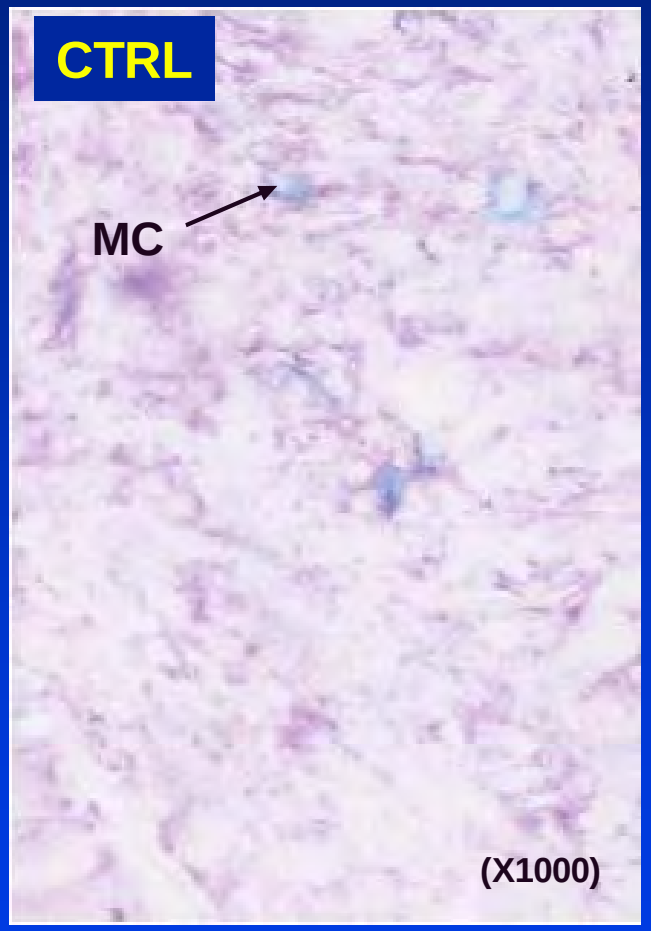
PAIN



(from Perdue et al. 2000)

Distribution of nerve terminals close to mast cell in IBS patients.





Red: nerve terminals (enolase labeling)
Blue: mast cells (alcian blue)

Mast cell number (mm2) (ileal mucosa)

PI-IBS…… 11.2 ± 2.8* (n=27)

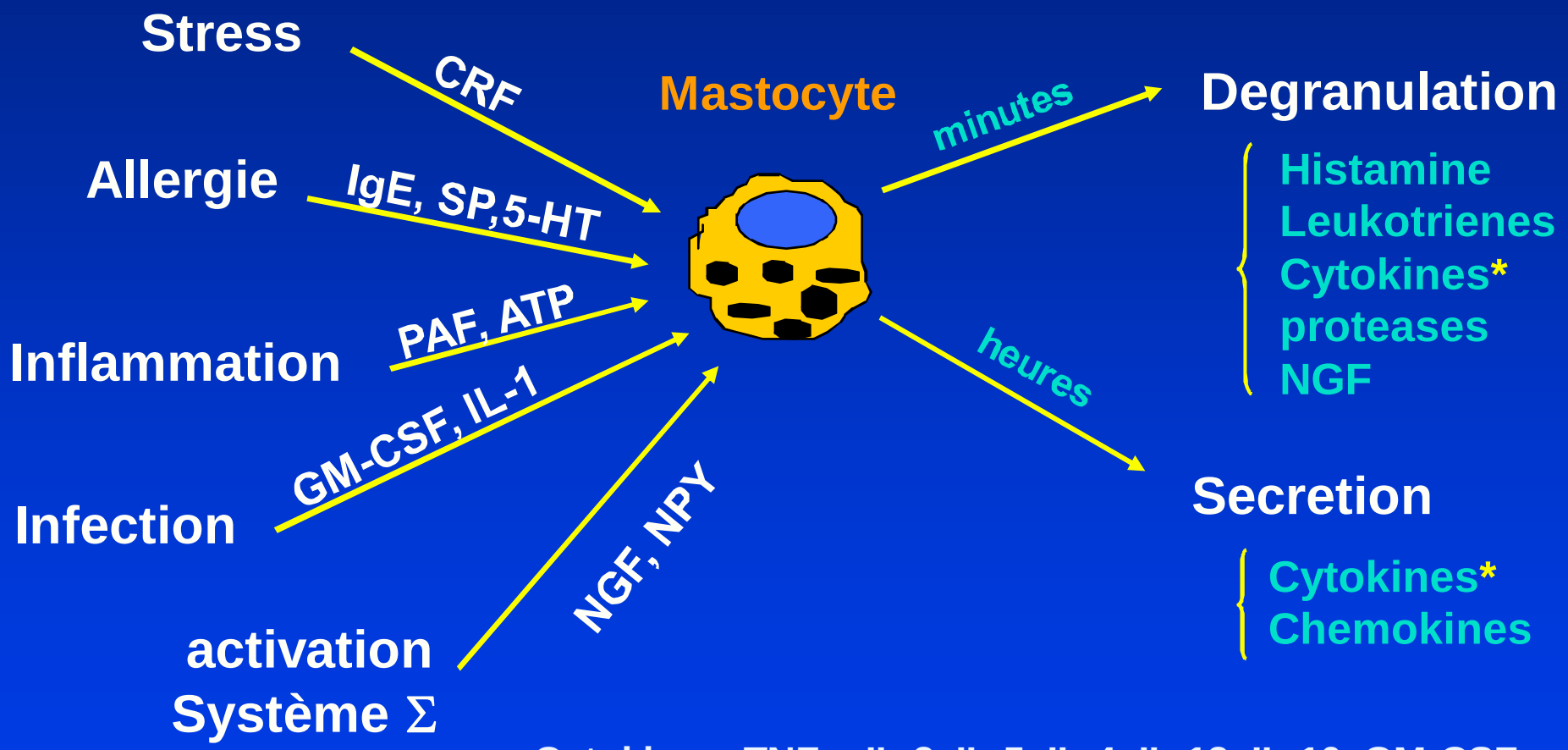
Non PI-IBS…..10.8 ±1.2* (n=29)

Control…….6.1±0.5 (n=12)

*: *from control at p<0.01*

(Wang et al. Gut 2004)

Facteurs principaux produisant la dégranulation ou l'activation des mastocytes muqueux du tube digestif



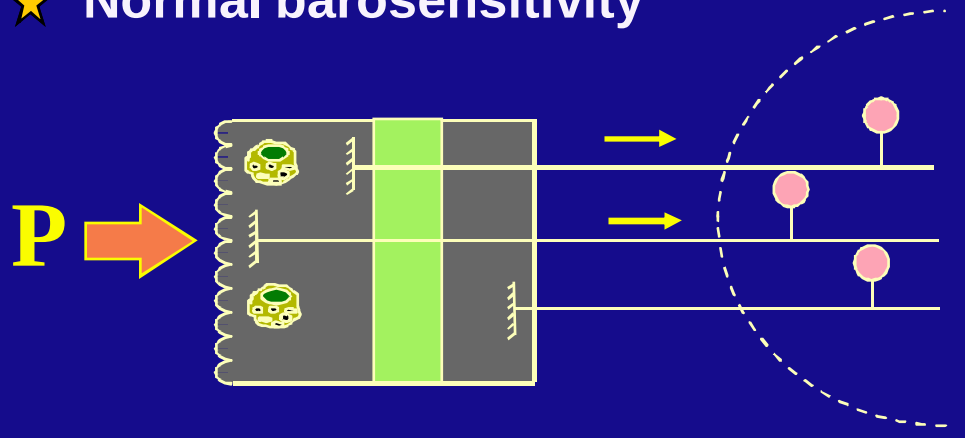
* Cytokines: TNFα, IL-3, IL-5, IL-4, IL-13, IL-10, GM-CSF

(adapted from Shakoory et al,2004, Penicci et al.2003)

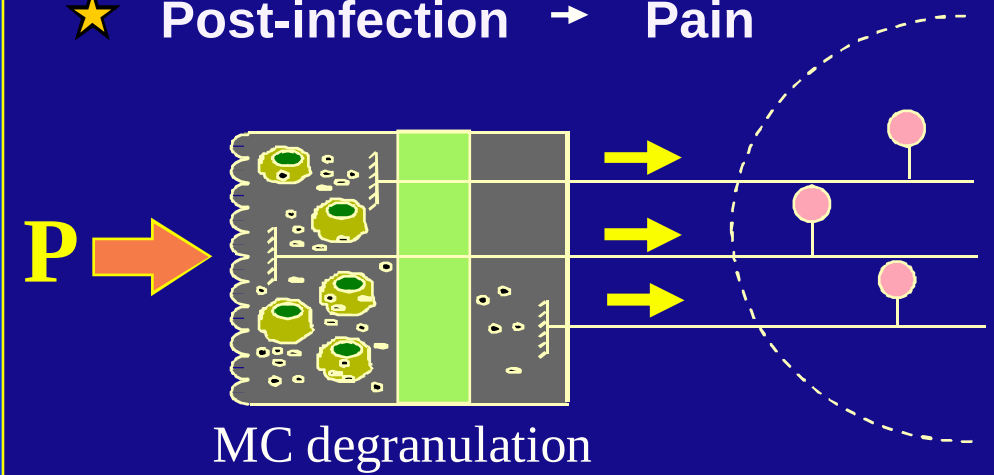
ROLE OF MAST CELLS IN VISCERAL PAIN: (degranulation in response to mechanical stimuli)

Density

★ Normal barosensitivity

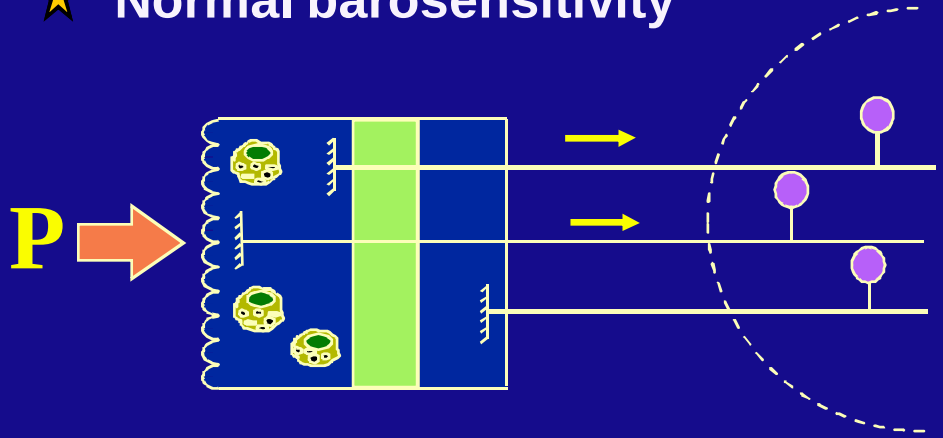


★ Post-infection → Pain

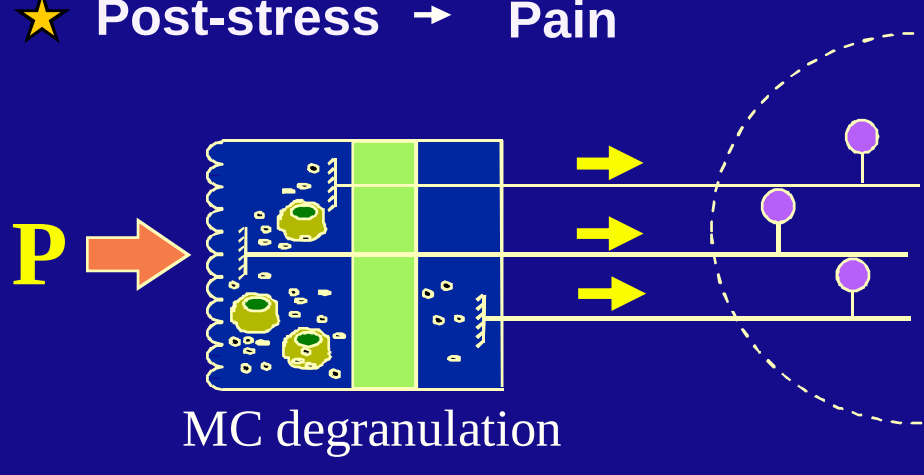


Sensitization

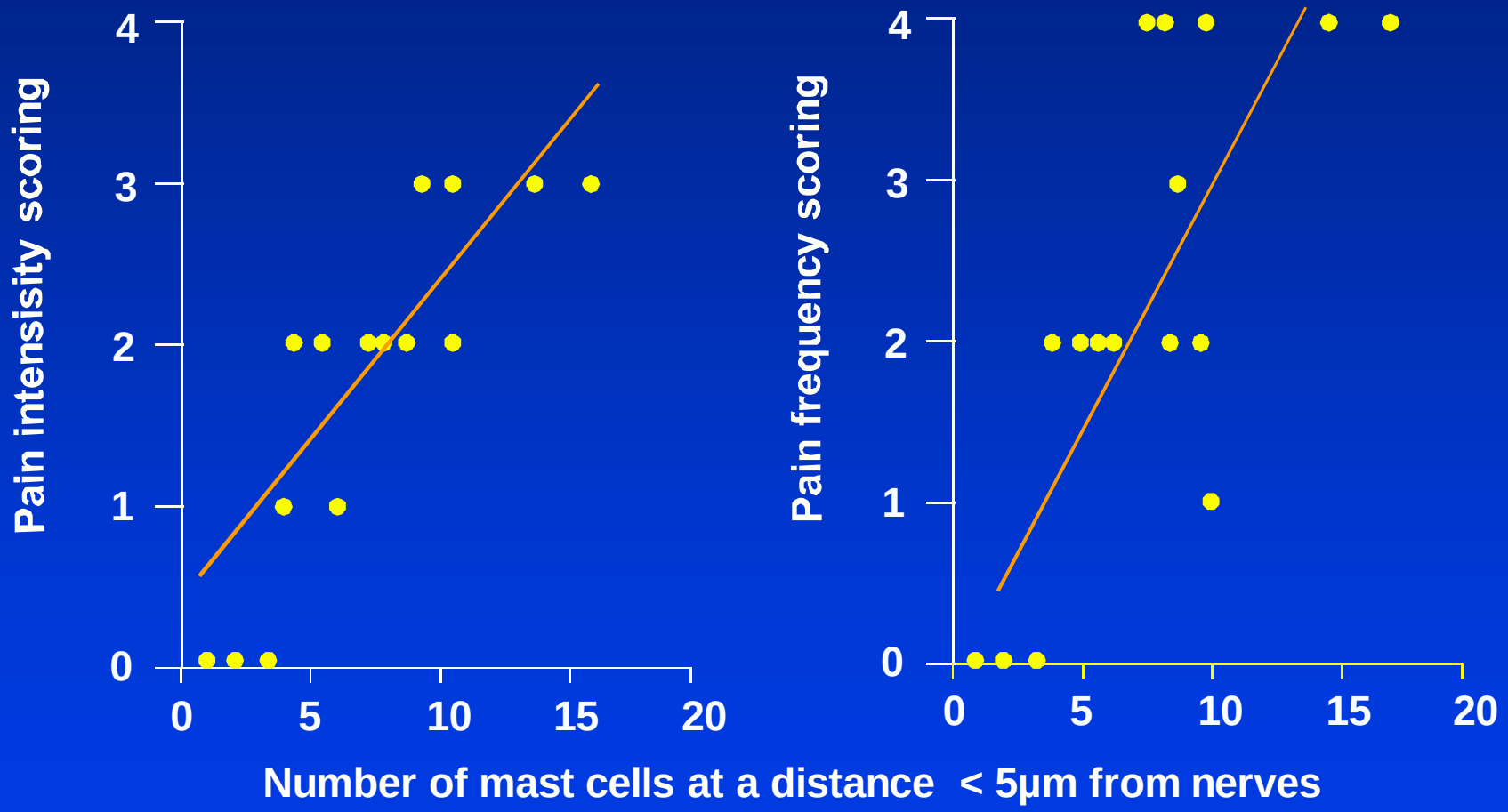
★ Normal barosensitivity



★ Post-stress → Pain

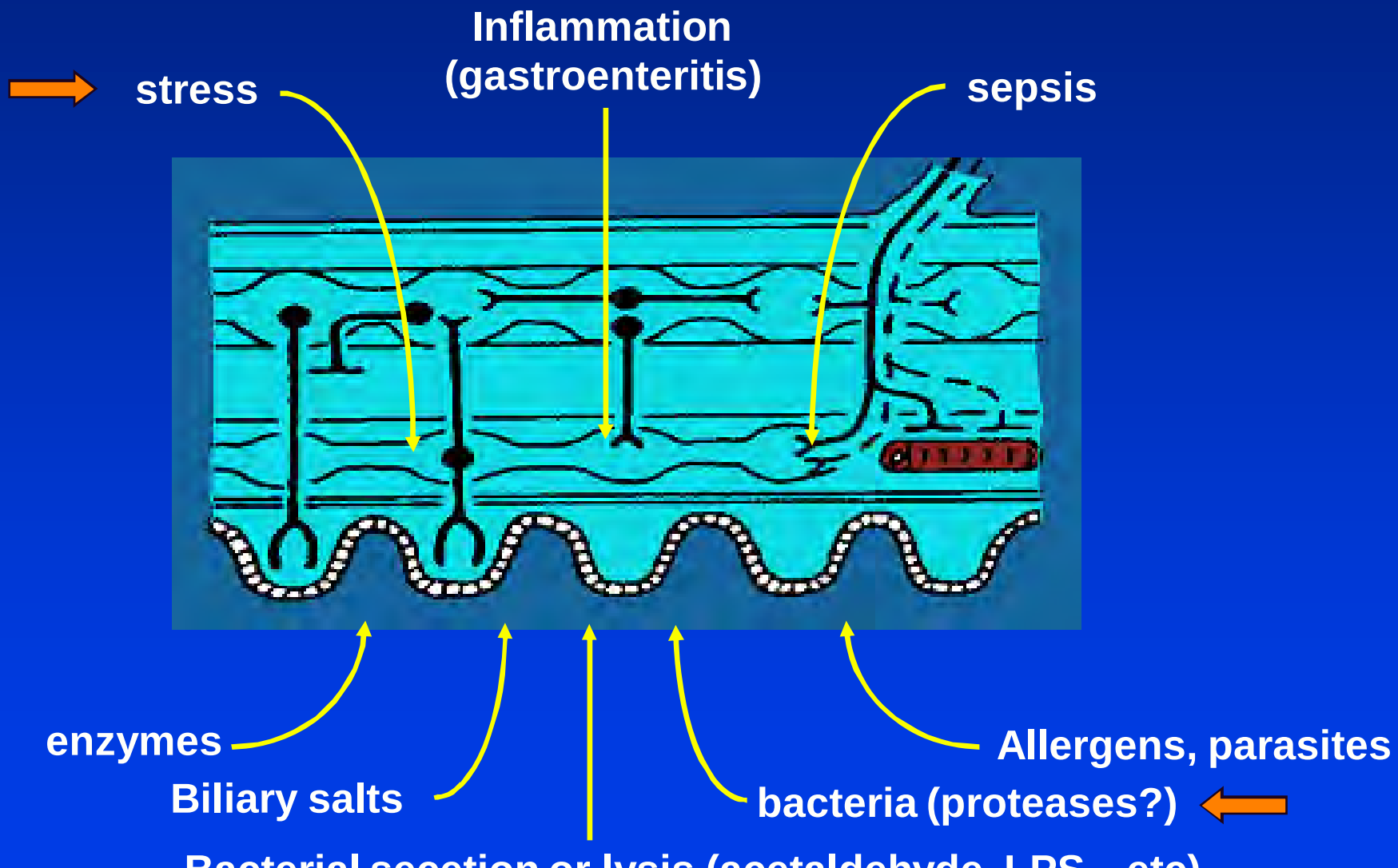


RELATIONSHIP BETWEEN MAST CELL-NERVES CONNECTION AND PAIN IN IBS PATIENTS

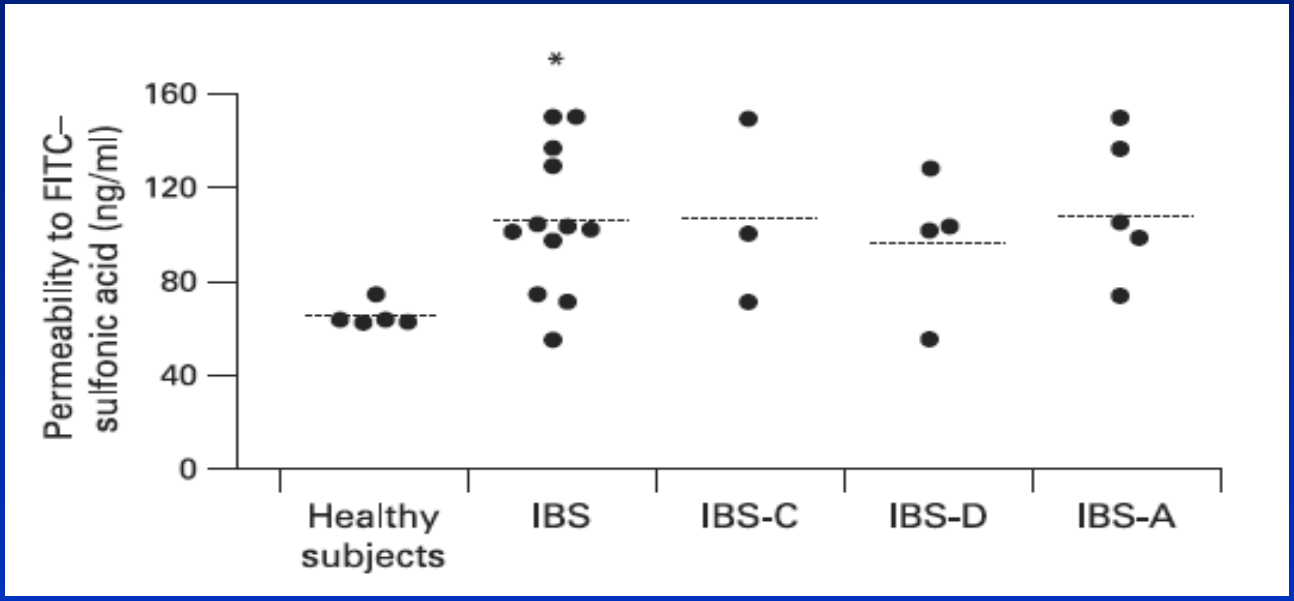


(Barbara et al. Gastro. 2004)

Factors able to alter gut permeability/sensitivity in FGID

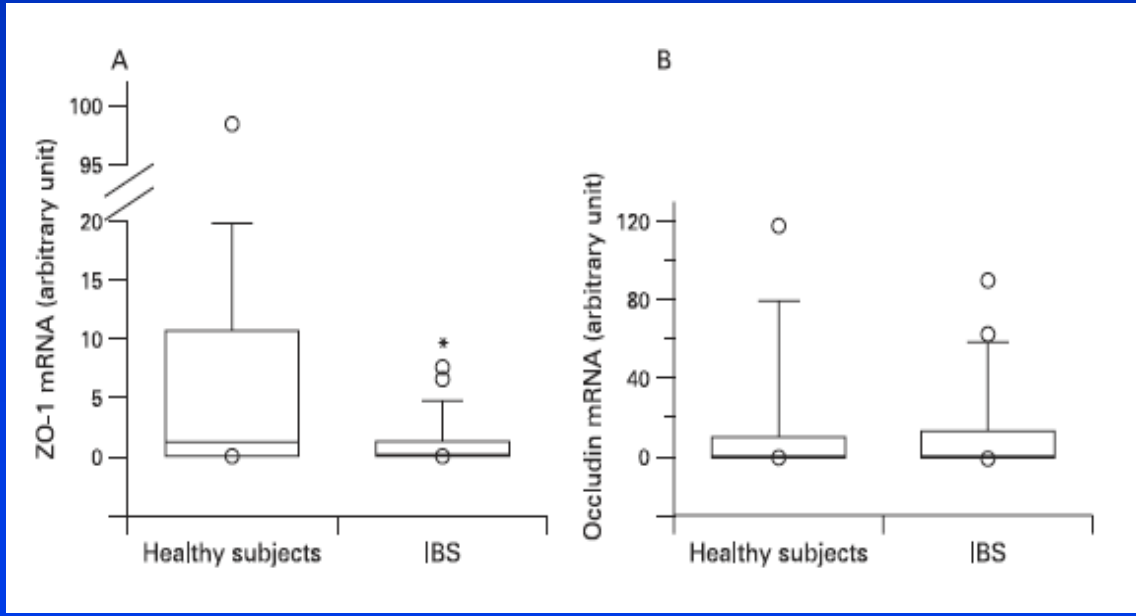


IN VITRO MEASUREMENT OF PARACELLULAR PERMEABILITY OF COLONIC BIOPSIES (Ussing chambers)



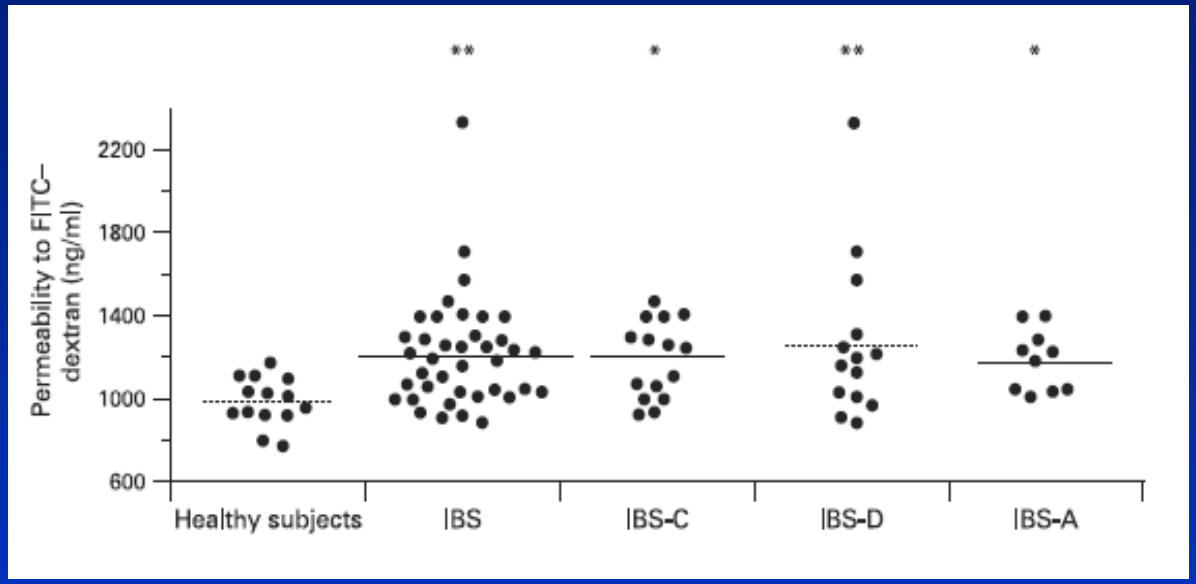
- The degree of porosity of biopsies from IBS patients is higher than that of healthy subjects independently of bowel habit alterations.

- This altered permeability is associated with a decrease in the expression of ZO-1, a protein linking the actinomyosin apical ring to the proteins of the TJs



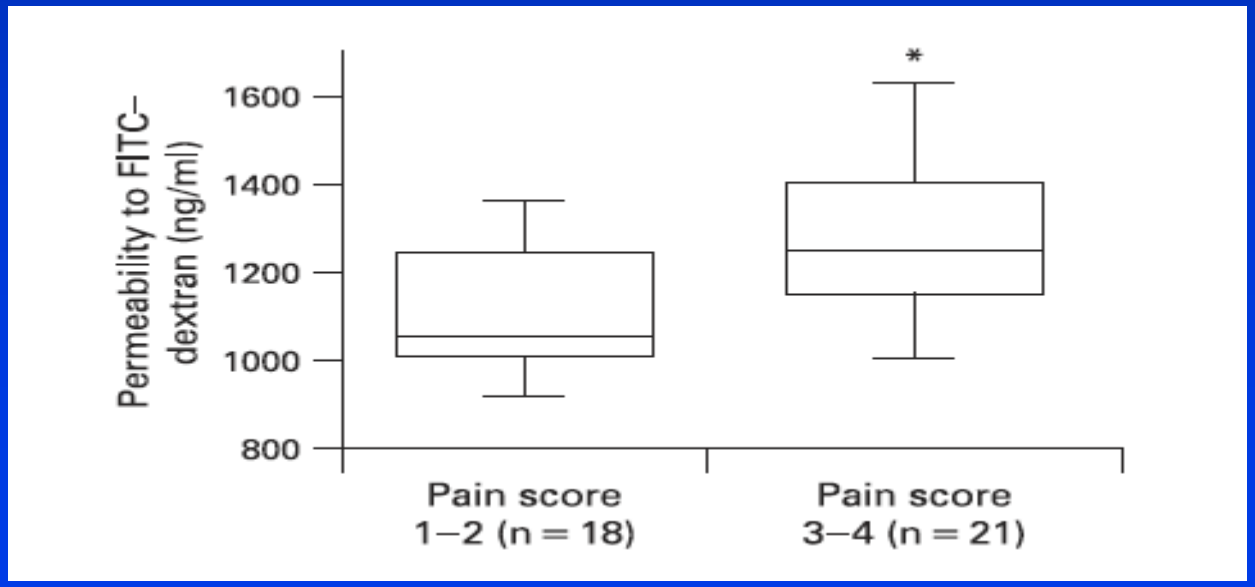
Piche et al. Gut 2009

EFFECTS OF COLONIC BIOPSY SUPERNATANT ON CaCo2 CELL PERMEABILITY AND CORRELATIONS WITH SYMPTOM SCORES



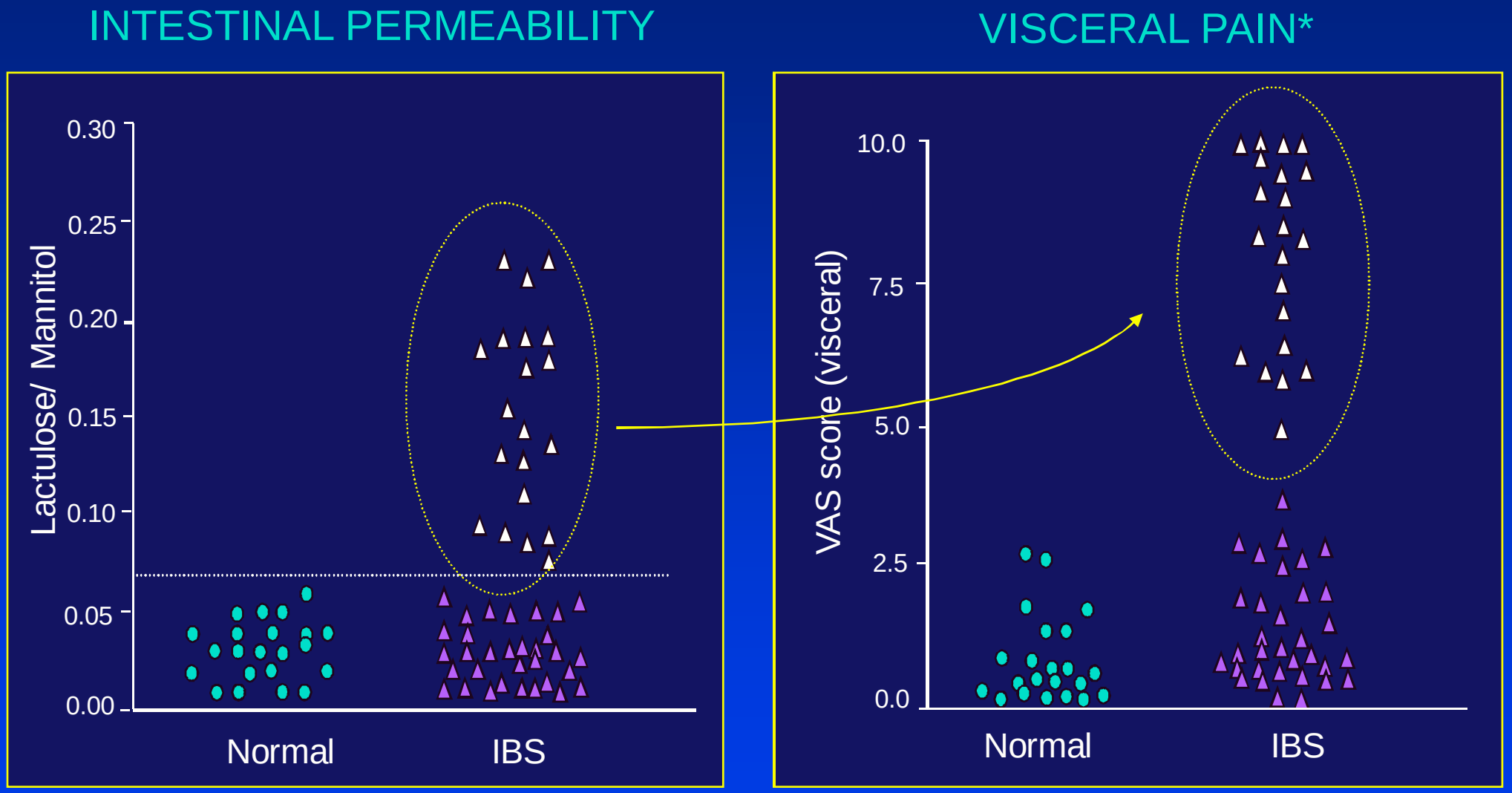
- Increase of permeability of CaCo2 cells, 48h after mucosal exposure with supernatant of biopsies from IBS paients

- Changes in permeability of CaCo2 cells is correlated with the pain score of explored IBS patients



Piche et al. Gut 2009

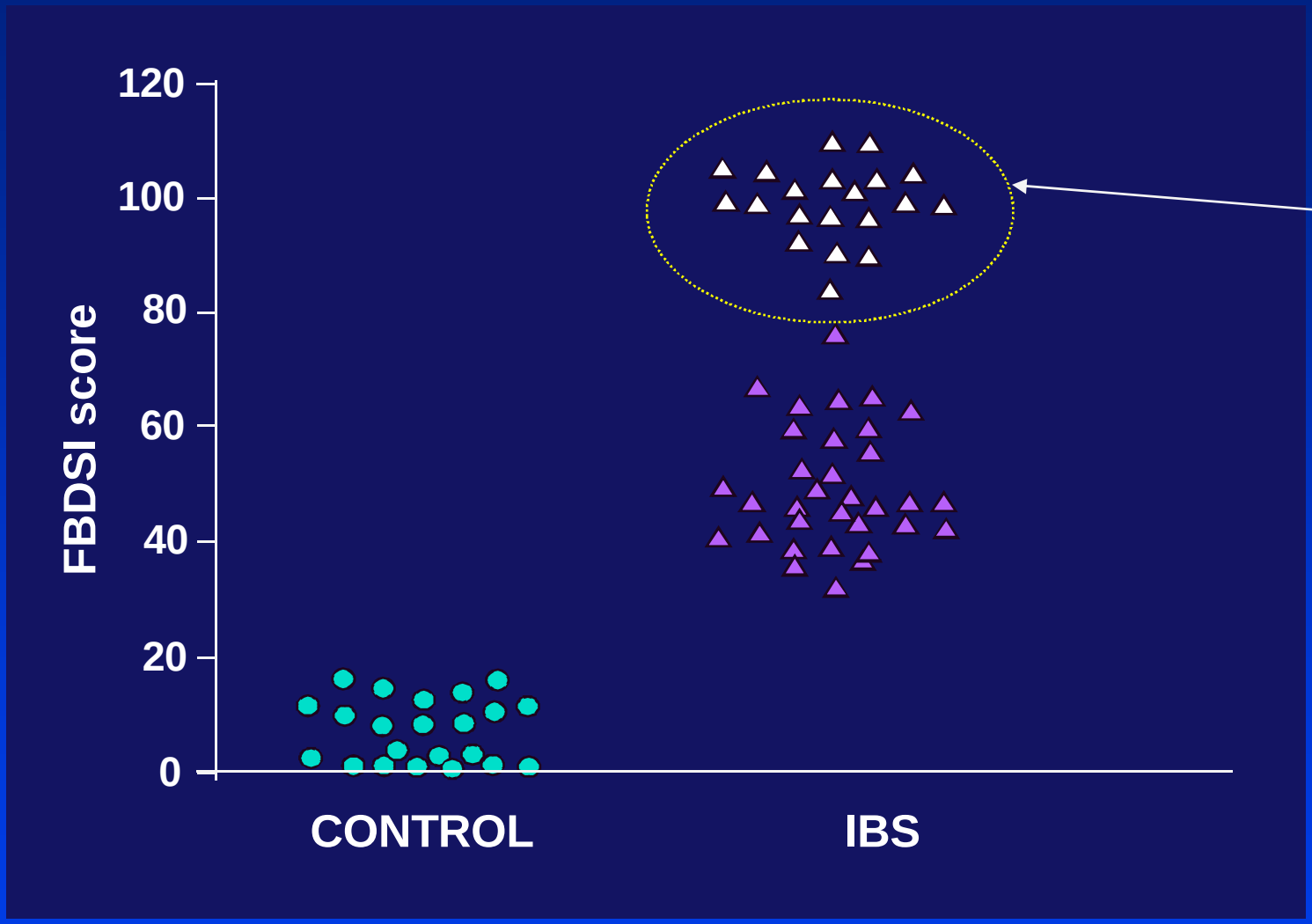
RELATIONSHIPS BETWEEN GUT PERMEABILITY AND PAINFUL SENSATIONS TO DISTENSION MEASURED IN VIVO



* *Pain measurement after repeated (2) 35mm Hg rectal distension performed during 30 sec. at 2 min. interval.*

Zhou et al. Pain 2009

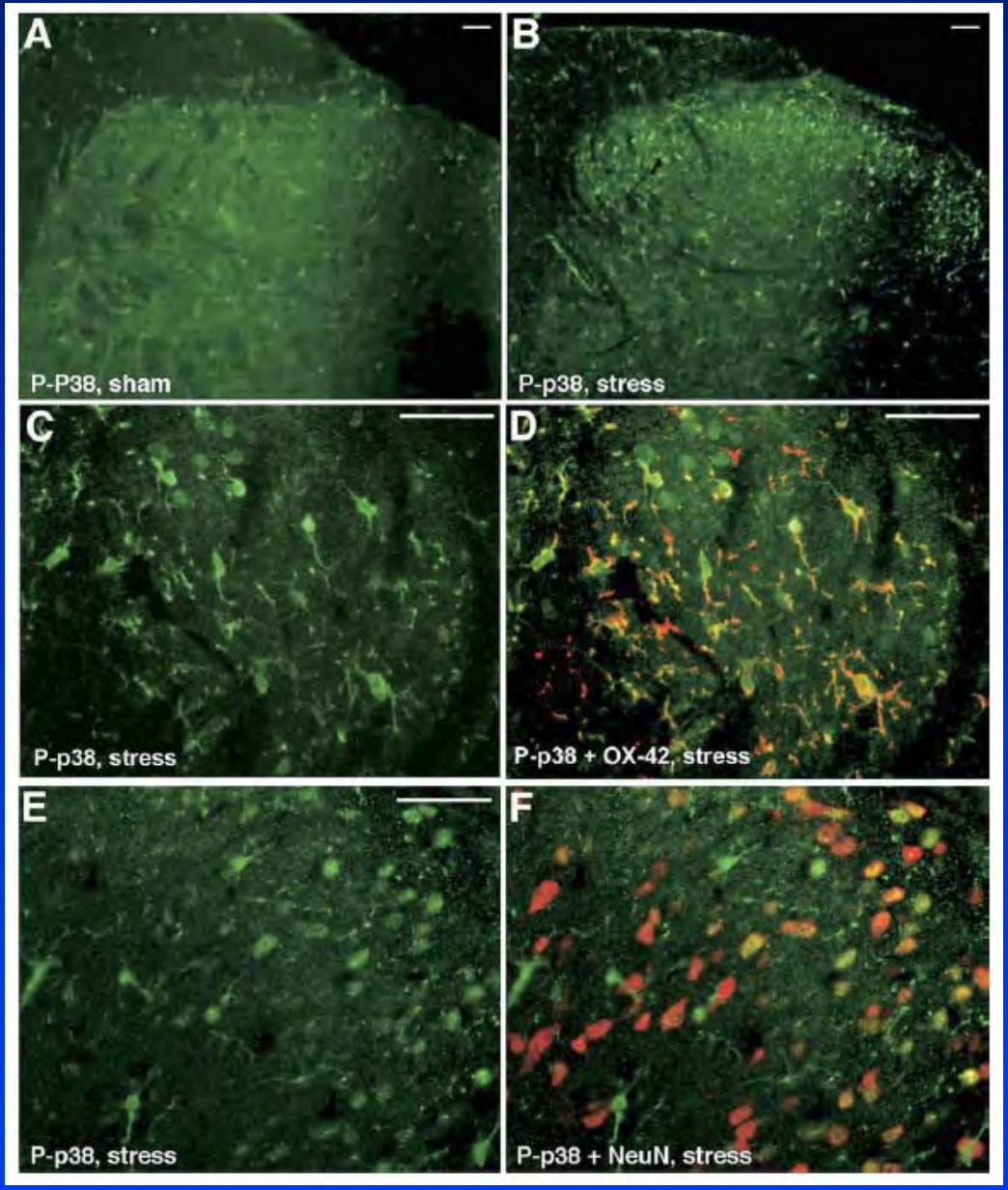
RELATIONSHIPS BETWEEN GUT PERMEABILITY AND SOMATIC* SENSITIVITY IN IBS PATIENTS

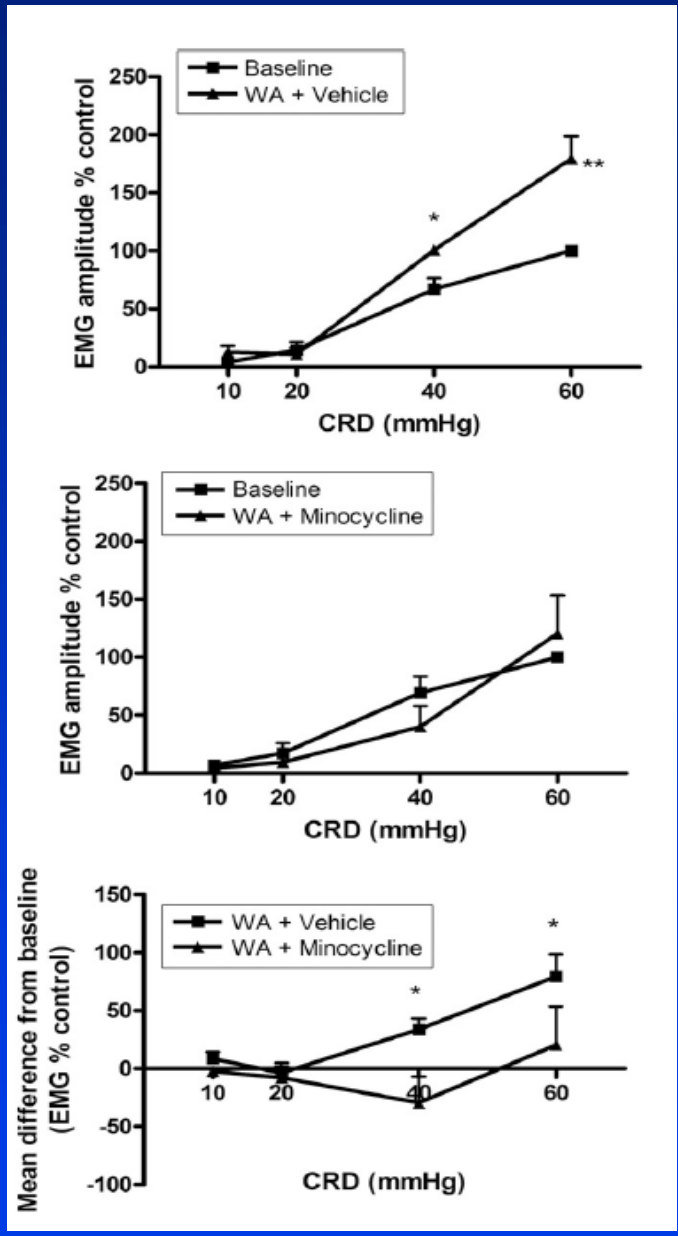


**skin thermal stimulus (Pelletier probe 3x3 cms) at 47 ℃ applied to the left hand during 10 sec.*

Zhou et al. Pain 2009

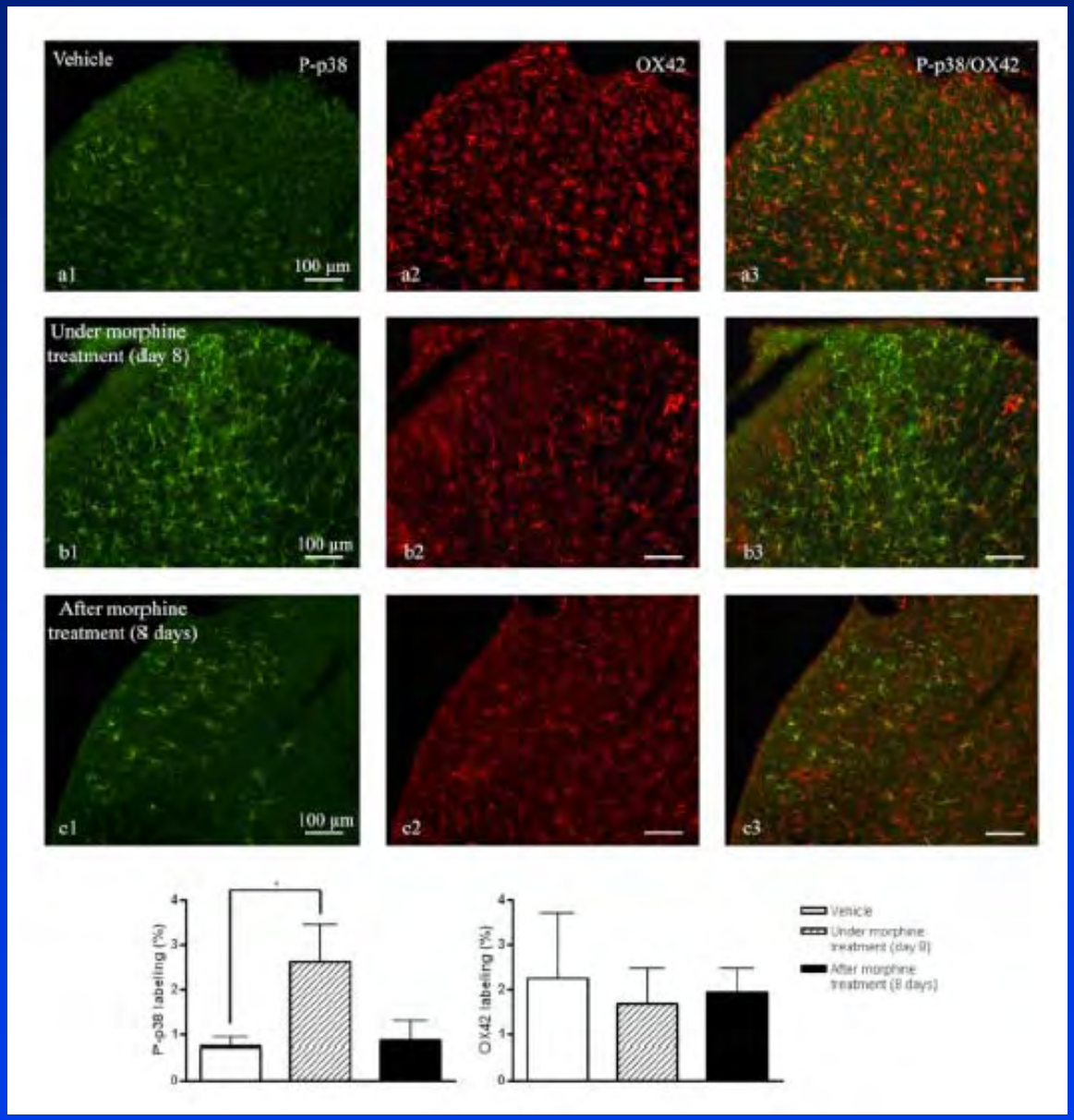
SPINAL MICROGLIA ACTIVATION IN STRESS -INDUCED VISCERAL HYPERALGESIA

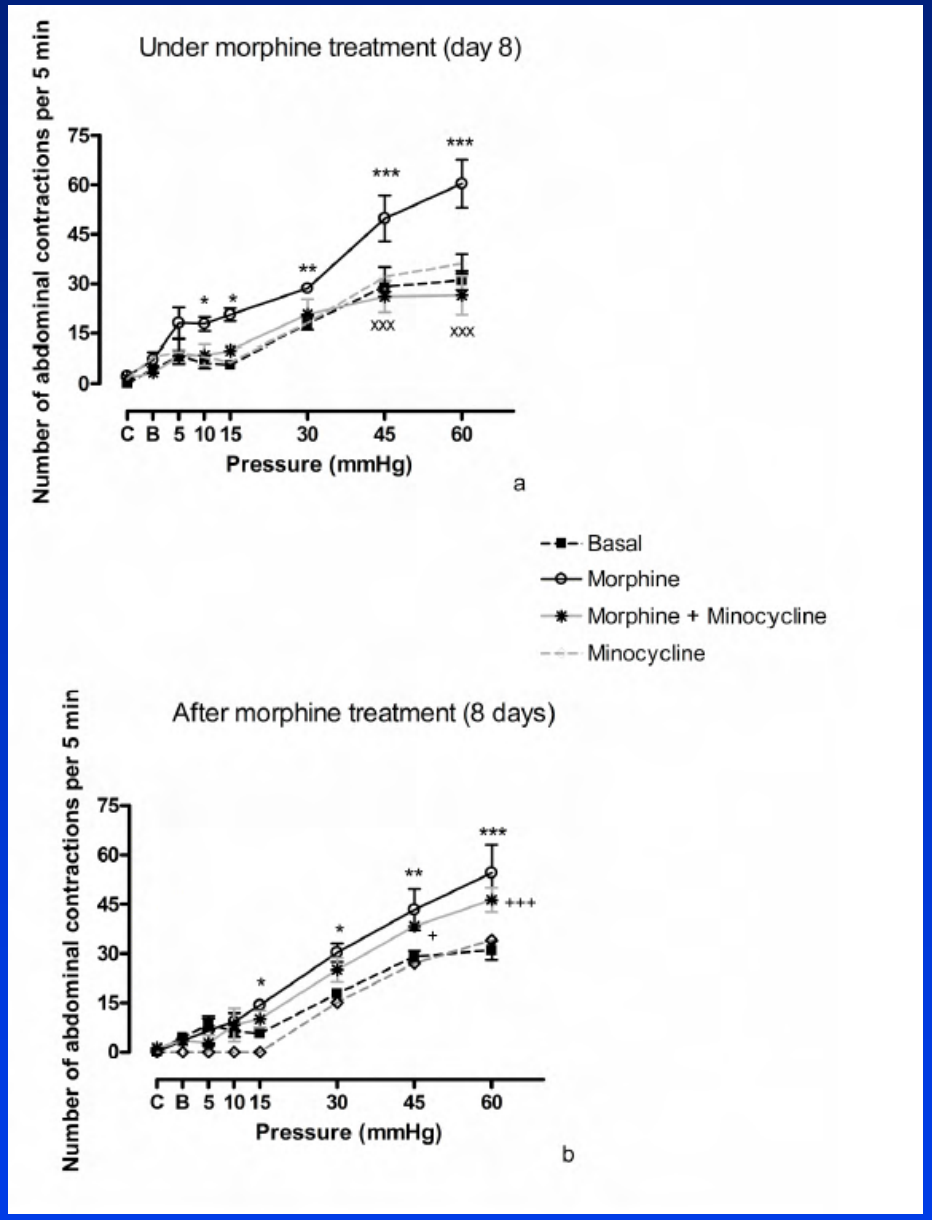




Bradesi et al. 2009

SPINAL MICROGLIA ACTIVATION IN “NARCOTIC BOWEL SYNDROME”





Agostini et al. 2010

CONCLUSIONS

- La douleur d'origine digestive est le plus souvent associée à une sensibilisation des mécano-récepteurs pariétaux principalement par les produits de dégranulation des mastocytes.

- La présence d'une micro-inflammation associée à une redistribution des terminaisons est un facteur majeur de l'hypersensibilité viscérale observée dans le SII.

- Des altérations de la perméabilité intercellulaire de l'épithélium intestinal sont en partie responsables de cet état micro-inflammatoire, ces altérations pouvant être générées par des facteurs locaux et systémiques

- Outre les facteurs locaux, des altérations non sélectives de la transmission spinale associée à un activation de la microglie sont à prendre en considération dans les douleurs viscérales chroniques comme le SII.