# Sensory and secretory responses to intestinal distension; implications for the pathophysiology of the irritable bowel syndrome

AKADEMISK AVHANDLING

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin vid Göteborgs universitet kommer att offentligen försvaras i Arvid Carlsson salen, Akademikum, Medicinaregatan 3

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av
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Fakultetsopponent:
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University of Oklahoma Health Sciences Center, USA

Avhandlingen baseras på följande delarbeten:

**I.** Larsson M.H, Simrén M, Thomas E.A, Bornstein J.C, Lindström E, Sjövall H
**Elevated motility-related transmucosal potential difference in the upper small intestine in the irritable bowel syndrome.**
*Neurogastroenterol. Motil. 2007; In press*

**II.** Larsson M.H, Sapnara M, Thomas E.A, Bornstein J.C, Svensson D.J, Lindström E, Sjövall H
**Pharmacological analysis of components of the change in transmural potential difference evoked by distension of rat proximal small intestine in vivo.**
*Manuscript.*

**III.** Larsson M.H, Arvidsson S, Ekman C & Bayati A.
**A model for chronic quantitative studies of colorectal sensitivity using balloon distension in conscious mice - effects of opioid receptor agonists.**
*Neurogastroenterol. Motil.* 2003; 15: 371-81.

**IV.** Larsson M.H, Rapp L & Lindström E.
**Effect of DSS-induced colitis on visceral sensitivity to colorectal distension in mice.**
*Neurogastroenterol. Motil.* 2006; 18: 144-152.

# ABSTRACT

## Sensory and secretory responses to intestinal distension; implications for the pathophysiology of the irritable bowel syndrome

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Irritable bowel syndrome (IBS) is a common gut disorder, characterized by abdominal pain and/or discomfort associated with disturbed bowel habits. The pathophysiology of IBS is complex and still largely unknown, although visceral hypersensitivity is frequently associated with the disease. The aim of the present thesis was to test alternative pathophysiological mechanisms involved in IBS and to establish relevant animal models.

In the first two papers, the role of intestinal secretomotor neurons was evaluated. The relation between intestinal pressure and transmural potential difference (PD) was used as a marker for activation of mechanosensitive secretomotor neurons. The pressure-PD relationship was studied by modified multilumen manometry in humans or by distension of an isolated duodenal segment in rats and mice. In the last two reports, a colorectal distension (CRD) model in mice was developed, and the effect of dextran-sodium sulphate (DSS)-induced colitis on visceral sensitivity was studied.

IBS patients had an increased propagation speed of the phase III of the migrating motor complex. Maximal PD during motor activity was elevated in both duodenum and jejunum and the return of PD to baseline levels at the end of phase III was prolonged in IBS patients. In anaesthetized rats and mice, the PD response to distension was biphasic, with an initial rapid phase followed by a sustained phase. Tetrodotoxin, a nerve-blocking agent, reduced both responses, implying that they are at least partially neurally mediated. The amplitude and rate of rise of the rapid response were reduced by ganglionic blockade with hexamethonium, by serosal lidocaine and by tachykinin receptor blockade (NK1). The sustained response was reduced by tachykinin receptor blockade (NK1 and NK3) and by blockade of the VIP-sensitive VPAC receptor. Electromyographic (EMG) recordings in mice correlated linearly with intracolonic balloon pressures between 10 and 80 mmHg. The response to CRD was reduced by μ- and κ-opioid receptor agonists, but was not affected by DSS-induced inflammation.

**Conclusions:** The data suggest an abnormal response of secretomotor neurons to phase III contractions in IBS patients. The complex time course and pharmacology seen in the animal experiments may reflect network behaviour of intrinsic primary afferent neurons. Most of the data can be explained by an equivalent circuit consisting of at least two parallel-coupled networks operating via tachykinin- and VPAC receptors. The sensory response to CRD can be readily monitored in conscious mice. However, DSS-evoked colitis does not appear to alter colorectal mechanosensitivity.

**Key words:** irritable bowel syndrome, secretion, transmucosal potential difference, migrating motor complex, colorectal distension, visceral sensitivity, colitis, enteric nervous system, rat, mouse

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