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Research Report

Proximal colon distension induces Fos expression in oxytocin-, vasopressin-, CRF- and catecholamines-containing neurons in rat brain

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ABSTRACT

Little is known about the chemical coding of the brain neuronal circuitry activated by nociceptive signals of visceral origin. We characterized brain nuclei activated during isovolumetric phasic distension of the proximal colon (10 ml, 30 s on/off for 10 min) in conscious male rats, using Fos as a marker of neuronal activation and dual immunohistochemistry to visualize co-localization of Fos expression and oxytocin (OT), arginine-vasopressin (AVP), corticotrophin-releasing factor (CRF) or tyrosine hydroxylase (TH). Proximal colon distension, compared with sham distension, induced a robust increase in Fos-like immunoreactive (IR) neurons in the paraventricular nucleus (PVN), supraoptic nucleus (SON) and accessory neurosecretory nuclei of the hypothalamus, nucleus of the solitary tract (NTS) and ventrolateral medulla (VLM), and to a lower extent, in the locus coeruleus (LC) and Barrington nucleus. Fos-IR neurons in the PVN after colon distension were identified in 81% of OT-IR, 18% AVP-IR and 16% CRF-IR neurons, while in the SON it represented 36% of OT-IR and 16% AVP-IR. Catecholaminergic cell groups in the pons (LC) and medulla (VLM, NTS) were also activated by proximal colon distension. Of the TH-IR neurons in VLM and NTS, 74% and 42% respectively were double labeled. These results indicate that colon distension stimulates OT-, AVP- and CRF-containing hypothalamic neurons, likely involved in the integration of colonic sensory information to modulate autonomic outflow and pain-related responses. Activation of medullary catecholaminergic centers might reflect the afferent and efferent limbs of the functional responses associated to visceral pain.

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Abbreviations: AP: area postrema; AVP: arginine-vasopressin; CRF: corticotrophin-releasing factor; DMV: dorsal motor nucleus of the vagus; DVC: dorsal vagal complex; IR: immunoreactive or immunoreactivity; LC: locus coeruleus; NTS: nucleus of the solitary tract; OT: oxytocin; PVN: paraventricular nucleus of the hypothalamus; SON: supraoptic nucleus; TH: tyrosine hydroxylase; VML: ventrolateral medulla

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1. Introduction

Enhanced colonic and rectal sensitivity to distension is frequently encountered as a clinical manifestation of irritable bowel syndrome (IBS) (Bouin et al., 2002; Drossman et al., 2002; Verne et al., 2003). In an attempt to develop experimental models that recapture this feature, the distension of the rectum and distal colon (colorectum) in rats has been extensively used to assess visceral pain and the underlying mechanisms of colonic sensitivity (Mayer et al., 2008; Ness and Gebhart, 1990). Processing of signals from visceral organs recruits neurons and transmitters in the brain that are important mechanisms regulating adaptive autonomic, neuroendocrine and pain-related responses. We previously used a model of proximal colon distension in conscious rats to study the neuronal pathways activated during noxious visceral mechanical stimulation (Martinez et al., 1998, 2006). This model uses a chronically implanted balloon in the proximal half of the colon, thus avoiding acute procedures of balloon insertion under anesthesia that cause interfering effects on neuronal activation (Martinez et al., 2006; Ness and Gebhart, 1988). After phasic distension of the proximal colon, neuronal activation, demonstrated by Fos-like immunoreactivity (IR), was found significantly increased in specific brain areas and spinal cord lumbosacral segments (Martinez et al., 1998, 2006). Main brain nuclei activated by distension of the proximal colon were located in the hypothalamus [paraventricular nucleus (PVN) and supraoptic nucleus (SON)] and the brainstem [nucleus tractus solitarius (NTS), ventrolateral medulla (VLM) and locus coeruleus (LC)–Barrington nucleus complex] (Martinez et al., 2006). These areas represent, respectively, centers of integration of neuroendocrine responses and the origin of efferent autonomic pathways involved mainly in the

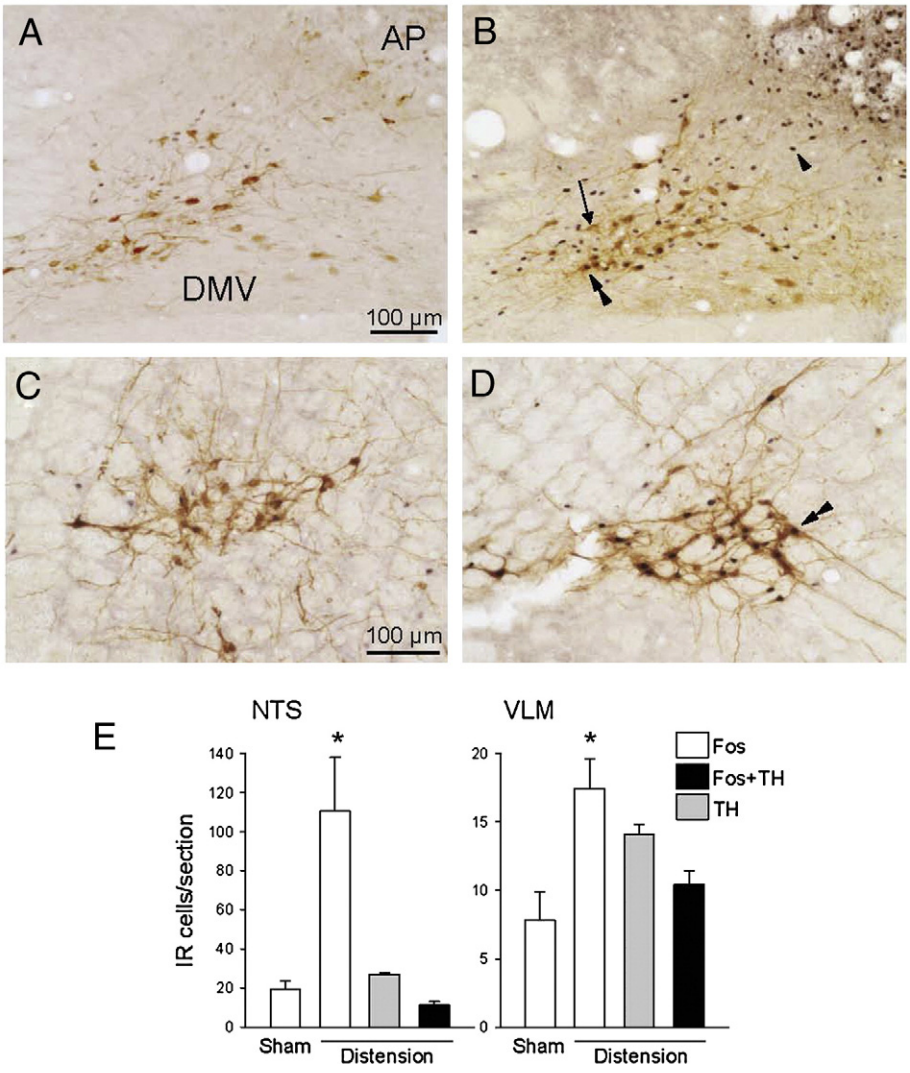

Fig. 1 – Double immunohistochemical staining of Fos- and TH-IR in the NTS (A and B) and VLM (C and D) and cell count (cells per section) in the same areas (E) 60 min after phasic proximal colon distension for 10 min (B and D) or sham distension (A and C) in conscious rats. Fos-IR is localized in nuclei and appears as dark blue-black dots and TH-IR is found in the cytoplasm as brown color. Arrow: TH-IR; arrowhead: Fos-IR; arrowheads: Fos/TH-IR; AP: area postrema; DMV: dorsal motor nucleus of the vagus. Data are mean ± SEM; $n = 5$; $^{*}P < 0.05$ vs sham distension group. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)