

Projections of calcitonin gene-related peptide immunoreactive neurons in the vagal ganglia of the rat

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ARTICLE INFO

Article history:

Received 20 August 2010

Received in revised form 1 November 2010

Accepted 9 November 2010

Available online 17 November 2010

Keywords:

Immunohistochemistry

Retrograde tracing

Nociceptive neurons

Nucleus tractus solitarii

Jugular ganglion

Vagus nerve

Vagal sensory neurons

ABSTRACT

We have studied the connections of calcitonin gene-related peptide immunoreactive (CGRP-ir) sensory neurons in the ganglia of the vagus nerve. Many CGRP-ir neurons were identified in the jugular ganglion located in the cranial cavity, while fewer CGRP-ir neurons were found in the nodose ganglion located at the level of the jugular foramen. Application of Fluorogold to the cut end of the cervical vagus nerve resulted in many Fluorogold-labeled neurons in both the jugular and the nodose ganglia. Application of Fluorogold to the cut end of the subdiaphragmatic vagus nerve resulted in Fluorogold-labeled neurons mostly in the nodose ganglion with only a few labeled neurons in the jugular ganglion. Injection of Fluorogold into the heart resulted in Fluorogold-labeled neurons in both the jugular and the nodose ganglia. Double labeling combining CGRP immunohistochemistry and Fluorogold retrograde tracing showed that in cases of both the application of Fluorogold to the cut end of the cervical vagus nerve and the injection of Fluorogold into the heart, about 40% of the Fluorogold-labeled neurons in the jugular ganglion expressed CGRP-like immunoreactivity. These results indicate that many CGRP-ir neurons in the jugular ganglion innervate the cervical and thoracic visceral organs, including the heart, but only a few CGRP-ir neurons project to the abdominal visceral organs.

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1. Introduction

Calcitonin gene-related peptide immunoreactive (CGRP-ir) sensory ganglion neurons are thought to send nociceptive information to the brainstem (Gibbins et al., 1985; Lundberg et al., 1985; Skofitsch and Jacobowitz, 1985; Hammond and Ruda, 1991). Many CGRP-ir fibers and terminals are characteristically distributed in the lateral, the intermediate, the dorsal, the interstitial, and the commissural subnuclei of the nucleus tractus solitarii (NTS) (Kawai et al., 1985; Kruger et al., 1988). These CGRP-ir fibers and terminals are considered to come from the glossopharyngeal nerve or the vagus nerve, but not from the trigeminal nerve (Sugimoto et al., 1997). Our previous study revealed that the CGRP-ir neurons in the superior glossopharyngeal ganglion that innervate the oral and the pharyngeal regions project to the rostral part of the NTS (Hayakawa et al., 2010).

Transganglionic anterograde tracing studies using cholera toxin subunit b (CT) or wheat germ agglutinin (WGA) conjugated to horseradish peroxidase (HRP) have revealed that the central subnucleus receives sensory afferents mainly from the esophagus, the gelatinous subnucleus from the stomach, the interstitial

subnucleus from the larynx and the trachea, and the commissural subnucleus from the heart (Altschuler et al., 1989; Hayakawa et al., 2001, 2003). The distribution of CGRP-ir terminals in the NTS overlapped with the afferent terminals of the neurons that innervate the heart and the larynx, but not the esophagus and the stomach. Double-labeling studies combining immunohistochemistry and retrograde tracers have shown that there are CGRP-ir neurons in the jugular ganglion that innervate the cervical esophagus and the trachea, but only a few CGRP-ir neurons that innervate the lung (Green and Dockray, 1987). Thus, it is likely that the nociceptive CGRP-ir neurons of the vagal ganglia innervate the cervical and the thoracic visceral organs. On the other hand, many CGRP-ir fibers are found in the mucous membrane of the gastrointestinal tract, the trachea, and the heart (Parsons and Neel, 1987; Berthoud and Neuhuber, 2000; Hayakawa et al., 2009). These organs receive sensory afferent projections from not only the vagal ganglion neurons, but also spinal dorsal root ganglion neurons (Hopkins and Armour, 1989; Kuramoto and Kuwano, 1995; Dutsch et al., 1998; Berthoud and Neuhuber, 2000). However, it is not clear whether the CGRP-ir vagal ganglion neurons innervate these visceral organs, and which vagal ganglion neurons send fibers to these organs.

The caudal part of the NTS receives heavy projections from the vagal sensory neurons that innervate the heart (Xie et al., 1999; Corbett et al., 2005). The distribution of CGRP-ir terminals in the

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caudal part of the NTS overlaps with the region that receives afferent projections from the heart (Batten et al., 1989; Sugimoto et al., 1997). Immunohistochemical studies have reported that there are CGRP-ir neurons in the jugular and the nodose ganglia (Helke and Hill, 1988; Ichikawa et al., 2007). However, the number of CGRP-ir neurons in the nodose ganglion and the jugular ganglion

seem to be small compared to the number of the CGRP-ir fibers and terminals in the caudal NTS. The previous authors did not mention the ganglion neurons of the vagus nerve located in the cranial cavity. In the glossopharyngeal ganglia, numerous CGRP-ir neurons are found in the superior glossopharyngeal ganglion located in the cranial cavity (Hayakawa et al., 2010). The general

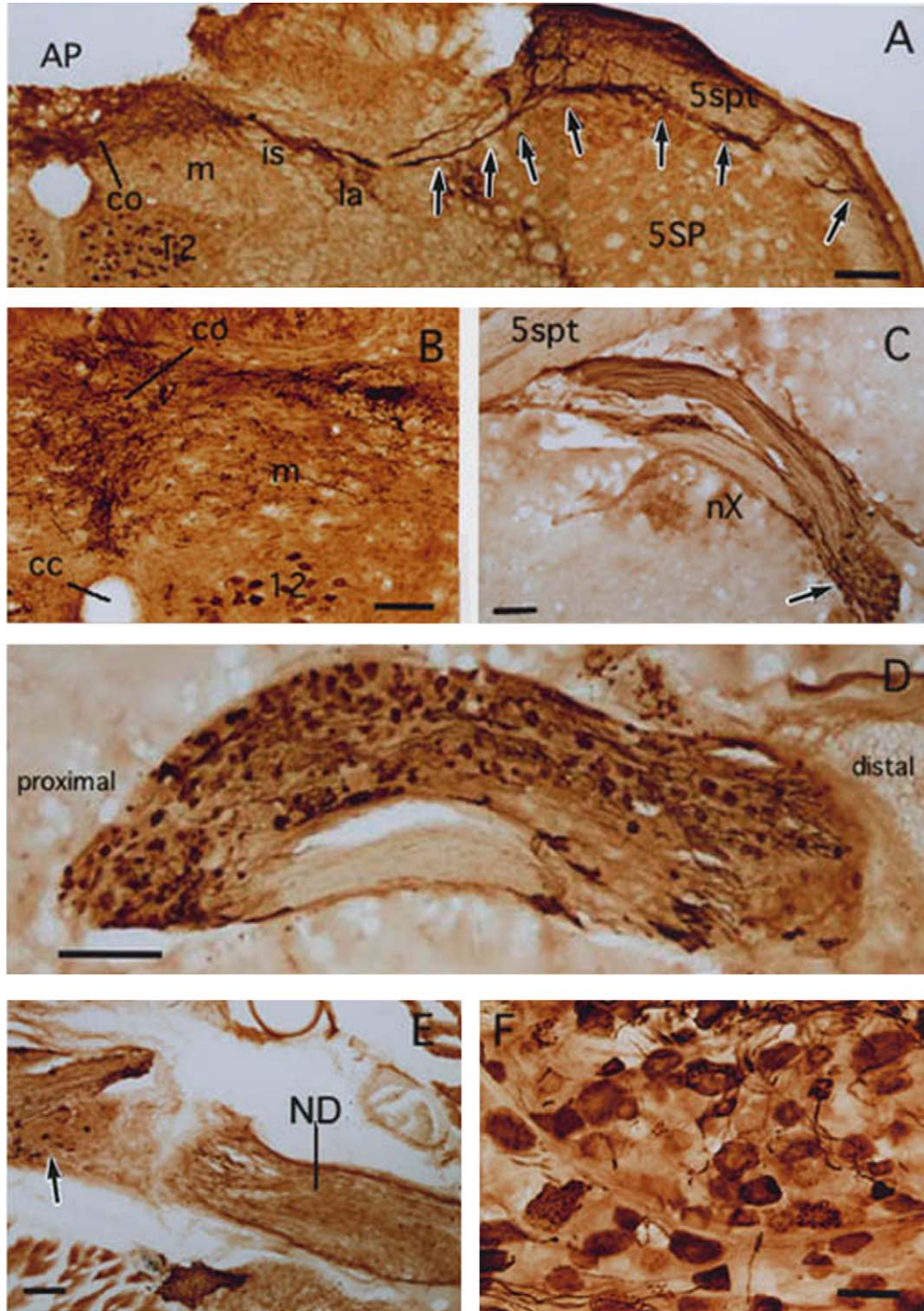


Fig. 1. Distribution of CGRP in the left nucleus tractus solitarius (NTS) and proximal vagus nerve sensory ganglia. (A) CGRP-ir fibers (arrows) running through the spinal trigeminal tract (5spt) and the spinal trigeminal nucleus (5SP), and entering into the lateral (la), the interstitial (is), the dorsal part of the medial (m) and the commissural (co) subnuclei of the NTS. 12, hypoglossal nucleus; AP, area postrema. (B) Numerous CGRP-ir fibers and terminals in the commissural subnucleus (co) of the NTS. 12, hypoglossal nucleus; cc, central canal; m, medial subnucleus of the NTS. (C) CGRP-ir fibers in the vagus nerve (nX) adjacent to the spinal trigeminal tract (5spt). Horizontal section. Arrow indicates CGRP-ir neurons in the jugular ganglion. (D) Numerous CGRP-ir neurons in the jugular ganglion located in the cranial cavity. (E) CGRP-ir neurons (arrow) located proximal to the nodose ganglion (ND). Note that only a few CGRP-ir neurons were found in the nodose ganglion. (F) High-power photomicrograph of CGRP-ir neurons in the jugular ganglion. Scale bars: 250 μ m in (A and D), 100 μ m in (B), 200 μ m in (C and E), and 40 μ m in (F).

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