Title: NEURAL PATHWAYS MEDIATING RESPONSES TO VISCERAL STRESS: NEUROANATOMICAL STUDIES IN THE RAT BRAIN

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Introduction. The use of pharmacologic agents to blunt bodily responses to surgical and anesthetic manipulations has thus far been conducted without knowledge of specifically where these agents might be acting. Indeed, until very recently, the neural structures which normally mediate stress responses in intact animals had not even been initially identified, much less characterized. Recent developments in neuroanatomical tract-tracing methodology have made it possible to elucidate pathways within the nervous system with greater sensitivity and specificity than was previously possible. We herein report the results of studies on the projection system which originates from the main vagal sensory nucleus in the lower brainstem. This system is among the most likely to mediate autonomic and endocrine responses to surgical and anesthetic stress.

Methods. Neuroanatomical tract-tracing studies were carried out in thirty-nine adult albino rats. Anterograde tracing experiments were performed with tritiated leucine and proline as tracers; an autoradiographic technique was used to visualize their final location. These experiments indicated the course and destination of fibers arising from the neurons injected with the label. Retrograde tracing experiments were performed by the horseradish peroxidase method, with diaminobenzidine as the visualizing reagent. These experiments revealed the neurons giving rise to fibers projecting to or through the areas injected, and provided information complementary to the anterograde studies. Finally, immunohistochemical localization of somatostatin was carried out in the hypothalami of four albino rats, using a peroxidase-antiperoxidase technique. The methodology for all techniques used is detailed elsewhere (1,2).

Results. Taken together, the experiments indicate that the central projection system arising from the main vagal sensory nucleus, the caudal portion of the nucleus of the solitary tract; (nts), comprises primarily five structures, which might be considered the "pipeline" of the vagal afferent mechanism. These structures are, in the brainstem, the nts and the parabrachial area, and, in the forebrain, the central nucleus of the amygdala, the bed nucleus of the stria terminalis, and the paraventricular nucleus of the hypothalamus (pvn). The pvn itself can be subdivided into at least twelve discrete neuron populations, each with unique chemical and connectional properties. For example, the lateral magnocellular portion of the pvn contains antidiuretic hormone (ADH) and projects axons to the posterior pituitary. The periventricular parvocellular portion contains somatostatin and projects to the median eminence, the entry zone to the pituitary portal circulation. Both direct and indirect projections from the nts impinge upon the latter cell group, very probably giving information carried by the sensory fibers of the vagus and glossopharyngeal nerves important access to mechanisms regulating growth hormone secretion. The ADH-containing cell group does not receive direct fiber projections onto its cell bodies from the nts or the parabrachial area. Our data suggests that such projections may exist onto dendrites of ADH neurons, or onto neighboring cells which might act as "interneurons". Other parts of the pvn project directly to the spinal cord. Others have shown that these projections terminate within the preganglion sympathetic neurons of the intermediolateral horn. Our data support the existence of at least two groups of spinal-projecting neurons within the pvn: the dorsal parvocellular group projects to upper thoracic spinal cord, and probably modulates heart rate and inotropic responses, while the ventral parvocellular group projects to low thoracic/high lumbar cord and may well influence the adrenal and the kidney via preganglionic sympathetic outflow.

Discussion. The highly specific tracing of neural pathways paves the way for an understanding of the mechanisms underlying stress responses and the ways in which drugs modulate these responses. For example, the present data suggest a pathway which should be studied with respect to ADH responses to positive pressure ventilation: the pathway originates in left atrial stretch receptors and proceeds through the vagus, nts, parabrachial area, pvn, and to the neurohypophysis. The effect of ventilation in reducing left atrial stretch (by compressing pulmonary vessels) could be communicated to the brain as hypovolemia, and this oligosynaptic pathway could activate renal antidiuretic mechanisms aimed at conserving blood volume. If this proves to be the case, then the chemical characterization of this pathway could lead to pharmacologically blunting such "inappropriate" secretion.

References.

1. Koh ET:Anatomical evidence of a visceral map within the paraventricular nucleus of the hypothalamus. PhD thesis, Harvard, 1981.
2. Ricardo JA, Koh ET: Brain Research 153 (1978) 1-26.