

Saper C B, Loewy A D, Swanson L W & Cowan W M. Direct hypothalamo-autonomic connections. *Brain Res.* 117:305-12, 1976.

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The hypothalamus regulates all of the body's organ systems and coordinates them with ongoing behavior and emotion. This paper identified the anatomical basis for hypothalamic control of the autonomic nervous system. [The *SC1*® indicates that this paper has been cited in over 495 publications.]

## Hypothalamic Control of the Autonomic Nervous System

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November 22, 1989

The importance of the hypothalamus in the coordination and regulation of the autonomic nervous system has been understood since the turn of the century. However, when I began my graduate studies in the early 1970s, the neural pathways that mediate this control were not known. Classical neuroanatomical methods had failed to demonstrate direct projections from the hypothalamus to autonomic control areas in the brain stem and spinal cord, convincing many workers that the pathways involved polysynaptic relays in the mid-brain reticular formation.<sup>1</sup> This organization would make it difficult if not impossible to unravel the intricacies of autonomic control.

A new generation of neuroanatomical tracing techniques, introduced in the early 1970s by my graduate adviser, W. Maxwell Cowan, and several of his colleagues, offered the opportunity to reexamine this problem.<sup>2</sup> The axonal transport methods were much more sensitive than the earlier techniques that relied on neuronal degeneration after injury. Larry Swanson, then a postdoctoral fellow, and I had begun to apply these methods to the hypothalamus when, in 1975, H.G.J.M. Kuypers and V.A. Maisky provided the first convincing evidence for a long descending projection from the hypothalamus to the spinal cord.<sup>3</sup> They

did not, however, identify the cells of origin of the pathway or their terminal distribution.

About this same time, Arthur D. Loewy and Harold Burton, also at Washington University, were examining brain stem projections to the spinal cord using the retrograde transport of horseradish peroxidase. Intrigued by the observations of Kuypers and Maisky, Arthur cut and stained sections through the hypothalamus in a few animals. One day he called me into his office to help him identify the hypothalamic cell group that was retrogradely labeled.

As soon as I looked through the microscope at the labeled cells in the paraventricular nucleus, I knew that this was a major finding. The paraventricular nucleus had previously been considered mainly a neuroendocrine structure, secreting oxytocin and vasopressin from its axon terminals in the posterior pituitary gland. The possibility now was apparent that a single nucleus, if not individual neurons in the hypothalamus, might control and integrate both autonomic and endocrine responses. Furthermore, our findings raised the possibility that the hormones vasopressin and oxytocin might serve as neurotransmitters in autonomic control (a conjecture that later proved to be correct).<sup>4,5</sup>

Within a few months of feverish activity, our tracer studies had demonstrated that the neurons in the paraventricular nucleus and lateral hypothalamus contact autonomic control areas in the brain stem and the spinal cord, including the preganglionic neurons of both the sympathetic and parasympathetic nervous system. We quickly published our results, which appeared nearly simultaneously with an independent study by Michael B. Hancock also establishing the paraventricular nucleus as a source of spinal projections.<sup>6</sup>

Within a year of its appearance, this study became frequently (and sometimes inappropriately) cited as providing an anatomical basis for forebrain control of the autonomic nervous system. In retrospect, I believe our results were readily accepted because they provided a simple and straightforward answer to an important biological question that had previously seemed unapproachable.

1. Nauta W J H & Haymaker W. Hypothalamic nuclei and fiber connections. (Haymaker W, Anderson E & Nauta W J H, eds.) *The hypothalamus*. Springfield, IL: Thomas, 1969. p. 136-209. (Cited 295 times.)
2. Cowan W M, Gottlieb D I, Hendrickson A E, Price J L & Woolsey T A. The autoradiographic demonstration of axonal connections in the central nervous system. *Brain Res.* 37:21-51, 1972. (Cited 1,200 times.)
3. Kuypers H G J M & Maisky V A. Retrograde axonal transport of horseradish peroxidase from spinal cord to brain stem cell groups in the cat. *Neurosci. Lett.* 1:9-14, 1975. (Cited 435 times.)
4. Swanson L W & Kuypers H G J M. The paraventricular nucleus of the hypothalamus: cytoarchitectonic subdivisions and organization of projections to the pituitary, dorsal vagal complex and spinal cord as demonstrated by retrograde double-labeling methods. *J. Comp. Neurol.* 194:555-70, 1980. (Cited 320 times.)
5. Cechedo D F & Saper C B. Neurochemical organization of the hypothalamic projection to the spinal cord in the rat. *J. Comp. Neurol.* 272:579-604, 1988.
6. Hancock M B. Cells of origin of hypothalamo-spinal projections in the rat. *Neurosci. Lett.* 3:179-84, 1976. (Cited 90 times.)