

# The neuroanatomy revolution of the 1970s and the hypothalamus

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By the 1960s, a vast amount of physiological evidence indicated that the hypothalamus plays a critical role in the expression of behaviors that are essential for the survival of the individual and for the species as a whole, along with the coordinated expression of appropriate autonomic and neuroendocrine responses. Karplus and Kreidl provided the seminal observations related to autonomic responses beginning in the 1910s. The field in general was advanced enormously in the 1930s and 1940s by Ranson and by Hess (who was awarded the Nobel Prize in 1949), and it then matured in the 1950s and 1960s under the leadership of Neal Miller, S.P. Grossman, Elliot Stellar, Phillip Teitelbaum and many others [1].

In contrast, very little was known with certainty about the structural organization of neural circuits mediating this integration of behavioral, autonomic, and neuroendocrine responses. The most complex fiber system in the brain, the medial forebrain bundle, courses through the hypothalamus, which was viewed as quite undifferentiated—as perhaps a rostral extension of the reticular formation. What little was known about the neuroanatomy of the mammalian hypothalamus was summarized brilliantly by Nauta and Haymaker in 1969 [4], and their conclusions bear almost no resemblance to what has been learned since.

The reason for this change can be traced to the neuroanatomy revolution of the 1970s: the introduction of methods based on cell biology and chemistry, which included pathway tracing via anterograde and/or retrograde axonal transport, and the immunohistochemical localization of neurotransmission-related molecules [8]. Combinations of these methods allowed dissection of hypothalamic circuits at a resolution previously unimagined.

I had begun re-examining hypothalamic connections with the autoradiographic method as a postdoc in W.M. Cowan's laboratory in St. Louis, MO, guided by Nauta and Haymaker's conclusion that the hypothalamus influences autonomic and other responses via a series of short, descending, multisynaptic projections through the reticular formation. Then one day in 1975 I picked up the single most influential paper I remember having read—a brief report in the first issue of *Neuroscience Letters* by Kuypers and Maisky [2], who had gone to the heroic length of making some 150 HRP injections in the spinal cord of individual cats and had found retrogradely labeled neurons in an unidentified medial region of the hypothalamus. They had discovered a direct projection from hypothalamus to spinal cord, which we soon showed arises partly

in the paraventricular nucleus and ends in the intermediolateral column [5] and marginal zone [6].

This was one of many surprises related to hypothalamic circuitry revealed by the new anatomical methods—for example, another projection from the paraventricular nucleus—to the median eminence [10]; a direct retinal input to the suprachiasmatic nucleus [3]; the identification of subicular complex not hippocampus as the origin of fornix inputs to the mammillary body [9]; and the immunohistochemical characterization of neuroendocrine motoneuron pools in and around the periventricular hypothalamus, based on the earlier Nobel prize-winning work of DuVigneaud, Schally, and Guillemin [7]. The time has come for another cycle of physiological work to clarify the functional dynamics of this newly characterized circuitry.

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