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A physiological perspective on the neuroscience of eating

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HIGHLIGHTS

- An essay on the occasion of the SSIB distinguished career award, discussing
- The 'physiological' perspective in analyses of endocrine controls of eating
- Molecular methods that comprise the cutting edge of the neuroscience of eating
- Future directions in neuroscience of eating

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ABSTRACT

I present the thesis that 'being physiological,' i.e., analyzing eating under conditions that do not perturb, or minimally perturb, the organism's endogenous processes, should be a central goal of the neuroscience of eating. I describe my understanding of 'being physiological' based on [i] the central neural-network heuristic of CNS function that traces back to Cajal and Sherrington, [ii] research on one of the simpler problems in the neuroscience of eating, identification of endocrine signals that control eating. In this context I consider natural meals, physiological doses and ranges, and antagonist studies. Several examples involve CCK. Next I describe my view of the cutting edge in the molecular neuroscience of eating as it has evolved from the discovery of leptin signaling through the application of optogenetic and pharmacogenetic methods. Finally I describe some novel approaches that may advance the neuroscience of eating in the foreseeable future. I conclude that [i] the neuroscience of eating may soon be able to discern 'physiological' function in the operation of CNS networks mediating eating, [ii] the neuroscience of eating should capitalize on methods developed in other areas of neuroscience, e.g., improved methods to record and manipulate CNS function in behaving animals, identification of canonical regional circuits, use of population electrophysiology, etc., and [iii] subjective aspects of eating are crucial aspects of eating science, but remain beyond mechanistic understanding.

1. Introduction

It was a great honor to be selected by the Society for the Study of Ingestive behavior [SSIB] for the 2013 Distinguished Career Award. Receiving the award surrounded so many highly respected colleagues, many of whom I count among my closest friends, was a wonderful moment that I shall always cherish.

As part of the award, SSIB invited me to contribute something worthwhile to the Special Issue of *Physiology and Behavior* that serves as the Annual Meeting proceedings. This essay is the result. It has two parts. In Section 2, I give thanks to the mentors and colleagues who made decisive contributions to my career. In Sections 3–7, I consider the neuroscience of eating from what I call a 'physiological' perspective. In the usual way, my perspective is strongly colored by my own education and research interests, in particular, endocrine controls of eating. Nevertheless, as I argue, it has wider significance. The essay is impressionistic rather than systematic, for which I beg the reader's indulgence. I do not review my own work here, but refer the interested reader elsewhere [glucagon [55,77], estrogens [6,8], synergy [58]].

2. Mentors and colleagues

2.1. Charles G. Gross

I began experimental psychology after my initial plan to do mathematics foundered on Riemann's geometry of n-dimensional "manifolds," a cornerstone of modern mathematics that had been introduced a century earlier [120]. One of my first courses was Charles G. Gross's "physiological psychology." Then an assistant professor, Charlie went on to a distinguished career at Princeton University and was elected to the National Academy of Sciences of the USA in 1998. His logical, programmatic analysis of the neural bases of perception and behavior was

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enormously seductive. An amateur historian [73], he also introduced us to many giant figures in neuroscience, including Santiago Ramón y Cajal [26] and Charles Sherrington [36,139]. The first sight of one of Cajal's Golgi-stained brain sections was unforgettable [Fig. 1]; even more impressive were the brilliant insights about CNS function that Sherrington garnered from the study of spinal reflexes [Fig. 2]. Their contributions to the fine structure and information-processing mechanisms of the CNS are the foundation of the central heuristic of neuroscience [18,24,25,35,46,76,109,136]. Charlie also described some of the latest results in his specialty, visual science [Fig. 3], then as now one of the most advanced areas of neuroscience [45,74,87]. These lectures gave me a vocation, and their indelible imprint was a constant reminder to try to infuse my own lectures with both the intellectual structure of the material and my own fascination with it.

2.2. Erwin Scharrer

After military service, I entered graduate school at Brown with the intent of studying biological motivation. Unfortunately, my advisor became chronically ill and eventually gave up his position. This left me adrift, and I left Brown without completing my degree. I found some papers on eating [130,150] by a German scientist named Erwin Scharrer and volunteered to work in his lab in Munich. Erwin, probably not coincidentally, immediately did just what I needed — he put me to work on a project involving a number of different methods [64] and, finally, I began to learn what it meant to be a bench scientist. Erwin stimulated me intellectually as well, and encouraged me to return to Brown to finish my PhD and then to get a fellowship to return to his lab. I did so. Immediately after my return to Munich, Erwin hired a remarkably talented student, Wolfgang Langhans, who became very enthusiastic about the field despite that for almost a year nothing we tried together worked. His persistence paid off — his DVM thesis earned the German Nutrition Society's Hans-Adolf-Krebs Award as the outstanding thesis of 1980 [63,96]. Erwin received the 2006 SSIB Distinguished Career Award.

2.3. Gerard P. Smith

I returned to the USA for a second post-doctoral fellowship with Gerry Smith at the Bourne Behavioral Research Laboratory, New York Hospital-Weill Cornell Medical College. The Bourne Lab was a

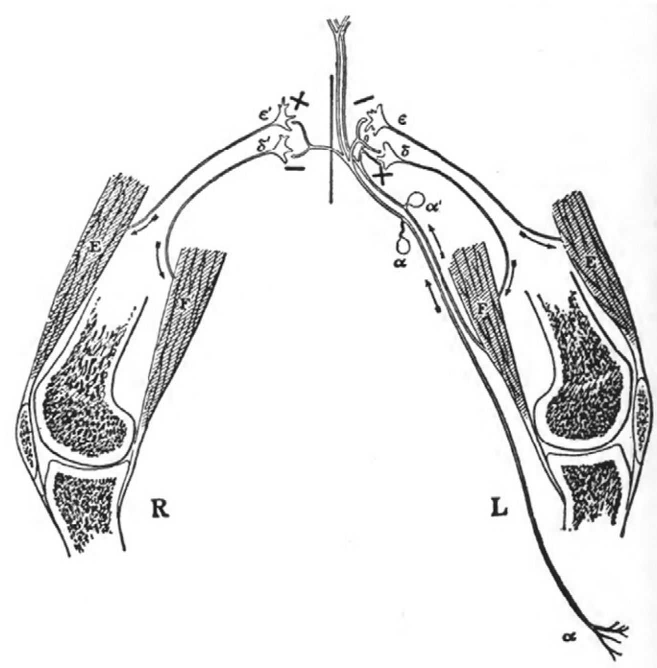

Fig. 2. Sherrington's schematic of the synaptic circuitry of the flexor and crossed-extensor reflexes of the dog [Fig. 37 in [139]]. Shown are lower motor neurons [ε, δ, ε′ and δ′] innervating flexor [F] and extensor [E] muscles of the right [R] and left [L] knee joints and sensory neurons arising in the skin of the left leg [α] and in a left knee flexor [α′]. Noxious stimulation that stimulates the cutaneous afferent or muscle stretch stimulating the muscle afferent both stimulates [+] the ipsilateral flexor and the contralateral extensor and inhibits [−] the ipsilateral extensor and contralateral flexor. Sherrington was aware that the inhibitory control involved interneurons, but omitted them here for clarity. The somatic lower motor neurons in the brain stem and spinal cord that contribute particular reflexes were termed "the final common pathway." One of the important results that led Sherrington to his conception of synaptic information processing was the differences between responses elicited by stimulation of afferents controlling the reflex versus stimulation of final common path neurons, for example, the endogenous rhythm of the scratch reflex elicited by the former but not the latter. Analysis of another characteristic, synaptic delay, later became an important part of the demonstration of chemical neurotransmission [35]. Sherrington's view that behavior results from synaptic competition for control of final common pathways, and by extension control of "intermediate" pathways at every level of CNS, remains the basic heuristic of CNS function [24,25,35,46,109,136]. Analyses of synaptic information processing in neural networks underlying eating have begun [32,153].

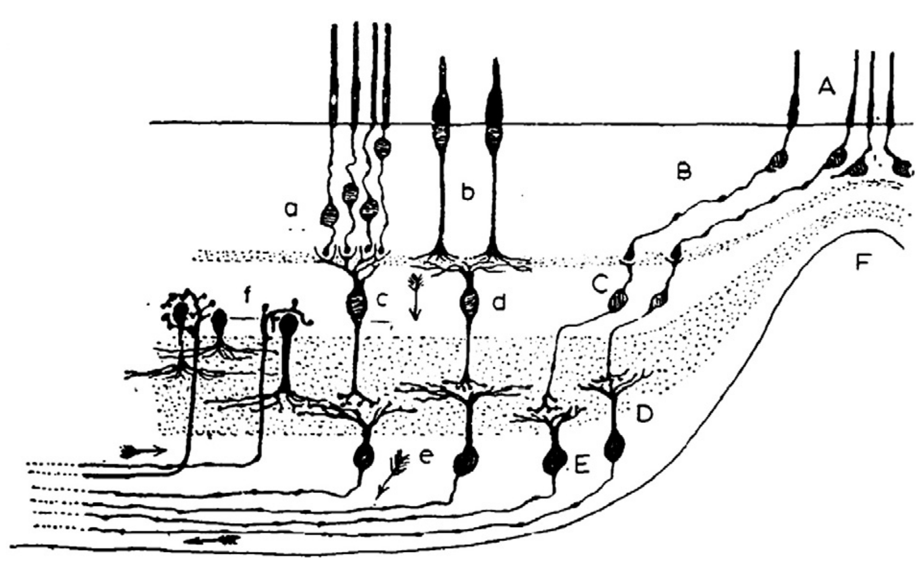

Fig. 1. Drawing of a Golgi-stained section of vertebrate retina presented by Cajal during his Nobel-prize award lecture [26]. Compare to Fig. 14, in which the cell types are labeled. Cajal's representations of the microanatomy of different tissues, different species, during development, etc., were among the strongest evidence leading to acceptance of the neuron doctrine, that individual nerve cells are the structural and functional unit of the CNS, and led Sherrington in 1897 [138] to name the synapse and propose synaptic function to underlie neuronal information processing [35,76,136].