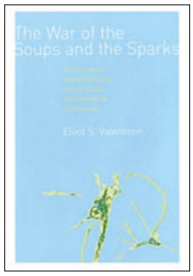
Synaptic transmission makes history



The War of the Soups and the Sparks

By Elliot S Valenstein

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Reviewed by Nicholas C Spitzer

This tidy volume recounts an exciting and important piece of neuroscience history, when investigators strove to understand the basis of synaptic transmission. The recognition of Cajal's 'neuron doctrine' (rewarded with the Nobel Prize in 1906) created a vexing problem: given that each neuron is a separate entity, how do they communicate? Was it chemical, via 'soups' – or electrical, via 'sparks'? Debate raged back and forth between pharmacologists and neurophysiologists. Elliot Valenstein colorfully describes the varied educational backgrounds and richly textured personalities of the key figures, making for lively reading.

One of the most stimulating stages in scientific research is the formulation of the approach to the problem to be solved. Appropriate framing of a problem is crucial to its solution. How can the problem be reduced to tractable components, what is the best preparation to investigate it, and what methods seem most appropriate? Valenstein vividly recounts the trajectory of investigation as the ways to solve the problem became clearer, and the answer drew closer. We learn about missed opportunities, some of which were seized successfully later on, and the blind alleys that led away from the answers.

The observation that drugs could mimic the effects of nerve stimulation was a useful clue and led to the notion that they combine with 'receptor substances'. Demonstration first by Otto Loewi, and then by Henry Dale, of a substance released upon nerve stimulation that could mimic the effect of nerve stimulation was a giant leap and brought them the Nobel Prize in 1936, even though it was established only later whether the substance was released from the nerve or the muscle. The criteria that qualify a substance as a true neurotransmitter gradually became clear as the investigation progressed: synthesis and storage presynaptically, release on nerve stimulation, quantitative mimicry of the effect of nerve stimulation, identical pharmacology to that of responses to nerve stimulation, and a mechanism for removal of the compound.

Dale discovered in 1914 that acetylcholine was effective in mimicking parasympathetic responses, but then concluded that there was no evidence for acetylcholine in the body—it was just a great drug. He envisioned that "its "extraordinarily evanescent" action" could be due to rapid hydrolysis, but refrained from speculating that parasympathetic nerves release acetylcholine. This work set the stage for Loewi, whose idea for the experiment demonstrating neurohumoral transmission appeared in a dream. In 1921, Loewi collected the effluent saline from a frog heart after vagus nerve stimulation and showed that it caused slowing of the heartbeat of a second, uninnervated heart. Loewi (in 1926) and Dale (in 1929) subsequently provided evidence that 'Vagusstoff', or 'vagus material', was acetylcholine. Fortune smiled on Loewi because subsequent work identified numerous ways in which the experiment could have failed, but the responses of his critics spurred him on to carry out controls and further key experiments to firmly establish neurohumoral transmission in the heart.

Did chemical transmission act only to regulate the pacing of the heart? Dale's interest in acetylcholine was reawakened by Loewi's discoveries. Skeletal muscle contracted after local application of acetylcholine, but whether or not motor nerves secrete it remained unknown. Dale needed a sensitive method for detection of the small amounts of acetylcholine released from nerve terminals and became aware of Wilhelm Feldberg's sensitive leech muscle preparation. When Feldberg had to leave Germany early in 1933, Dale arranged to bring him to London. Hungarian leech muscle sensitized with eserine proved much more sensitive than the English, German or Israeli leech muscle preparations, and permitted quantitative estimates of the acetylcholine present after nerve stimulation. Loewi had made the initial speculative leap, guided in part by Dale's earlier findings. Dale, in turn, demonstrated the more general role of chemical transmission at the neuromuscular junction and in the autonomic nervous system.

Even in the face of this evidence, leading neurophysiologists did not believe that chemical transmission was rapid enough to account for impulse transmission in the brain. Led by John Eccles, they marshaled evidence for electrical transmission. Eccles and Dale were active sparring partners, and the good humor of their exchanges is delightful to read. Each recognized that their disputes provided useful incentive for more and better experiments. In 1951, Eccles, Coombs and Brock made intracellular recordings from spinal motor neurons while stimulating the inhibitory Renshaw cells, and they obtained evidence for membrane hyperpolarization and amplification of the response, neither of which could be simply accounted for by electrical transmission. They concluded that "inhibitory synaptic action is mediated by a specific transmitter substance." Valenstein is surprised by the persistent reluctance to accept chemical neurotransmitters in the brain, but the scientists who had established chemical transmission in the peripheral nervous system were all too aware of the difficulties in establishing this role in the CNS. As evidence began to emerge in the 1950s suggesting that mental illness might be caused by abnormalities in brain chemistry, the neurophysiologist Ralph Gerard is said to have remarked that "there is no twisted thought without a twisted molecule".

In an era in which we seem wedded to sophisticated instrumentation for our experiments, it is worth noting that the pivotal successes of Loewi and Dale entailed the imaginative use of simple bioassays. The book is a fun, fast read, covering more than the title implies, and it can substantially broaden the modern reader's thinking about useful experimental approaches to solving problems.

Nicholas Spitzer is at the Neurobiology Section, Division of Biological Sciences, University of California, San Diego, 9500 Gilman Drive, La Jolla, California 92093-0357, USA.
e-mail: nspitzer@ucsd.edu