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CC/NUMBER 49
DECEMBER 9, 1985

Kandel E R, Spencer W A & Brinley F J, Jr.—I; **Kandel E R & Spencer W A**—II; **Spencer W A & Kandel E R**—III & IV. Electrophysiology of hippocampal neurons. I, II, III & IV. *J. Neurophysiology* **24**:225-42; 243-59; 260-71; 272-85, 1961.
[Lab. Neurophysiology, Natl. Insts. Mental Health, NIH, Bethesda, MD]

The application of intracellular recording to the study of identified pyramidal cells of the hippocampus revealed a family of novel cellular properties. [The *SCI*® indicates that these papers have been cited over 910 times in 735 publications since 1961.]

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October 2, 1985

Reading these papers brings back the sense of privilege and excitement I experienced in collaborating with Alden Spencer. Although we did not collaborate again, we continued our friendship and interacted daily, first at NYU and then at Columbia, where our colleagueship was sadly disrupted by Alden's untimely death of amyotrophic lateral sclerosis in 1977. We met in 1958 at NIH, having just finished our medical internships. From the outset, we sought to bring the methods of cell biology to the study of learning. I had already started work on the hippocampus, the part of the mammalian brain that neurosurgeons had shown to be critically involved in human memory, and, when he arrived at NIH, Alden immediately agreed that this might be a good place to begin. We wanted to see whether the electrophysiological properties of the hippocampal neurons were fundamentally different from those of the only two other vertebrate central neurons that had been studied, the motor neurons of the spinal cord and of the motor cortex.

We were immediately successful in our attempts, due in part to two reasons. First, working next door to us was Karl Frank, who, following Eccles, was also pioneering the use of intracellular techniques in the study of spinal motor neurons. We rapidly learned from his technician, Mary Becker, all about the manufacture of glass microelectrodes and their use. Second, being young, naive, and brash, we were not reluctant to tackle what appeared to others to be a difficult technical problem: intracellular recordings from cortical neurons in a pulsating brain. To the contrary, we thought that, memory aside, the hippocampus offered several advantages. It has a cellular architecture that is remarkably conserved throughout mammals, and the main cells, called the pyramidal cells, are clustered in a discrete layer, an easy target for microelectrodes. These cells send their axons out into the fornix, which also allows them to be identified electrophysiologically by backfiring them. Thus, with a powerful new set of methodologies applied for the first time to this cortical structure, it is not surprising that we picked some of the low-lying intellectual fruits.

First, we found that the action potential in hippocampal neurons was initiated not only at the axon hillock, as is the case in motor neurons, but also at a second site that we inferred to be the dendrites. Dendritic action potentials, which we named *fast prepotentials*, in turn triggered the discharge of the main trigger zone in the axon hillock. Second, we found that hippocampal neurons were not silent, as were motor neurons, but tended to fire spontaneously and that this often took the form of bursts of spikes that were maintained by the addition of summated, depolarizing afterpotentials. Third, the hippocampal neurons engaged a powerful recurrent inhibitory system, which gave rise to a prolonged inhibition of 200 to 400 msec, several orders of magnitude longer than the inhibition previously encountered in the spinal cord.

These studies formed the background for subsequent studies of the electrical properties of the hippocampal pyramidal cells. For example, Alden and I went on to study for the first time the cellular events that underlie seizure.[1] Here we encountered two completely different types of seizure—excitatory or inhibitory, depending on whether we stimulated the afferent (excitatory) or the recurrent (inhibitory) pathway.

These papers are probably cited often for several reasons. First, together with the studies of Phillips on the pyramidal cells of the neocortex,[2] they were the first systematic study of neurons above the spinal cord. They showed that the electrophysiological techniques that were so useful in the spinal cord could be applied to an analysis of higher brain regions. In addition, the development of hippocampal slices in 1966, first by Yamamoto and McIlwain[3] and then by Andersen and others,[4] brought further interest to the hippocampus. In the slice, it is possible to study the hippocampus without the technical problems produced by vascular pulsation and to record for long periods of time from the dendrites as well as from the cell body. Second, our studies showed that it was possible to analyze the biophysical mechanisms of seizure activity; the hippocampus continues to be a favorable structure for analyzing these mechanisms. Finally, the discovery of long-term posttetanic potentiation in the hippocampus by Lomo, Bliss, and Gardner-Medwin[5,6] and its analysis in hippocampal slices by Andersen,[7] Lynch,[8] Brown,[9] Johnston,[10] Schwartzkroin,[11] and others[12] made it possible to study an elementary mechanism for memory.

1. **Kandel E R & Spencer A W.** The pyramidal cell during hippocampal seizure. *Epilepsia* 2:63-9, 1961.
2. **Phillips C G.** Action of antidromic pyramidal volleys on single Betz cells in the cat. *Quart. J. Exp. Physiol.* **44**:1-25, 1959. (Cited 245 times.)
3. **Yamamoto C & McIlwain H.** Electrical activities in thin sections from the mammalian brain maintained in chemically defined media *in vitro*. *J. Neurochemistry* **13**:1333-43, 1966. (Cited 200 times.)
4. **Andersen P, Bliss T V P & Skrede K K.** Unit analysis of hippocampal population spikes. *Exp. Brain Res.* **13**:208-21, 1971. (Cited 215 times.)
5. **Bliss T V P & Lomo T.** Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path. *J. Physiology* **232**:331-56, 1973. (Cited 310 times.)
6. **Bliss T V P & Gardner-Medwin A R.** Long-lasting potentiation of synaptic transmission in the dentate area of the unanaesthetized rabbit following stimulation of the perforant path. *J. Physiology* **232**:357-74, 1973. (Cited 200 times.)
7. **Andersen P, Sundberg S, Green O & Wigstrom H.** Specific long-lasting synaptic transmission in hippocampal slices. *Nature* 266:736-7, 1977. (Cited 130 times.)
8. **Dunwiddie T & Lynch G.** Long-term potentiation and depression of synaptic responses in the hippocampus: localization and frequency dependency. *J. Physiology* **276**:353-61, 1978. (Cited 105 times.)
9. **Barrionuevo G & Brown T H.** Associative long-term potentiation in hippocampal slices. *Proc. Nat. Acad. Sci. US* **80**:7347-51, 1983.
10. **Hopkins W F & Johnston D.** Frequency-dependent noradrenergic modulation of long-term potentiation in the hippocampus. *Science* **226**:350-2, 1984.
11. **Schwartzkroin P & Wester K.** Long-lasting facilitation of a synaptic potential following tetanization in the *in vitro* hippocampal slice. *Brain Res.* **89**:107-19, 1975. (Cited 140 times.)
12. **Douglas R M & Goddard D.** Long-term potentiation of the perforant path-granule cell synapse in the rat hippocampus. *Brain Res.* **86**:205-15, 1975. (Cited 215 times.)