This Week's Citation Classic®

Ribak C E. Aspinous and sparsely-spinous stellate neurons in the visual cortex of rats contain glutamic acid decarboxylase. *J. Neurocytology* 7:461-78, 1978.
[Division of Neurosciences, City of Hope National Medical Center, Duarte, CA]

Glutamic acid decarboxylase (GAD) is the synthesizing enzyme for the inhibitory neurotransmitter, γ-aminobutyric acid. Immunocytochemical methods were used to localize GAD within neuronal somata and dendrites that had the features of aspinous and sparsely-spinous stellate cells. In addition, GAD-immunoreactive axon terminals formed symmetric synapses with every neuronal type in the cerebral cortex. The results indicated that some stellate neurons provide cortical inhibition. [The *SCI*® indicates that this paper has been cited in over 230 publications.]

Charles E. Ribak
Department of Anatomy and Neurobiology
University of California
Irvine, CA 92717

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In 1975 I completed my PhD with Alan Peters at Boston University, where I had analyzed the neurocytology of the rat visual cortex. Our studies were stimulated by the pioneering research of David Hubel and Torsten Wiesel, who won the Nobel Prize for physiology and medicine in 1981 and who were located across town at Harvard Medical School. They had demonstrated the anatomical correlates of physiologically defined ocular dominance columns in the visual cortex of monkeys.

Subsequently, I began a postdoctoral position at the City of Hope Medical Center with James E. Vaughn and Eugene Roberts (then chairman of the Division of Neurosciences). Roberts discovered the neurotransmitter γ-aminobutyric acid (GABA) in brain tissue in 1951 and developed an ambitious plan to localize GABA neurons with immunocytochemical methods.[1] Since many of the technical flaws had been solved by Barbara J. McLaughlin, John G. Wood, Robert Barber, and Vaughn prior to my arrival, I was confident that I would be able to localize the GABA neurons in the visual cortex. Such an analysis would provide the anatomical substrate for the well-defined cortical inhibition.[2,3]

After a few months of research, I obtained some good light- and electron-microscopic preparations of GABAergic axon terminals in the visual cortex as well as in the hippocampus, substantia nigra, and olfactory bulb. The analysis of the substantia nigra interrupted my study of the visual cortex because it displayed the densest concentration of GABA terminals in the entire brain, and it was rationalized that the immunocytochemical method could be improved by changing fixation parameters of this tissue. Also, Roberts was very interested in the basal ganglia and influenced me with his enthusiasm to analyze this brain region and other related structures.

Unfortunately, the cell bodies of GABA neurons were not labeled consistently in each examined brain region. Based on discussions with previous members of the laboratory, Vaughn and I came up with a few plausible explanations. One involved the rapid movement of glutamic acid decarboxylase (GAD) via axonal transport to the terminals. To test this hypothesis we decided to block axonal transport in the hippocampus and the cerebellum with colchicine in an attempt to label the cell bodies of GABA neurons: this experimental approach was successful.

I spent the following two years collecting the best preparations of the visual cortex. When it came time to write the paper on these results, I consulted Peters, who shared with me pertinent unpublished electron-microscopic data that he had obtained for the aspinous and sparsely-spinous stellate neurons in the rat visual cortex.[4] His findings utilized a combined Golgi electron-microscopic method that revealed valuable new information about the synaptic relationships of the local circuit neurons of the cerebral cortex. The results of my study showed that the basket plexus that surrounds virtually every pyramidal neuron was composed of numerous GABAergic axon terminals. In fact, the axon terminals that contact the axon initial segments of these same neurons were also GABAergic. These findings suggested that two types of stellate neuron, basket and chandelier cells, used GABA as a neurotransmitter.

Although I was the sole author of this paper, Vaughn should have been a coauthor because he provided me with essential criticisms to improve the study. However, he encouraged me to author the paper alone so that I could gain independent recognition for this work. It is interesting that he accurately predicted the influence of this paper and its effect on my career. Less than five years after the paper was published, I was appointed to the editorial board of the same journal that published it.

Following the article's publication, my interests shifted to the field of epilepsy, where the role of GABA in seizure activity had been suggested. My efforts in this area have shown that GABA terminals and neurons are lost at sites of experimental epileptic foci in the cerebral cortex.[5] The role of GABA neurons in normal cortical function and epilepsy probably received much more interest from the neuroscience community as a result of the *Classic* paper. In addition, the original observations have been replicated by many investigators throughout the world using different antibodies to GAD as well as antibodies to GABA.

1. **McLaughlin B J, Wood J G, Saito K, Barber R, Vaughn J E, Roberts E & Wu J-Y.** The fine structural localization of glutamate decarboxylase in synaptic terminals of rodent cerebellum. *Brain Res.* 76:377-91, 1974. (Cited 245 times.)
2. **Dreifuss J J, Kelly J S & Krnjević K.** Cortical inhibition and γ-aminobutyric acid. *Exp. Brain Res.* 9:137-54, 1969. (Cited 155 times.)
3. **Sillito A M.** The contribution of inhibitory mechanisms to the receptive field properties of neurones in the striate cortex of the cat. *J. Physiology* 250:305-29, 1975. (Cited 85 times.)
4. **Peters A & Fairén A.** Smooth and sparsely-spined stellate cells in the visual cortex of the rat; a study using a combined Golgi-electron microscope technique. *J. Comp. Neurol.* 181:129-72, 1978. (Cited 130 times.)
5. **Ribak C E.** Neurocytology and chemistry of focal epilepsy. (Pedley T A & Meldrum B S, eds.) *Recent advances in epilepsy*. Edinburgh: Churchill Livingstone, 1986. p. 1-20.

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