

This Week's Citation Classic®

Whittaker V P. The application of subcellular fractionation techniques to the study of brain function. *Prog. Biophys. Mol. Biol.* 15:39-96, 1965.

[Agricultural Research Council, Institute of Animal Physiology, Babraham, Cambridge, England]

This review describes the application to brain tissue of the then relatively new technique of subcellular fractionation and my discovery that the application of liquid shear detaches nerve terminals to form sealed structures (synaptosomes) that subsequently can be isolated. The implications of this finding are discussed. [The SCI® indicates that this paper has been cited in over 330 publications.]

Victor P. Whittaker
Arbeitsgruppe Neurochemie
Max-Planck-Institut für Biophysikalische
Chemie
D-3400 Göttingen
Federal Republic of Germany

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I vividly remember that the initial invitation to write the review arrived early in 1963 at a time when I was feeling particularly hard-pressed, and I first reacted by refusing it. I had already just written a shorter review¹ than this turned out to be. A little later I regretted passing up an offer to put the whole developing synaptosome story together in a review journal with a particularly wide audience and wrote to the editor, H.E. Huxley, asking if I could change my mind. He graciously agreed. I was given a year in which to write it, and it was actually submitted in May 1964. Rereading the review brings back the intense excitement and hard work of those days with a very small team of postdocs and technicians, one of whom (Gordon Dowe) is still with me!

I began my review with an acknowledgment of the influence that the lysosome work of C. de Duve and the isolation of chromaffin granules by H. Blaschko and by N.A. Hillarp

had on my own decision to use similar techniques to explore the nature of bound acetylcholine. My discovery of the synaptosome is told historically (the key paper is also a *Citation Classic*),² but no mention is made of the fact that the word itself suddenly occurred to me as I was taking a bath one Saturday morning early in June 1963.

Our work at that time had two main thrusts: to establish the synaptosomal localization of a range of putative neurotransmitters in addition to acetylcholine and their synthesizing enzymes, and to subfractionate disrupted synaptosomes in order to obtain homogeneous fractions of synaptic vesicles and other synaptic components. The fractions had to be carefully characterized biochemically and morphologically, and new microassay and electron-microscope techniques were developed for the purpose. The resulting paper³ was the first to contain the word "synaptosome"; this has entered the scientific vocabulary and is often used unreferenced like "mitochondrion."

Some attempts had been made to study synaptosomes as metabolic units, but these were not very successful and were not immediately followed up. What a mistake! It was subsequently shown that synaptosomes under metabolizing conditions perform extremely well, generating membrane potentials and releasing transmitters in a Ca²⁺-dependent manner in response to stimulation, and also take up a variety of transmitters, transmitter precursors, and energy-yielding substrates by carrier-mediated processes. It is this aspect more than any other that has sustained interest in the synaptosome, as more recent reviews show.^{4,5}

The 1965 review has been frequently cited for its historical significance and the stimulus it gave to the development of modern neurochemistry, which has since seen the isolation of most types of neural cells, cerebellar glomerulae, and much else. I have received the Lashley award of the American Philosophical Society and the Thudichum medal of the UK Biochemical Society⁶ in recognition of my work.

1. Whittaker V P. The separation of subcellular structures from brain tissue. *Biochem. Soc. Symposium* 23:109-26, 1963.
2. Gray E G & Whittaker V P. The isolation of nerve endings from brain: an electron microscopic study of cell fragments derived by homogenization and centrifugation. *J. Anatomy* 96:79-87, 1962. (Cited 2,000 times.) [See also: Gray E G & Whittaker V P. Citation Classic. (Barrett J T, ed.) *Contemporary classics in the life sciences. Volume 1: cell biology*. Philadelphia: ISI Press, 1986. p. 13.]
3. Whittaker V P, Michaelson I A & Kirkland R J A. The separation of synaptic vesicles from nerve-ending particles ('synaptosomes'). *Biochemical J.* 90:293-303, 1964. (Cited 905 times.)
4. Whittaker V P. The synaptosome. (Lajtha A, ed.) *Handbook of neurochemistry: second edition. Volume 7. Structural elements of the nervous system*. New York: Plenum, 1984. p. 1-39.
5. ———. The cellular basis of synaptic transmission: an overview. (Zimmermann H, ed.) *Cellular and molecular basis of neuronal signalling and synaptic transmission*. Berlin, FRG: Springer-Verlag, 1988. p. 1-23.
6. ———. The structure and function of cholinergic synaptic vesicles. *Biochem. Soc. Trans.* 12:561-76, 1984.