

This Week's Citation Classic

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. Anat. Lond.* **96**:79-87, 1962.

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The authors present a method for the bulk isolation of synaptic complexes (synaptosomes) from brain which permits investigation of synaptic structure, biochemistry, and physiology in a way hitherto impossible, including the isolation of the various components of the synapse, e.g., synaptic vesicles, external presynaptic membranes, membrane proteins, and junctional complexes. Antibodies can now be prepared for study of the individual synaptic proteins. [The SC[®] indicates that this paper has been cited over 1,100 times since 1962.]

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"E. G. Gray: Traditionally at University College London, coauthors were placed in alphabetical order on publications. The concept of the senior author with its obvious advantages and disadvantages has, of course, changed all of this. Certainly, Victor Whittaker is the undisputed 'senior author' in the work described here.

"As I recall it, as soon as synaptic vesicles were discovered with the electron microscope (EM) and postulated to contain the transmitter substance (about 1954), Victor and Catherine Hebb seized on the feasibility of isolating the vesicles by subcellular fractionation. After some two years of effort they were finally able to produce a subfraction rich in postulated transmitters (acetylcholine, etc.). However, although particles resembling synaptic vesicles were present in the subfraction,¹ these were much smaller than sedimentation speed demanded.

"One afternoon in 1959, Victor visited my lab and explained his problem. In the first

sections I looked at, under the F.M., the anomaly immediately clarified. The subfraction, in fact, contained pinched-off nerve endings often with attached postsynaptic membranes—structures already so familiar to me from my cortex studies. Furthermore, their dimensions fitted exactly the sedimentation speeds. Victor, in fact, was seeing synaptic vesicles in his original studies, but these were derived from the nerve ending particles, which were breaking down during fixation because of his less sophisticated methods. At this stage I turned to other problems and Victor, having acquired his own EM unit, continued the work he and Hebb had pioneered

"Victor P. Whittaker: I shall always remember the day, March 30, 1960, when I met George Gray's train at Cambridge Station and he said to me as we walked to my car: 'You have isolated vesicles, Victor, but inside pinched-off nerve endings.' As we examined George's micrographs later a vast vista opened before me and I knew what I should be doing for the next ten years. I was shortly leaving for America and the first announcement of the results was made in a lecture. I gave in George Koelle's department of pharmacology in Philadelphia. During the US trip my technicians had instructions to repeat the experiments; this was done twice without success! When I got back I discovered that this was due to inadequate control of the temperature and osmotic pressure of the fixative. This confirmed the comparative lability of synaptosomes and explained why no one had identified them earlier. There was an unfortunate delay in publishing the full paper because it was rejected by the *Journal of Physiology!*

"Initially I used the acronym NEPs (nerve ending particles) for the detached nerve endings; then an American worker introduced PONEs (pinched-off nerve endings). While I was working on the isolation of synaptic vesicles,² I decided a more euphonious name was needed; one Saturday morning during a leisurely bath, the word synaptosome came to me. This was incorporated into the title of my paper, but the editors insisted on putting it between inverted commas. Now it has attained the distinction of being used unreferenced, like 'mitochondrion,' and has been incorporated into most European languages."

1. Whittaker V P. The isolation and characterization of acetylcholine-containing particles from brain. *Biochemical J.* **72**:694-706, 1959.

2. 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.