

# This Week's Citation Classic®

**Winkler H.** The composition of adrenal chromaffin granules: an assessment of controversial results. *Neuroscience* 1:65-80, 1976.

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This paper surveyed the available data on chromaffin granules (the catecholamine-storing subcellular organelles of the adrenal medulla) and, by a critical analysis, settled some controversial questions. It was proposed that chromaffin granules should serve as a "model organelle" for vesicles storing hormones or neurotransmitters. [The SC<sup>1</sup>® indicates that this paper has been cited in over 255 publications, making it the most-cited paper from this journal.]

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My own interest in chromaffin granules began in 1964, when I obtained a scholarship to work in the Department of Pharmacology at the University of Oxford. This was, of course, the best place to study these subcellular organelles since my supervisor there was H. Blaschko, who in 1953 provided the first evidence that such subcellular vesicles exist.<sup>1</sup> I spent three years amongst "the dreaming spires" of Oxford, although not dreaming myself but working in a very stimulating and enjoyable cooperation with A.D. Smith.

In 1964 it was still sufficient to read a few dozen papers in order to be well informed about chromaffin granules. This, however, changed soon, since at that time several labs around the world began to take up this topic. Isolation methods were perfected, biochemical analyses were performed, and then it was established that secretion from these organelles is brought about by a process of exocytosis in which the total content of the chromaffin granules is expelled directly into the extracellular space.

An early comprehensive and well-written review<sup>2</sup> of this field was given by Smith in 1968. By 1976, when I wrote my review article, the field had further expanded. Not sur-

prisingly, this resulted in some conflicting data. I attempted to settle these controversies by the critical analysis of the literature reviewed here, and by now one can state that the conclusions reached then have since been confirmed. The second purpose of this review was to compile all data available on the biochemical composition of these organelles in order to provide a concept of how a subcellular organelle that specialized in storing compounds like adrenalin is organized. Based on these data, I proposed that chromaffin granules should serve as a model organelle for vesicles storing hormones or neurotransmitters.

Recent research has indeed demonstrated that all of these vesicles have common properties. Just to give a few examples: uptake of amines and other transmitters is driven by a chemiosmotic proton gradient;<sup>3</sup> the acidic proteins of chromaffin granules, the chromogranins, have a widespread distribution in endocrine tissues and in brain;<sup>4</sup> and chromaffin granules and many other storage vesicles contain high amounts of neuropeptides, e.g., enkephalins.<sup>5</sup>

My review in 1976 was the first commentary published in the newly founded journal *Neuroscience*, which, in the meantime, has become one of the leading journals in this field. The review was dedicated to Blaschko on the occasion of his 75th birthday. I was very happy that I could write further commentaries for his 80th birthday<sup>6</sup> and for his 85th birthday.<sup>4</sup> Their titles demonstrate the increasing degree of sophistication in the field: from the composition of chromaffin granules we advanced to the molecular organization<sup>6</sup> and finally to the molecular function.<sup>4</sup>

My first review was published just before the field expanded significantly. The fact that it provided a critical analysis of what was known at that time probably led to its frequent citation. I hope that it contributed towards making chromaffin granules more popular among scientists.

1. Blaschko H & Welch A D. Localization of adrenaline in cytoplasmic particles of the bovine adrenal medulla. *Naunyn-Schmied. Arch. Pharmacol.* 219:17-22, 1953. (Cited 60 times since 1955.)
2. Smith A D. Biochemistry of adrenal chromaffin granules. (Campbell P N, ed.) *The interaction of drugs and subcellular components on animal cells*. London: Churchill, 1968. p. 239-92. (Cited 135 times.)
3. Johnson R G, Carty S & Scarpa A. A model of biogenic amine accumulation into chromaffin granules and ghosts based on coupling to the electrochemical proton gradient. *Fed. Proc.* 41:2746-54, 1982.
4. Winkler H, Apps D K & Fischer-Colbrie R. The molecular function of adrenal chromaffin granules: established facts and unresolved topics. *Neuroscience* 18:261-90, 1986.
5. Schultzberg M, Lundberg J M, Hökfelt T, Terenius L, Brandt J, Elde R P & Goldstein M. Enkephalin-like immunoreactivity in gland cells and nerve terminals of the adrenal medulla. *Neuroscience* 3:1169-86, 1978. (Cited 325 times.)
6. Winkler H & Westhead E. The molecular organization of adrenal chromaffin granules. *Neuroscience* 5:1803-23, 1980.