PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

Introduction to Molecular and Cellular aspects of exocytosis. Proceedings of a symposium held in Milan, Italy on 24 and 25 June 1998

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THE ROYAL SOCIETY

Introduction

BRUNO CECCARELLI: INFORMATION ABOUT HIS SCIENTIFIC LIFE AND ABOUT THE ASSOCIATION ESTABLISHED BY HIS COLLEAGUES AND FRIENDS

The International Symposium on the Molecular Aspects of Exo- and Endocytosis, from which the present issue originates, was organized (with the support and collaboration of the institutions listed below) by a small Association of friends and colleagues, ten years after the death of Bruno Ceccarelli. Bruno (figure 1) had been together with us from the beginning of the laboratory (*ca*. 1965), when a small team of young MD graduates started to play around with an electron microscope, trying to open an Italian road to cell biology. For all of us, the key step occurred when we succeeded in joining a major international laboratory demonstrating, to us more than to the rest of the scientific community, that ours was indeed a road worth running. In the case of Bruno, who had an excellent background in surgery (i.e. he had incredible dexterity) and who had already carried out important re-innervation experiments in sympathetic ganglia (Ceccarelli *et al*. 1971), the choice was for the small, but stimulating group of Alex Mauro at Rockefeller in New York. Alex (who also left us a few years ago) was a classical biophysicist, therefore interested primarily in membrane voltages and currents. In addition, however (as acknowledged by his friend, George Palade), he was also highly interested in nerve cell structure, and was prepared to combine his two passions by studying the most popular neurobiological model structure, the neuromuscular junction of the frog. The collaboration of Bruno with Alex and with his colleague, Paul Hurlbut, led to a long list of important discoveries, most of which were made while competing with another well-known group, that of John Heuser and Tom Reese: fusion of synaptic vesicles with the presynaptic membrane of stimulated nerves (Ceccarelli *et al*. 1972); recycling of these vesicles, as revealed by their labelling with extracellularly applied horseradish peroxidase (Ceccarelli *et al*. 1973); localization of the synaptic vesicle fusions not only at, but also outside the active zones of the presynaptic membrane (Ceccarelli *et al*. 1979*a*,*b*); purification and study of α-latrotoxin, the active component of the black widow spider venom (Frontali *et al*. 1976; Ceccarelli & Hurlbut 1980; Fesce *et al*. 1986). At the beginning of the Eighties, the introduction to the laboratory of the technique of quick-freezing, by which presynaptic terminals can be semi-vitrified within a few milliseconds from the electrical stimulation of the nerve, to be then analysed in the electron microscope, led Bruno and the colleagues that had grown up around him (including Riccardo Fesce, Fabio Grohovaz and Flavia Valtorta) to the most important and still up-to-date conclusion of his work: the possibility that recycling of exocyzed synaptic vesicles occurs not only by the relatively slow, clathrin-coated-assisted mechanism that, up to recently has been mostly accepted, but also by a faster, parallel process (Torri-Tarelli *et al*. 1985) that today, based on the title of a mini review published after Bruno's death, is widely referred to as the kiss-and-run process (Fesce *et al*. 1994). At the time, the evidence in favour of this second alternative originated from quick-freezing results showing, at stimulated synapses, images of vesicles fused not completely, but only partially, with the appearance at the

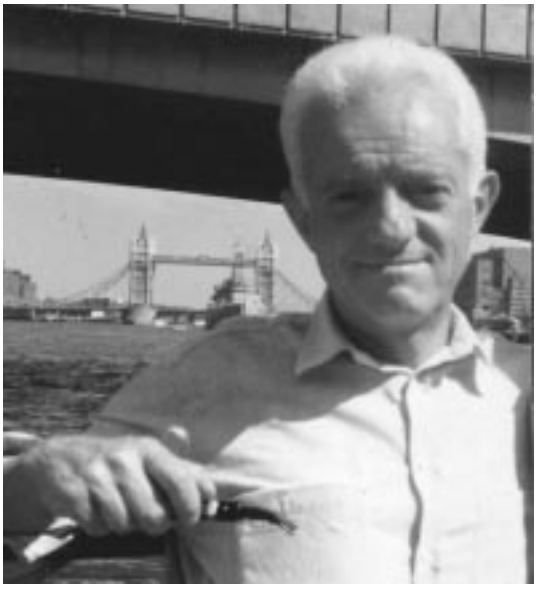

Figure 1. Bruno Ceccarelli in London a few months before his departure.

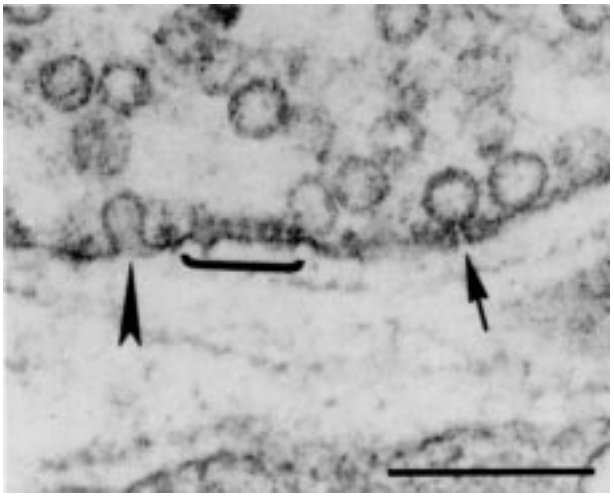

Figure 2. Exocytosis of synaptic vesicles triggered at the frog neuromuscular junction by stimulation applied to the nerve 10 ms before quick freezing. Notice to the left (arrow head) a conventional, Ω-shaped vesicle fusion, a type of image that could be seen occasionally and only a few milliseconds after stimulation, whereas vesicles connected to the plasmalemma via a narrow pore (right, arrow head), indicative of kiss-and-run, were much more frequent, especially at early times of stimulation. Scale bar, 0.2 μm. Reproduced with permission from Fesce *et al*. (1994).

sites of membrane interaction of thin diaphragms, probably proteinaceous in nature (figure 2; Torri-Tarelli *et al*. 1985; Fesce *et al*. 1994). Later on, electrophysiological and imaging studies (see among others Henkel & Betz 1995; Smith & Neher 1997; Henkel & Almers 1996; Klingauf *et al*. 1998) revealed events that might well correspond to the morphological data. At the moment, therefore, the kiss-and-run hypothesis is among the most exciting issues in synaptic physiology, also because of its obvious advantages of speed and specificity with respect to the conventional recycling process.

That mentioned so far covers only part of Bruno's research activity. However, it might be enough to give some idea of his enthusiasm, his incurable experimental perfectionism, and his profound understanding of synaptic events. Additional features of Bruno's personality, which all his friends remember, were his love for sincerity and his dedication to the development of science, in particular of cellular neurobiology in Italy. Based on these considerations, Bruno's friends decided, a few years ago, to found the Bruno Ceccarelli Association dedicated to the overall goals of his scientific career, which operates now with the generous support of Schering-Plough. The Association organizes a programme of main lectures, given twice a year at the San Raffaele Institute, that are attracting the interest not only of specialists but also of doctors and students dealing with various main fields of neurobiology. The present 1998 Symposium was another enterprise of the Association. Many others, we hope, will follow in the years ahead, demonstrating that Italy's interest in neurosciences is growing quickly and to high scientific levels. We conclude therefore that, although Bruno is no longer with us, his memory has still a major role in the progress of our scientific community.

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Francesco Clementi

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PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

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