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Invited review

Calcium in the function of the nervous system: New implications

Piotr Bregestovski [a,*], Nicholas Spitzer [b]

[a] *Institut de Neurobiologie de la Méditerranée (INMED), Parc Scientifique de Luminy, BP13, 13009 Marseille, France*
[b] *Neurobiology Section, Division of Biological Sciences, UCSD, La Jolla, CA 92093, USA*

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Calcium is a unique ion that is used in a wide variety of biological processes. The importance of Ca^{2+} for biological tissues was discovered by Sydney Ringer in the early 1880s. Conducting experiments on isolated hearts, Ringer observed that adding a small amount of Ca^{2+} to distilled water dramatically prolonged the time that hearts would continue to beat [1]. This was a key discovery that led to introduction of a famous physiological solution, acknowledged by subsequent generations of physiologists as "Ringer's solution". Since then, a large variety of functions have been established for this almost universal intracellular messenger. Calcium controls a diverse range of cellular processes, such as gene transcription [2], ion channel function [3], muscle contraction and cell proliferation [4]. To control multiple functions specifically, the distribution of Ca^{2+} is highly regulated in the dimensions of space, time and concentration [5,6].

The existence of Ca^{2+} microdomains was recognized a decade ago. In 1992, Augustine and Neher wrote "Intracellular Ca^{2+} (Ca_i) signals should be restricted to spatial compartments of very small volume (typically less than 1 μm in diameter). Within such tight quarters, the rises in Ca_i are predicted to be very large, on the order of tens or hundreds of micromolar" [7]. Indeed, at the squid giant synapse and in turtle hair cells [8,9] Ca^{2+} entry was observed to generate intracellular elevations of Ca^{2+} of 100 μM or more, initially restricted to regions <1 μm in diameter, indicating highly localized action of Ca^{2+}. Fluorescence imaging in hippocampal neurons demonstrated that elevations of Ca_i can be independently restricted to individual dendritic spines [10] or to dendrites [11]. More recent observations of Ca^{2+} microdomains on dendritic spines [12] and on aspiny dendrites [13] suggest that Ca^{2+} can control functions in extremely limited volumes, estimated in nanometers ("nanodomains").

The key role of Ca^{2+} for neurotransmitter release was established by Katz and Miledi in the 1960s. Although the importance of Ca^{2+} in synaptic transmission was mentioned in a number of earlier studies [14–16], two types of experimental observations, obtained by Katz and co-workers [17,18], provided convincing evidence of the pivotal role of Ca^{2+} for neurotransmitter release.

The first clear evidence was presented by Katz and Miledi [17] in elegant experiments on the frog motor nerve terminal. The preparation was immersed in a Ca^{2+}-free Ringer's solution and a focal electrode filled with 0.5 M $CaCl_2$ was placed on a synaptic spot. This electrode was the only source of controlled application of Ca^{2+}. The same electrode was also used for extracellular recording of pre- and post-synaptic responses to nerve stimulation (see scheme in Fig. 1A). When a strong negative potential was applied to the pipette to stop Ca^{2+} efflux, only pre-synaptic deflection was observed (Fig. 1B, b). Decreasing the negative voltage allowed release Ca^{2+} from the pipette and resulted in appearance of post-synaptic responses with a fluctuating synaptic delay (Fig. 1B, a). The deflection due to the pre-synaptic spike was almost unchanged by variations of Ca^{2+}. The authors conclude: "the action of calcium is concerned directly with the release of the transmitter" [17].

Direct evidence was obtained from the squid giant synapse [18]. This preparation allows simultaneous intracellular monitoring of pre- and post-synaptic potentials (Fig. 2A). When the preganglionic nerve was stimulated at intervals of 1–5 min following replacement of artificial sea water by "Ca^{2+}-free" solution, the rise time of stimulation-induced post-synaptic potentials (PSP) began to decline (Fig. 2B). As a result, the PSP-induced action potential "arose progressively later. . ., until eventually only the synaptic potential remained. The PSP continued to fall and became undetectable after a time

* Corresponding author. Tel.: +33 4 91 82 81 19.
E-mail addresses: pbreges@inmed.univ-mrs.fr (P. Bregestovski), nick@biomail.ucsd.edu (N. Spitzer).

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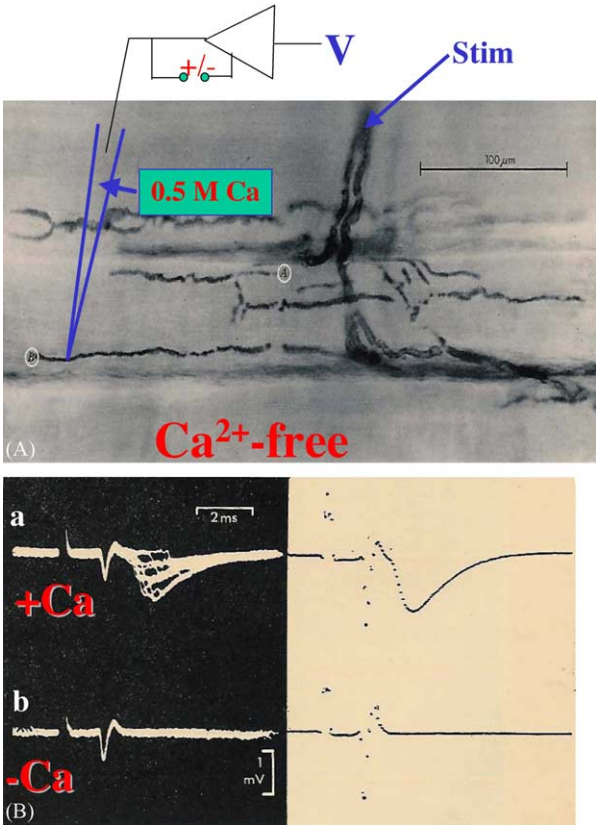

Fig. 1. Calcium is a key ion for neurotransmitter release: evidence from the frogs neuromuscular junction. (A) Experimental design of a focal recording from a junctional spot of a frog sartorius muscle. The muscle was immersed in Ca^{2+}-free Ringer's solution containing 0.84 mM $MgCl_2$. The recording pipette contained 0.5 M $CaCl_2$. Efflux of Ca^{2+} was controlled electrophysiologically, by applying a "strong" or "weak" negative voltage to the pipette. (B) Effect of Ca^{2+} on neuromuscular transmission; (a) weak negative voltage was applied to the pipette, allowing efflux of Ca^{2+}. Note post-synaptic responses consisting of single unitary potentials with fluctuating synaptic delay (on the left); (b) Ca^{2+} efflux was stopped by applying a strong negative voltage to the pipette. Note absence of post-synaptic responses. On the left, several superimposed traces are shown at each stage; on the right, automatically obtained average of 600 traces at each stage (modified from Katz and Miledi [17,20]).

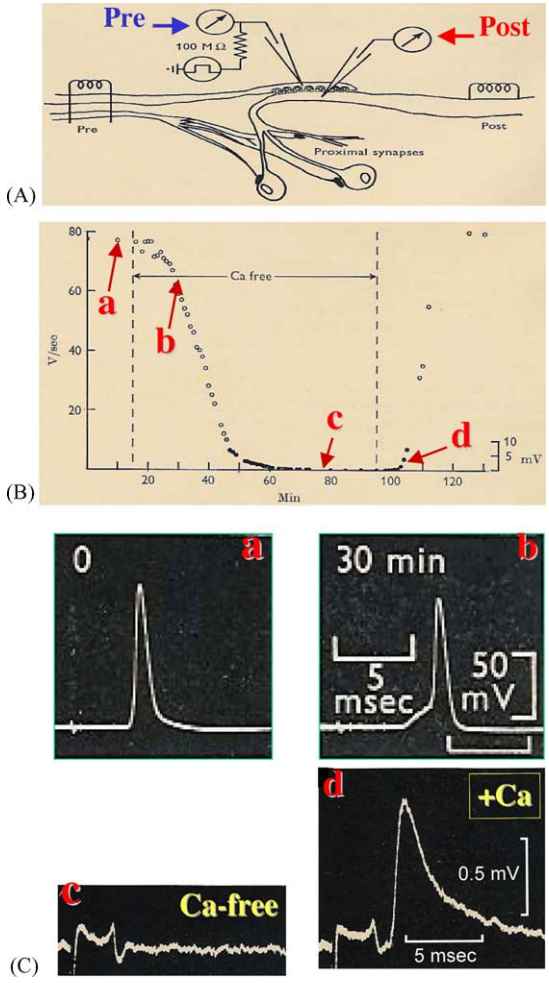

Fig. 2. Calcium is a key ion for neurotransmitter release: evidence from the squid giant axon. (A) Experimental design for simultaneous intracellular recording of pre- and post-synaptic potentials from the isolated stellate ganglion of the squid (*L. pealii*). (B) Effect of Ca^{2+} on post-synaptic responses in the giant squid synapse. Vertical dashed lines indicate the time when the artificial sea water (containing 9 mM Ca^{2+}) was replaced by "Ca^{2+}-free" solution. Open circles indicate maximal slope of the post-synaptic potential. Closed circles show amplitudes of the post-synaptic potential after Ca^{2+}-induced abolition of the action potential on the post-synaptic side. (C) Examples of traces corresponding to different times of recording in the "Ca^{2+}-free" solution (a–c) and during the wash with artificial sea water (d). Note the different voltage scales in (a) and (b), and (c) and (d). The post-synaptic potential is abolished in a "Ca^{2+}-free solution" and has largely recovered 8 min after starting perfusion with artificial sea water containing 9 mM Ca^{2+} (d) (modified from Miledi and Slater [18]).

which varied from 0.5 to 3 h in different preparations" [18] (Fig. 2B and C). This effect was reversible (Fig. 2C, d). The amplitude and properties of pre-synaptic action potential were not modified by changes of Ca^{2+} concentration.

These observations allowed to Katz and Miledi to conclude that "at the squid giant synapse as well as at the neuromuscular junction, external calcium ions are indispensable for synaptic activity" [19].

Although roles of Ca^{2+} in brain function are well documented, there has been remarkable progress in recent years in defining novel implications of this ion in the development and function of the nervous system. This area has expanded extremely rapidly. The goal of this issue is to discuss accumulating knowledge and key observations of the involvement of Ca^{2+} in formation of neuronal networks and modulation of synaptic function.

The volume can be divided into three main parts. The first focuses on "Ca^{2+} and development", i.e. the role of Ca^{2+} in neuronal induction and signal transduction during differentiation, neuronal migration and process extension, and network formation. The second, "Ca^{2+} and neuronal network function" discusses strategies and progress made in imaging techniques for analysis of properties of neuronal microcircuits. The third addresses "Ca^{2+} and synaptic transmission", i.e. the functions of Ca^{2+} in regulating neurotransmitter release and the activity of post-synaptic channels.

Each review is accompanied by a short summary, so we will not provide the reader with descriptions of the articles by each contributor. Instead we invite you to continue reading, which we hope will extend your knowledge of the multifaceted roles of Ca^{2+} in development and function of the nervous system.

Finally, we would like to mention that this special issue continues the series of 'Cell Calcium' issues dedicated to the general aspects of molecular physiology of Ca^{2+} signaling [21–25]. Particularly important for the neuronal Ca^{2+} signaling are 2003–2004 special issues dedicated to the molecular physiology of TRP receptors [26–50] and the role of Ca^{2+} in ischemic brain damage [51–66], which we wholeheartedly recommend to the reader to complement the current collection of papers.

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