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European Journal of Pharmacology 447 (2002) 115–117

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Preface

The calcium ion is a truly extraordinary ion. It regulates such a remarkably wide range of biological processes that it is perhaps not too much of exaggeration to call it an "ion of life". However, in further testament to its near-universal regulatory functions, it can also be viewed, as described in many articles in this issue, as an "ion of death". The scientific story of calcium began in 1808, when Sir Humphry Davy (Fig. 1) was able to show that lime (which had hitherto been considered to be an inseparable element) was actually a combination of metal and oxygen (hence *Calcium*—from Latin *Calx* for chalk). Sir Humphry tried to purify calcium by exposing a mixture of lime and mercuric acid to electric current; he succeeded in obtaining an amalgam of calcium, but further separation of mercury was so difficult that even Davy himself was not certain of whether he had obtained pure metallic calcium. In fact, he never managed to isolate this new metal in a pure form, and metallic calcium remained a laboratory curiosity for another 50 years, until Henry Moissan obtained 99% pure calcium by electrolysing calcium iodide.

Discovery of the biological importance of calcium ions was the critical achievement of Professor Sidney Ringer (Fig. 2), who demonstrated that Ca^{2+} is required for normal muscle contraction and heartbeat, for development of fertilised eggs and tadpoles and for the adhesion of cells to one another (Ringer, 1883a, 1886, 1890; Ringer and Sainsbury, 1894). Yet, his most fundamental discovery, which he presented to The Physiological Society on 13th of December 1883 (Ringer, 1883b), remains largely overlooked by modern physiologists. In that presentation, Sidney Ringer reported the results of amazingly simple, albeit highly important experiments, in which he examined the dependence of fish survival on various inorganic salts. Ringer found that fish could survive for weeks in fresh tap water. However, when placed in distilled water, they died on average in 4.5 h. By systematically adding inorganic salts to the distilled water, he found that: "Calcium chloride added to distilled water sustains life much longer than either corresponding quantities of sodium or potassium salts. For instance, with 30 cc of 1 per cent. solution of calcium chloride to the 1000 c.c. of distilled water, six fish died on average in 47 hours; whilst nine were still alive on the 12th day" (Ringer, 1883b). Although the addition of sodium or potassium salts "greatly assisted calcium chloride to prolong life", the presence of calcium ions was the prerequisite for fish survival. This was the first observation, to be repeated afterwards in countless experiments, directly demonstrating the special powers of the calcium ion and its essential role in sustaining life. Ringer's observations were followed up and extended by many prominent physiologists (e.g., Locke, Loeb, Mines, Loewi, Hopkins, Heilbrunn—see the extraordinarily well-written historic review by Antony Campbell (1983) who not only confirmed that Ca^{2+} was required for maintaining normal physiological processes, but also showed that it plays important roles in mediating the action of various neurotransmitters, hormones and pharmacological agents.

Among these many milestones, particularly important were the observations of Locke and Overton who demonstrated that Ca^{2+} is required for transmission of nerve impulses to muscles and between one nerve and another (Locke, 1894; Overton, 1904), thus implying a key role for calcium ions in intercellular communication. These observations were substantiated and extended by Harvey and

Fig. 1. Sir Hamphry Davy.

PII: S0014-2999(02)01835-6

Fig. 2. Sydney Ringer, Professor of Physiology.

MacIntosh (1940) who demonstrated that removal of external Ca^{2+} inhibits acetylcholine secretion from nerve terminals in sympathetic ganglia. This was the first step in the development of the modern theory of chemical transmission of nerve impulses, in which Ca^{2+} entry into the terminals is considered a prerequisite for regulated exocytosis. The modern form of this theory gradually took shape in the 1950s and 1960s, importantly stimulated by the discovery of Ca^{2+}-mediated action potentials (Fatt and Ginsborg, 1958; Fatt and Katz, 1953). This key finding initiated the search for, and eventual identification of Ca^{2+} currents and voltage-gated Ca^{2+} channels (Hagiwara and Byerly, 1981; Kostyuk et al., 1975). Almost simultaneously, several in depth investigations then revealed the steep Ca^{2+} dependence of stimulated secretion, i.e., that the probability of release of transmitter vesicles during an action potential increases with the fourth power of extracellular Ca^{2+} concentration (Dodge and Rahamimoff, 1967). One year later, the seminal paper by Katz and Miledi (1967) set forth the contemporary view on synaptic transmission by postulating that the action potential opens voltage-gated Ca^{2+} channels in the presynaptic terminal, thereby triggering a local flux of Ca^{2+} into the cytosol, which in turn activates vesicular release of neurotransmitter via a specific Ca^{2+} sensor. This hypothesis is now universally accepted.

Since then, as attested to by many of the articles here, Ca^{2+} has been implicated as a second messenger in a remarkably broad range of signalling cascades and processes essential for neuronal survival (Berridge et al., 2000; Carafoli et al., 2001). It has also become clear that at different intracellular concentrations, Ca^{2+} triggers very different sets of signalling pathways, leading to such contrasting phenomena as long-term potentiation and long-term depression (Lynch et al., 1983; Lisman, 1989; Cummings et al., 1996; Yang et al., 1999). Perhaps not surprisingly, given its diverse functions in sustaining excitable cells, abnormally elevated or reduced intracellular concentrations of Ca^{2+} can also trigger signalling cascades that result in necrotic or apoptotic cell death (Lipton and Rosenberg, 1994; Nicotera and Orrenius, 1998; Zipfel et al., 2000). Ca^{2+}, in fact, has been widely viewed as a "final common pathway" of excitable cell death.

Yet, Ca^{2+} is critically important not only for the physiological functions of neurones or neuronal terminals and effector organs, they also form a basis for excitability of another cellular circuit in the brain, namely that of astroglial networks. The latter cells communicate with each other via propagating intercellular Ca^{2+} waves, initially discovered by Cornell-Bell et al. (1990). These waves integrate glial networks and provide for active interactions between glial and neuronal circuits (Haydon, 2001; Verkhratsky et al., 1998; Budd and Lipton, 1998).

Hence, Ca^{2+} regulation and Ca^{2+} homeostasis within many types of cells and in the extracellular matrix are of eminent importance for the normal functioning of the brain and multiple other systems. Consequently, it is not surprising that disturbances of Ca^{2+}-regulating systems result in severe pathological changes in nearly every organ and system and in particular, trigger disease states of the brain.

We assembled this special issue dedicated to Ca^{2+} signalling systems in the nervous system with the aim of presenting the reader with a coherent picture of the numerous ways in which Ca^{2+} is involved in regulating physiological and pathophysiological processes in the brain. The first part of the issue addresses various Ca^{2+}-regulating and Ca^{2+} signalling systems and is focussed on the normal physiology of Ca^{2+} signalling. The second part emphasises the disregulation of Ca^{2+} homeostasis in brain pathology.

We hope very much that this collection of papers will further intrigue the reader with the vast significance, complexities and mysteries of Ca^{2+} signals. In putting together this special issue, we are greatly indebted to all the contributors, and to the editing team of the European Journal of Pharmacology, whose efforts in bringing this issue into existence would be difficult to overestimate.

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