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Calcium dyshomeostasis and pathological calcium signalling in neurological diseases

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> *"All of the vital mechanisms, however varied they may be, have always one goal, to maintain the uniformity of the conditions of life in the internal environment. The stability of the internal environment is the condition for the free and independent life." (Claude Bernard [1]).*

The incredible diversity and complexity of life forms, which populated and still continue to populate the Earth, are built around several core principles, the most important of which is the principle of homeostasis. Indeed the main aim of every living creature, from primitive bacteria to the highly complex organisms of mammals and humans is the preservation of the *status quo*, preservation of quite narrow optimum of physical conditions that are compatible with life. Furthermore, this struggle for balance always comes at the expense, as it requires energy, and therefore the strategy of minimizing the effort is also generally employed. At the very same time, the more complex the living creatures are, the more they have to develop, from the single cell gamete that carries genetic code, to the full grown organism, that carries the gamete into the future from generation to generation. The complex programme of development as well as the need for co-ordination of cells within the multicellular body called for signalling systems, both inter- and intracellular. The intercellular signalling between physically separated cells (e.g. between majority of neurones) utilises simple chemical molecules, the transmitters, which, by diffusing between cells convey the information. The intracellular signalling system has a daunting task to convert the extracellular incoming signals (originating either from the environment or from the neighbouring cells) into cellular reaction.

There are surprisingly few molecular ensembles responsible for both inter- and intracellular signalling. The intercellular signalling is realised through ~ 10 major transmitters and ~50 major hormones. The intracellular signalling systems are built around several second messengers and enzymatic cascades regulated by these messengers. The most ubiquitous intracellular signalling cascade utilises Ca^{2+} ions as universal and omnipresent second

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messenger [2]. The evolution has chosen Ca^{2+} ions as major intracellular signaller very early [3] probably at the same moment when ATP emerged as the intracellular energy substrate (the reactions involving ATP require low Ca^{2+} concentration). Indeed, each and every cell on the Earth has a very low intracellular free Ca^{2+} concentration, and maintenance of this low cytoplasmic Ca^{2+} is vital. Therefore from very early in evolution the cells developed a robust Ca^{2+} homeostatic system that equilibrates transmembrane Ca^{2+} fluxes so that number of Ca^{2+} ions entering the cell equals number of Ca^{2+} ions leaving the cytosolic compartment. This homeostatic system is build by several molecular cascades, which either scavenge an excess of cytosolic Ca^{2+} (Ca^{2+} buffers) or relocate the excess of Ca^{2+} across cellular membranes (Ca^{2+} transporters; for the details on Ca^{2+} homeostasis signalling see [4-16]). This homeostatic system also provides the backbone for Ca^{2+} signalling as the concentration difference between extra- and intracellular space creates the driving force for Ca^{2+}, underlying its diffusion through membrane channels. The membrane channels for Ca^{2+} emerged very early in the evolution, being, to all probability, the first forms of membrane channels [17-19]; first Ca^{2+} channels appeared in the form of non-proteinaceous structures [20, 21] and subsequently in the form of gated transmembrane channels that are present in both plasmalemma and endomembranes [22-26]. These channels, together with Ca^{2+} homeostatic mechanism form the basis for Ca^{2+} signalling system. The intracellular decoding of Ca^{2+} signals, created by coordinated influx and efflux of Ca^{2+} ions is accomplished by an extended family of Ca^{2+}-sensitive enzymes, known as Ca^{2+} sensors.

Importantly, Ca^{2+} regulation is not uniform throughout the cell, and different compartments, represented by intracellular organelles, such as endoplasmic reticulum or mitochondria, are endowed with the specific Ca^{2+} regulating systems. In the ER, which represents the major cellular organelle involved in wide variety of functions from protein synthesis and posttranslational modification to long-range trafficking of various molecules, the free Ca^{2+} concentration is high, being comparable with the extracellular free Ca^{2+}. This high intra-ER Ca^{2+} is instrumental for many functions of the ER, as it maintains activity of chaperones, regulates various ER-originating signalling events and makes the ER a dynamic Ca^{2+} store [14, 27, 28]. The mitochondrial Ca^{2+} homeostasis is also peculiar, as mitochondria utilise Ca^{2+} entry as an “energy demand” signal, however an excess of Ca^{2+} in mitochondrial matrix can damage the organelle [29].

This signalling machinery has proven to be omnipresent, versatile and robust. The stability of Ca^{2+} homeostatic (and hence signalling) machinery is provided by numerous feedbacks, which are mostly represented by Ca^{2+} ions themselves. Indeed, every element of Ca^{2+} homeostatic/signalling system is Ca^{2+} dependent. Increase in cytosolic Ca^{2+} invariably inactivates membrane Ca^{2+} channels, be they of ligand-operated or voltage-operated variety [30-33]. The same increases in cytosolic Ca^{2+} stimulate Ca^{2+} extrusion by membrane pumps and exchangers. In the ER the Ca^{2+} gradient between the lumen and the cytosol controls the availability of the Ca^{2+} release channels and also regulates the velocity of Ca^{2+} uptake by sarco(endo) plasmic reticulum Ca^{2+} ATPases (SERCA pumps - [34]).

It is not surprising therefore, that Ca^{2+} is intimately involved in cell damage and death in pathological conditions. The concept of Ca^{2+} toxicity has been recognised about 3 decades ago [35-37], and this concept is now firmly established. Failure of Ca^{2+} homeostasis with subsequent Ca^{2+} overload triggers necrotic cell death that generally accompanies all types of acute traumatic insults [38]. At the same time Ca^{2+} is instrumental in initiating and progressing the programmed cell death, which is critically important for development and is widespread in different forms of pathology [38, 39]. The dysregulation of Ca^{2+} homeostasis and pathological Ca^{2+} signalling however are not confined to acute insults; chronic changes in Ca^{2+} signalling machinery and in the intracellular Ca^{2+} distribution can occur over many years this contributing to the pathogenesis of various chronic diseases [40-44].

This special issue is dedicated to the role of imbalanced Ca^{2+} homeostasis and pathological Ca^{2+} signalling in the neurological diseases. These diseases are many, spreading from peripheral neuropathies to a devastating neurodegenerative processes that cause dementia – the decline of the intellect, the form of pathology most feared by the mankind. Nonetheless there are striking similarities in molecular pathogenesis of these diseases as they all involve dysregulation of Ca^{2+} homeostasis and signalling. We hope that this collection of papers may be of interest to a wide audience of scientists engaged in the neuropathological research.

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