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Review

Calcium and normal brain ageing

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ABSTRACT

Normal brain ageing is associated with a varying degree of cognitive impairment. Although ageing is a complex, multifactorial process, and no single process could explain the ageing phenotype, a number of processes and homeostatic systems, due to their central roles in cellular physiology, have been identified as playing important roles in the process of normal ageing. In this review we revisit the basic tenets of the Ca^{2+} hypothesis of neuronal ageing and stress the major conceptual changes that occurred between the time of its original proposal and now, in particular in respect to the extent of neuronal loss in normal ageing. We provide a general overview of the most important ageing-associated changes in neuronal Ca^{2+} homeostasis and then discuss in some detail how such homeostatic changes are affecting basic neuronal properties, such as intrinsic excitability and how, by extension, such changes could lead to significant perturbations in the activity of whole neuronal network ensembles. Since some of these network activities, such as the synchronisation of neuronal activity in the gamma frequency range, have been linked to learning and cognition, understanding the metabolic substrates and homeostatic dysregulation that underpin them could provide a novel basis for attempts at counteracting the cognitive decline of older individuals.

1. Shifts in "Ca^{2+} hypothesis of ageing and neurodegeneration"

The involvement of Ca^{2+} homeostasis as a potential factor explaining at least some of the deficits of cognitive performance that are associated with normal ageing date back to last century, when the first proposal of the "Ca^{2+} hypothesis of ageing" was proposed [1].

In its mature formulation, the hypothesis aimed at providing a working hypothesis for explaining not only the ageing process but also Alzheimer's disease (AD). Drawing on many neurophysiological processes and mechanisms, the hypothesis contained six interrelated key elements [2], providing a wide explanatory blanket. The exposition of these elements is worth repeating not only for historical reasons and to illustrate the breath of the proposal, but also because it still represents the source of some misunderstandings.

The first element of Khachaturian's construct (see Fig. 1) was simply that the cellular mechanisms that control Ca^{2+} homeostasis will, when altered, play an important role in the process of ageing and neurodegeneration.

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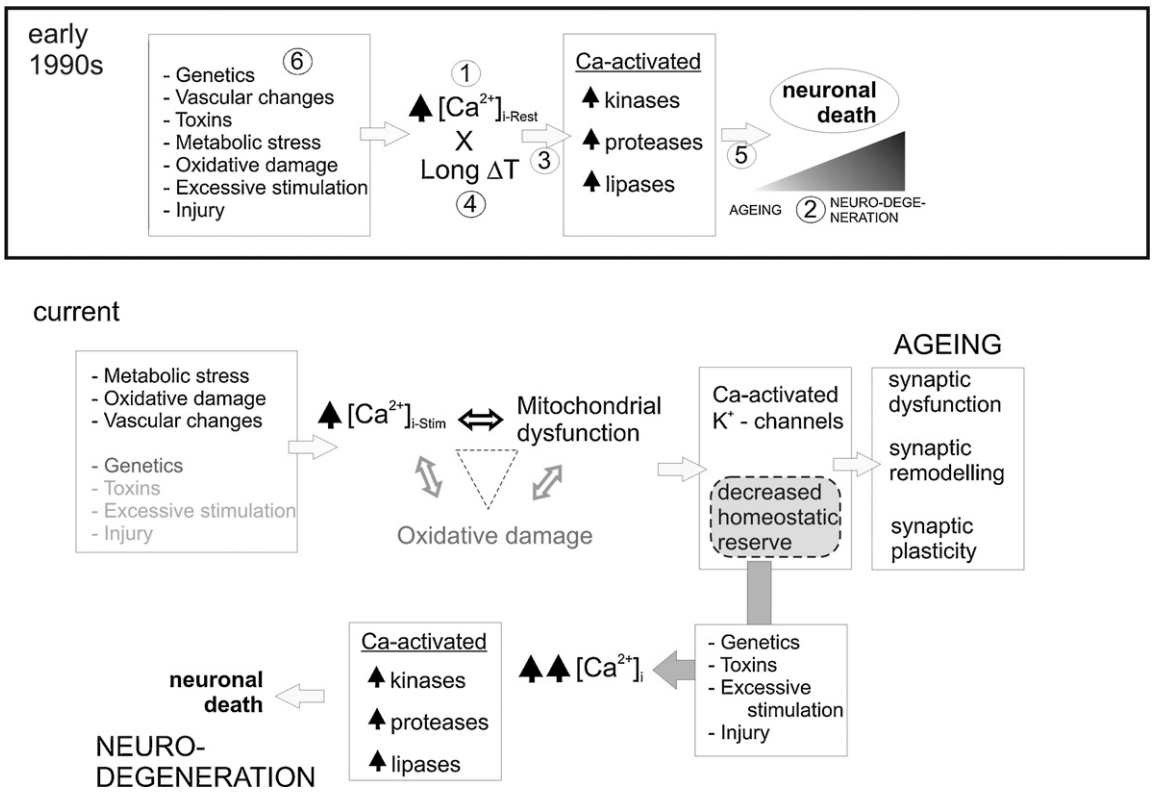

Fig. 1. Diagram representing the conceptual changes in the last two decades in the "Ca^{2+} hypothesis" of brain ageing. Top panel is a free adaptation of a table in Ref. [2], and the numbers in the panel refer to the six elements of the original Ca^{2+} hypothesis of brain ageing and degeneration, which are discussed here in the first section. Bottom panel represents a schematic representation of the current view of the Ca^{2+} hypothesis of ageing. Central to this view is the fact the brain ageing is not associated with gross neuronal loss. Instead changes at synaptic level, both morphological and functional, lead to a more subtle and variable expression of the ageing phenotype. The basis for this functional perturbation is a dysregulation of the triad: Ca^{2+}–mitochondrial function–free radical production, which lead to a decreased homeostatic reserve, as defined in Ref. [23]. This decrease in homeostatic reserve is also the basis for ageing representing such an important risk factor for the majority of the neurodegenerative diseases. These are characterised by a significant amount of neuronal loss, which usually involve from the activation of a variety of Ca^{2+}-dependent cell-death effectors, as described in the original version of the Ca^{2+} hypothesis of ageing.

The second, implicit, element was that normal ageing and the process of neurodegeneration, as in AD, are simply part of a continuum of development and restructuring of the nervous system throughout life. Thus, the dendritic pruning and the loss of synapses and neurones involve the same mechanisms that direct neuroplasticity in the developing or mature brain.

The plasticity of the nervous system architecture and connectivity must be, at any time point, a balance between growth/regeneration and decaying/degeneration processes, and in many of these processes the intracellular free Ca^{2+} concentration ($[Ca^{2+}]_i$) plays a crucial role. As Ca^{2+} signalling is involved with a wide variety of cellular physiological processes [3], the "Ca^{2+} hypothesis" viewed the neuronal dysfunction of the aged or the AD brains as resulting from the breakdown of one or another of the homeostatic mechanisms regulating $[Ca^{2+}]_i$, leading to an imbalance between growth and degeneration.

The next, rather contentious element dealt with the temporal dimension of the ageing/neurodegenerative processes and proposes that the functional product of the perturbation in $[Ca^{2+}]_i$ homeostasis and time is a constant. Thus, small changes in $[Ca^{2+}]_i$ (as those resulting, for example, from a less efficient Ca^{2+} extrusion pump, or an enhanced Ca^{2+} channel activity) exerted over a long period of time would have the same functional or morphological effects as a much larger, but acute insult.

A fifth element took into account the fact that a number of pathways that lead to cellular death are activated by increased $[Ca^{2+}]_i$ and thus proposed that Ca^{2+}-mediated processes are an important part of the final common pathway that lead to neuronal dysfunction and cell death. The model presented, at that point, a rather broad and conveniently flexible perspective, and perturbation of almost any element connected to one or more of the Ca^{2+} homeostatic mechanisms or any of the Ca^{2+} dependent processes could fit the bill of explaining the involvement of Ca^{2+} in the process of ageing and neurodegeneration.

This point was even further expanded by the sixth element that proposed that both the age-related and the AD-associated changes could be initiated by a wide variety of instances, acting alone or in combination, simultaneous or sequentially, over a long period of time.

The formulation of the Ca hypothesis reflected and integrated two of the prevalent scientific views of that moment. One view was that ageing and neurodegeneration are effectively two instances on the common continuous path of time-dependent loss of brain matter, principally neurones. The other view was that Ca is one of the most fundamental signalling systems, involved in almost all of pathways of cellular physiology [4], and the link between these two ideas was supported by the demonstration of Ca^{2+} involvement in the process of excitotoxicity and cell death [5], Today, the issue of ageing as a neurodegenerative process is very much disputed and animal studies showed that the moderate age-related cognitive decline does not involve any dramatic neuronal loss but a significant amount of synaptic restructuring [6] (Fig. 1). One of the important reasons for such a dramatic paradigm shift was technological, represented by the introduction of the modern unbiased, dissector method for counting neurones in brain samples [7]. Another reason was methodological, referring to the fact that in