Presynaptic roles of intracellular Ca\(^{2+}\) stores in signalling and exocytosis

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Abstract

The signalling roles of Ca\(^{2+}\)\(_{ic}\) (intracellular Ca\(^{2+}\)) stores are well established in non-neuronal and neuronal cells. In neurons, although Ca\(^{2+}\)\(_{ic}\) stores have been assigned a pivotal role in postsynaptic responses to G\(_\text{q}\)-coupled receptors, or secondarily to extracellular Ca\(^{2+}\) influx, the functions of dynamic Ca\(^{2+}\)\(_{ic}\) stores in presynaptic terminals remain to be fully elucidated. In the present paper, we review some of the recent evidence supporting an involvement of Ca\(^{2+}\)\(_{ic}\) in presynaptic function, and discuss loci at which this source of Ca\(^{2+}\) may impinge. Nerve terminal preparations provide good models for functionally examining putative Ca\(^{2+}\)\(_{ic}\) stores under physiological and pathophysiological stimulation paradigms, using Ca\(^{2+}\)\(_{ic}\)-dependent activation of resident protein kinases as sensors for fine changes in intracellular Ca\(^{2+}\) levels. We conclude that intraterminal Ca\(^{2+}\)\(_{ic}\) stores may, directly or indirectly, enhance neurotransmitter release following nerve terminal depolarization and/or G-protein-coupled receptor activation. During conditions that prevail following neuronal ischaemia, increased glutamate release instigated by Ca\(^{2+}\)\(_{ic}\) store activation may thereby contribute to excitotoxicity and eventual synaptopathy.

Introduction

It is well established in presynaptic nerve terminals that depolarization-dependent Ca\(^{2+}\)\(_{ex}\) (extracellular Ca\(^{2+}\)) influx through VDCCs (voltage-dependent Ca\(^{2+}\) channels) leads to the exocytosis of synaptic vesicles as well as the activation of signalling cascades leading to stimulation of protein kinases and phosphatases. Increasingly, a role of store-resident or intracellular Ca\(^{2+}\) in presynaptic function is being intimated, certainly in modulating neurotransmitter release and presynaptic plasticity [1], but also in the direct mediation of exocytosis in some cases [2].

In early studies with presynaptic terminals, the paucity of morphological evidence substantiating presynaptic Ca\(^{2+}\)\(_{ic}\) stores, akin to those found in the neuronal cell bodies, was posited as an argument for the exclusive regulation of Ca\(^{2+}\)\(_{ex}\) stores, akin to those found in the neuronal cell bodies, is postulated to occur through a trigger with a Ca\(^{2+}\) affinity in the tens of micromolar range, and highly cooperative binding of the ion (fourth or fifth power) [5,6]. Synaptotagmins 1, 2 and 9 fit this profile of fast Ca\(^{2+}\) binding proteins and are thereby cited as the Ca\(^{2+}\) sensors detecting localized increases in [Ca\(^{2+}\)] in nano- and/or micro-domains established transiently following the activation of P/Q- and/or N-type VDCCs by single action potentials [7].

Asynchronous release appears to occur as a result of extended elevation of cytosolic [Ca\(^{2+}\)], usually following repetitive stimulation of nerve terminals. Although this was initially thought to point to a Ca\(^{2+}\) sensor for asynchronous release with a higher affinity for Ca\(^{2+}\) than the aforementioned synaptotagmins, the functional data in fact evince an, as yet, unidentified trigger with an affinity comparable with that for synchronous release, but with slower binding and markedly lower co-operativity (second power) [5]. Finally, spontaneous release, perhaps surprisingly, depends on synaptotagmin 1 as it is affected by mutations altering the Ca\(^{2+}\)-binding affinity of the sensor. However,
Figure 1 | Presynaptic pathways in the regulation of Ca\textsuperscript{2+}ic and downstream effectors/signalling

4-AP-mediated depolarization of nerve terminals leads to Ca\textsuperscript{2+}ic-influx via VDCCs. The increase in cytosolic [Ca\textsuperscript{2+}]: (i) evokes small synaptic vesicle (SSV) exocytosis; (ii) leads to Ca\textsuperscript{2+}-dependent phosphorylation through CaM (W7-sensitive); (iii) mobilizes RyR-dependent Ca\textsuperscript{2+}ic stores (I) to produce ICR (ryanodine-sensitive); and (iv) stimulates Ca\textsuperscript{2+}-dependent PLC (U73122-sensitive), which effects breakdown of PtdIns(4,5)\textsubscript{2} (PI\textsubscript{2}) to second messenger diacylglycerol (DAG) and Ins\textsubscript{3} (IP\textsubscript{3}), the latter mobilizing IP\textsubscript{3}-R-dependent Ca\textsuperscript{2+}ic stores (II) and thus invoking ICR (2-APB-sensitive). (v) GPCRs such as mGluR1/5, coupled through G\textsubscript{q}, stimulate PLC to produce Ins\textsubscript{3} and thus mobilize IP\textsubscript{3}-R-dependent Ca\textsuperscript{2+}ic stores (II) to invoke ICR (2-APB-sensitive). Increases in cytosolic [Ca\textsuperscript{2+}] due to Ca\textsuperscript{2+}ic release from stores (I and/or II) could (vi) support exocytosis directly; or (vii) stimulate Ca\textsuperscript{2+}-dependent phosphorylation through CaM (W7-sensitive) to affect release indirectly. Ca\textsuperscript{2+}/CaM supports CaMKII directly, and ERK1/2 indirectly. (viii) CaMKII- and ERK1/2-dependent phosphorylation of synapsin I reduces the tethering SSVs to the actin cytoskeleton, to effectively recruit SSVs from a reserve pool (RP) into a readily-releasable pool (RRP) of neurotransmitter, and thereby facilitate neurotransmitter release. Na\textsuperscript{+}/K\textsuperscript{+}-ATPase is a major of user of nerve terminal ATP, and is thus a primary target of brain ischaemia. Direct pharmacological inhibition of Na\textsuperscript{+}/K\textsuperscript{+}-ATPase by ouabain simulates this situation in vitro, and leads to nerve terminal depolarization, VDCC activation and mobilization of Ca\textsuperscript{2+}ic stores (see above), which might underpin pathophysiological increases in neurotransmitter (glutamate) release.

when synaptotagmin 1 is ablated, spontaneous release evidently adopts the Ca\textsuperscript{2+} sensor attributed to asynchronous release [8].

Notwithstanding the identity of Ca\textsuperscript{2+} sensors, if Ca\textsuperscript{2+}ic store-derived Ca\textsuperscript{2+} is to directly expedite exocytosis, the spatiotemporal characteristics of the elevation of cytosolic [Ca\textsuperscript{2+}] produced must, to some degree, mimic those occurring following Ca\textsuperscript{2+}ec influx (Figure 1). That is, to contribute to neurotransmitter release directly, the release of Ca\textsuperscript{2+}ic must be of sufficient magnitude and speed in the context of a single action potential. In situations where these strict criteria are not fulfilled, Ca\textsuperscript{2+}ic stores may nevertheless contribute to the facilitation of neurotransmitter release, through modulatory influences ultimately coding presynaptic plasticity.

Key factors that would be expected to affect the impact of Ca\textsuperscript{2+}ec release include the proximity of the Ca\textsuperscript{2+}ic stores to active zones, the intraterminal buffering capacity, the degree of loading of the Ca\textsuperscript{2+}ic, and the frequency of stimulation. There is ultrastructural evidence to suggest that putative Ca\textsuperscript{2+} stores are often juxtapositioned to active zones [3]. Coupled with the small size of many presynaptic boutons, it is feasible that Ca\textsuperscript{2+}ic stores could contribute to the Ca\textsuperscript{2+} microdomains that determine neurotransmitter release triggering. This is, however, obviously dependent on intraterminal Ca\textsuperscript{2+} buffers, but even with the diffusional constraints imposed by buffers, [Ca\textsuperscript{2+}]ec is predicted to peak in a few milliseconds or less in small terminals of \(\sim 1-2 \mu \text{m}\) radius. The size of the Ca\textsuperscript{2+}ic signal will also rather depend on the extent to which the store is loaded before stimulation; this may not only determine the amount of Ca\textsuperscript{2+} released when a store is replete, but also could alternatively reflect net Ca\textsuperscript{2+} uptake/buffering if the compartment is relatively depleted.

Finally, the impact of store-derived Ca\textsuperscript{2+}ic may possibly be realized under conditions of repetitive stimulation. Under this type of stimulation paradigm, residual Ca\textsuperscript{2+} levels following Ca\textsuperscript{2+}ec influx would in any case rise as a result of some mitigation of buffering capacity, but, importantly, this may additionally produce conditions under which the
Ca^{2+}_{ic} store-derived signal can actually manifest in directly triggering neurotransmitter release (Figure 1).

### Ca^{2+}_{ic} stores and pharmacological regulators

The major Ca^{2+}_{ic} stores derived from smooth endoplasmic reticulum, which are virtually omnipresent in mammalian cells, are those activated by RyRs (ryanodine receptors) and IP₃Rs (Ins₃P₃ receptors) [9]. Stores with RyRs support direct CICR (Ca^{2+}-induced Ca^{2+} release), whereas IP₃Rs underpin IICR (InsP₃-induced Ca^{2+} release), which occurs following second messenger InsP₃ liberation from membrane PtdIns(4,5)P₂ metabolism by GPCR [G (Gq)-protein-coupled receptor]-activated PLC (phospholipase C). Indeed, as IICR appears to require the synergistic action of InsP₃ and Ca^{2+}, there may well be signal amplification through reciprocal interaction between IICR and CICR from independent or co-resident Ca^{2+}_{ic} stores.

RyR- and IP₃R-sensitive Ca^{2+}_{ic} stores are established and maintained by SERCA (sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase) pumps, which primarily contribute a major component of the Ca^{2+} sequestration in cells [9]. This capacity can be abrogated by SERCA pump inhibitors such as thapsigargin and cyclopiazonic acid. Interestingly, together with RyR- and IP₃R-activated Ca^{2+}_{ic} stores, there is accumulating evidence for another Ca^{2+}_{ic} store that is insensitive to thapsigargin, but is depleted by proton pump inhibitors such as bafilomycin, implying an acidic storage compartment [10]. This pool has several distinguishing characteristics, but most conspicuous is its mobilization by NAADP (nicotinic acid–adenine dinucleotide phosphate) and functional co-operation with RyR- and IP₃R-activated Ca^{2+} stores [10].

Presynaptically, even though Ca^{2+}_{ic} stores have been difficult to delineate morphologically, there is now good evidence for the presynaptic localization of both RyRs and IP₃Rs, therefore suggesting the existence of active intraterminal Ca^{2+}_{ic} stores [3]. Indeed, functional studies evince presynaptic activity-dependent mobilization of RyR-dependent Ca^{2+}_{ic} stores by CICR, as well as IICR, by presynaptic GPCR-coupled recruitment of IP₃R-dependent Ca^{2+}_{ic} pools [11]. The involvement of Ca^{2+}_{ic} stores in presynaptic function has been pharmacologically studied by the use of SERCA pump inhibitors such as thapsigargin or cyclopiazonic acid, which abrogate the Ca^{2+} sequestration aspect of RyR- and IP₃R-dependent stores. Additionally, putative modulators of RyRs, such as caffeine/theophylline (+), ryanodine (+/−), Ruthenium Red (−), dantrolene (−), and IP₃Rs, such as 2-APB (2-aminoethoxydiphenyl borate) (−) and xestospongin C (−), have also been employed to respectively elucidate the roles of CICR and IICR in a number of models, albeit with some caution given the multiplicity of targets for some of these agents. The following account reviews some of these studies in relation to neurotransmitter release at central synapses.

**Can Ca^{2+}_{ic} store-derived increases in cytosolic [Ca^{2+}] trigger exocytosis?**

A number of studies argue for the sufficiency of Ca^{2+}_{ic} stores in directly supporting exocytosis with experiments that correlate Ca^{2+}_{ic} store mobilization with spontaneous neurotransmitter release. Random increases in terminal [Ca^{2+}], variously described as ‘Ca^{2+} sparks’ and spontaneous Ca^{2+} transients [12–14], underlie increases in spontaneous neurotransmitter release indicated by increased frequencies of mIPSCs (miniature inhibitory postsynaptic currents) and mEPSCs (miniature excitatory postsynaptic currents) at inhibitory [12,13,15,16] and excitatory [17,18] synapses respectively.

Perhaps experimentally less tractable has been the delineation of the involvement of Ca^{2+}_{ic} stores in evoked release, not least because of the overarching predominance of extracellular Ca^{2+} influx through VDCCs supporting exocytosis during nerve terminal depolarization (Figure 1). Ca^{2+} responses to depolarization of hippocampal mossy fibre terminals are certainly sensitive to pharmacological manipulation of terminal and axonal Ca^{2+}_{ic} stores [19,20]. However, it would appear that, although these Ca^{2+}_{ic} stores play a modulatory role in synaptic plasticity at excitatory synapses (see below), they do not significantly affect single evoked EPSCs (excitatory postsynaptic currents) [17,21]. In contrast with the aforementioned situation at excitatory synapses, effects of CICR regulation have been noted on evoked IPSCs (inhibitory postsynaptic currents) in cerebellar Purkinje cells produced by GABA (γ-aminobutyric acid) release from basket cell terminals [22]. Arguably, the most convincing evidence for the sufficiency of Ca^{2+}_{ic} stores in supporting exocytosis has come from examples where depolarization-dependent activation of Ca^{2+}_{ic} stores and peptide release can be shown to occur in the absence of external Ca^{2+}, therefore not consequent on CICR as such, but as a result of L-type VDCCs potentially being physically coupled to the ryanodine-sensitive stores [23,24].

Interestingly, this and other studies looking at large dense-core vesicle release may well provide clear examples of exocytosis supported by Ca^{2+}_{ic} stores because of the higher-affinity Ca^{2+} sensor/trigger thought to be associated with amnergic and peptidergic exocytosis [25].

**Ca^{2+}_{ic} stores in the modulation of neurotransmitter release**

Notwithstanding the accumulating evidence for the direct role of Ca^{2+}_{ic} stores, certainly in spontaneous exocytosis, but also perhaps in evoked release in some instances, there are arguably firmer grounds for invoking Ca^{2+}_{ic} stores in the modulation of neurotransmitter release and thereby underpinning aspects of presynaptic plasticity. Apart from repetitive stimulation and influx of Ca^{2+}_{ic} via VDCCs, some ionotropic presynaptic receptors instigate Ca^{2+}_{ic} influx to initiate CICR, and subsequently contribute to presynaptic plasticity. For instance, kainate-type glutamate-receptor-mediated LTP (long-term potentiation) at mossy...
CICR are functionally interdependent. Not only can Ca\(^{2+}\) influx from nerve terminals, and thereby promotes neurotransmitter release.

Intriguingly, physical bridging of group 1 mGluRs with group 1 mGluRs through high-affinity Ca\(^{2+}\) influx 1), but it is evident that IICR may also be activated in the presence of postsynaptic Ca\(^{2+}\) stores, although it remains to be seen whether a similar mechanism operates presynaptically and indeed affects modulation of neurotransmitter release.

High-affinity presynaptic effector targets for Ca\(^{2+}\)\(_{\text{i,c}}\)

The foregoing data indicate that, in some circumstances, even when Ca\(^{2+}\)\(_{\text{i,c}}\) levels are insufficient to affect exocytosis directly, Ca\(^{2+}\)\(_{\text{i,c}}\) stores may nonetheless be of paramount importance in a regulatory role. Thus, mechanistically, Ca\(^{2+}\)\(_{\text{i,c}}\) store-derived Ca\(^{2+}\) may contribute to the modulation of steps upstream of exocytosis itself, e.g. during vesicle recruitment and priming. This is feasible because some of these steps are contingent on the activation of high-affinity Ca\(^{2+}\) sensors, which would be activated by cytosolic [Ca\(^{2+}\)] that may be an order of magnitude lower than the activation threshold for the relatively low-affinity Ca\(^{2+}\) triggering of exocytosis, but above the resting cytosolic [Ca\(^{2+}\)] (50–100 nM). The major candidate in this regard is the prototypic Ca\(^{2+}\)-binding protein CaM (calmodulin), which, with a Ca\(^{2+}\) affinity in the sub-micromolar range (500 nM) [40], is ideally suited to sense regulatory bulk changes in cytosolic [Ca\(^{2+}\)] resultant from Ca\(^{2+}\)\(_{\text{i,c}}\) influx or indeed Ca\(^{2+}\)\(_{\text{i,c}}\) store activation. Ca\(^{2+}\)\(_{\text{i,c}}\)-binding proteins with even higher affinity may well respond to resting [Ca\(^{2+}\)] [41].

CaM has numerous neuronal effectors, including proteins such as Munc13, myosin V, Rab3A and synaptobrevin, representing effectors that are either essential for exocytosis or are important for the modulation of neurotransmitter release [42]. Interestingly, in this regard, the essential Munc13 family of vesicle priming proteins are modulated by Ca\(^{2+}\)\(_{\text{i,c}}\) alone at low cytosolic [Ca\(^{2+}\)], but employ Ca\(^{2+}\)/CaM at the higher [Ca\(^{2+}\)] that prevails during nerve terminal activity [43]. One CaM effector that has major relevance in the activity-dependent modulation of presynaptic function is CaMKII (Ca\(^{2+}\)/CaM kinase II). The role of this effector in neurotransmitter release and its potential as a high-affinity sensor for Ca\(^{2+}\)\(_{\text{i,c}}\) store activation is discussed below.

CaMKII is a multifunctional protein kinase [44,45] with a conspicuous presence on synaptic vesicles [46,47]. As such, it was shown some years ago to facilitate neurotransmitter release [48] through a mechanism involving synapasin I [49], one member of a family of neuronal- and nerve-terminal-specific proteins (Figure 1) [50]. Synapasin I cross-links small synaptic vesicles with the actin cytoskeleton [51] and, in so doing, defines a reserve pool (Figure 1) of neurotransmitter release. Activity-dependent stimulation of CaMKII effects phosphorylation of synapasin I at specific sites and promotes the recruitment of synaptic vesicles [52] into a pool of vesicles that can be primed for entry into a readily-releasable pool (Figure 1). CaMKII activation can evidently occur with increases of cytosolic [Ca\(^{2+}\)], which are subthreshold with respect to triggering of exocytosis, but sufficient to effect synapasin I phosphorylation [53]. Consequently, CaMKII-dependent phosphorylation of synapasin I therefore represents a potential target for Ca\(^{2+}\) released by Ca\(^{2+}\)\(_{\text{i,c}}\) store activation, through either CICR or IICR (Figure 1). The former could well form the basis of action potential integration by Ca\(^{2+}\)\(_{\text{i,c}}\) store activation in isolated nerve terminals (synaptosomes), an ideal biochemical model for

Addressing Ca\(^{2+}\)\(_{\text{i,c}}\) store activation in isolated nerve terminals (synaptosomes), an ideal biochemical model for...
looking at neurotransmitter release, proves difficult because the small size of the terminals precludes the optical delineation of stores using fluorimetric reporters, even if reporters of appropriate affinity for detecting small changes in $[Ca^{2+}]_{ic}$ are available. Alternatively, the detection of discrete changes in cytosolic $[Ca^{2+}]$ can be expedited by virtue of the ability of the cation to activate CaM-dependent phosphorylation. Notably in this regard, activation of CaMKII [33] and synaptosomal ERK (extracellular-signal-regulated kinase) 1/2 [55,56] can be used as sensors for $Ca^{2+}$c stores mobilization (Figure 1).

$Ca^{2+}$ influx into synaptosomes throughVDCCs activated by the K+-channel blocker 4-AP (4-aminopyridine)-induced depolarization, or directly using the $Ca^{2+}$ ionophore ionomycin [56], evince CICR sensitive to the SERCA pump inhibitor thapsigargin (Figure 1) [35]. Thapsigargin is a well-established tool which depletes RyR- and IP3R-dependent inhibitor thapsigargin (Figure 1) [35]. These data suggest that activation of $Ca^{2+}$c stores by way of the inherent leakiness of these compartments, or the inability of stores to refill after previous activation/depletion. Tentative evidence for IICR arises in this model from the sensitivity of $Ca^{2+}$-dependent kinase phosphorylation/activation to the IP3R inhibitor 2-APB. Although the latter agent is known to have other targets [57], credence for a GPCR/PLC/IP3R signalling cascade has been provided by experiments using the mGluR1/5 receptor agonist DHPG (3,5-dihydroxyphenylglycine). mGluR1/5 activation couples, through Gq, to stimulate PLC to generate $P_{i}$3 from PtdIns(4,5)P2 [58]. DHPG-mediated increases in phosphorylation [59] were dependent on CaM (i.e. inhibited by the CaM inhibitor, W7) and were sensitive to thapsigargin pre-treatment (Figure 1) [35], invoking the role of $Ca^{2+}$c stores in the mGluR1/5-mediated facilitation of glutamate release reported previously [33,60].

Dysfunction of the regulatory roles of the invoked presynaptic $Ca^{2+}$c stores, could contribute to synaptopathies. Following neuronal/nerve terminal ischaemia, one immediate consequence of the resultant reduced levels of ATP would be a compromised Na+/K+-ATPase activity, which is responsible for the electrogenic maintenance of Na+-gradients (3 Na+ out/2 K+ in) across neurons and other excitable cells. To model this pathophysiological paradigm, synaptosomal Na+/K+-ATPase activity can be inhibited pharmacologically using the glycoside ouabain (Figure 1). This treatment has the advantage of leaving ATP levels intact, thus obviating any general effects on kinases which obviously use the nucleotide as a substrate. Ouabain treatment of synaptosomes increases $Ca^{2+}$-dependent kinase phosphorylation/activation, which was again sensitive to pre-treatment with the calmodulin inhibitor W7 and SERCA pump inhibitor thapsigargin (Figure 1) [35]. These data suggest that activation of CICR following Na+/K+-ATPase inhibition may lead to stimulation of signalling resulting in overactivation of exocytosis [61]. Thus, at central synapses, ‘inappropriate’ mobilization of intraterminal $Ca^{2+}$c stores (and downstream effects) may be one deleterious consequence of a compromised Na+/K+-ATPase activity. For instance, following ischaemic insult, initial hyperactivation of general $Ca^{2+}$-dependent signalling instigated by $Ca^{2+}$c store-derived $Ca^{2+}$ may initiate a sequence of events leading to an excessive stimulation of glutamate release, known to be instrumental in excitotoxicity.

**Conclusions**

There is increasing evidence to suggest that intracellular $Ca^{2+}$c stores resident in nerve terminals can directly support spontaneous neurotransmitter release in some models for neurotransmitter release, and also evoked release in other studies. Most compelling is the increasing evidence that $Ca^{2+}$c stores are instrumental in modulatory events upstream of exocytosis which may impinge on neurotransmitter release and presynaptic plasticity. Given the part played by $Ca^{2+}$c stores in nerve terminal function, dysfunction of this mechanism could underlie the pathophysiology following nerve terminal ischaemia.

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