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Review

Endoplasmic reticulum stress in insulin resistance and diabetes

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ABSTRACT

The endoplasmic reticulum is the main intracellular Ca^{2+} store for Ca^{2+} release during cell signaling. There are different strategies to avoid ER Ca^{2+} depletion. Release channels utilize first Ca^{2+}-bound to proteins and this minimizes the reduction of the free luminal $[Ca^{2+}]$. However, if release channels stay open after exhaustion of Ca^{2+}-bound to proteins, then the reduction of the free luminal ER $[Ca^{2+}]$ (via STIM proteins) activates Ca^{2+} entry at the plasma membrane to restore the ER Ca^{2+} load, which will work provided that SERCA pump is active. Nevertheless, there are several noxious conditions that result in decreased activity of the SERCA pump such as oxidative stress, inflammatory cytokines, and saturated fatty acids, among others. These conditions result in a deficient restoration of the ER $[Ca^{2+}]$ and lead to the ER stress response that should facilitate recovery of the ER. However, if the stressful condition persists then ER stress ends up triggering cell death and the ensuing degenerative process leads to diverse pathologies; particularly insulin resistance, diabetes and several of the complications associated with diabetes. This scenario suggests that limiting ER stress should decrease the incidence of diabetes and the mobility and mortality associated with this illness.

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1. Introduction

Insulin resistance is a systemic condition (affects all cells in the body) that is asymptomatic (which makes difficult to treat and prevent) and eventually could lead to different ailments, particularly diabetes, although has been involved in the genesis of other chronic degenerative diseases such as hypertension, non-alcoholic steatohepatitis, erectile dysfunction, Alzheimer, Parkinson, among others [1].

A major factor involved in the genesis of insulin resistance is stress of the endoplasmic reticulum (ER). This is a condition of endoplasmic reticulum dysfunction triggered by either chemical or physical signals that lead to homeostatic compensatory responses by the ER. These responses lead to restauration of cell function particularly if the stressful signals are not permanent. However, in many cases the stressful signals are maintained for prolonged periods of time and this leads to maladaptive ER stress responses that end up in cell death [2,3]. Once the cell reserve (present in all organs) has eroded, the symptoms arise and the illness manifests, giving physicians a limited room of action. Therefore, it is important to understand those conditions that lead to ER stress, to prevent them in order to reduce the rate at which cell reserve is spent, and retarding the appearance of the symptomatic stage of the disease.

The topics reviewed here are: (1) How the ER controls intracellular and intraluminal $[Ca^{2+}]$. (2) How ER communicates and regulates activity of other organelles in particular plasma membrane and mitochondria. (3) How ER stress is generated. (4) The role of ER stress in diabetes and particularly in endothelial cell (EC) dysfunction which is at the root of many diabetic complications. It is our believe that understanding the cell physiology of ER should lead to better translational approaches that might decrease the rate at

Abbreviations: AGES, advanced glycation end products; BI-1, Bax inhibitor-1; CPA, cyclopiazonic acid; CICR, calcium-induced calcium release; EC, endothelial cell; eNOS, endothelial nitric oxide synthase; ER, endoplasmic reticulum; IP_3R, inositol 1,4,5-trisphosphate receptor; NO, nitric oxide; PM, plasma membrane; ROS, reactive oxygen species; RyR, ryanodine receptor; SERCA, sarco/endoplasmic reticulum calcium ATPase; SOCE, store operated calcium entry; SOICR, store overload induced calcium release; SR, sarcoplasmic reticulum; STIM, stromal interaction molecule; STZ, streptozotocin; UPR, unfolding protein response.

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which cell reserve is diminished and accordingly, a reduction in the prevalence of non-communicable, chronic degenerative ailments.

2. Role of endoplasmic reticulum in controlling intracellular and intraluminal [Ca^{2+}]

The endoplasmic reticulum (ER) is a membrane compartment located throughout the cell, it surrounds the nucleus and is involved in different cell functions, such as synthesis of protein and lipids, folding and maturation of proteins, detoxification of drugs and chemicals, etc. However, it is also the major intracellular Ca^{2+} store that is always facing a conundrum of how to supply Ca^{2+} for different cell activities (contraction, secretion, plasma membrane excitability, ATP synthesis, gene transcription, etc.) without inducing ER stress due to the reduction of the luminal [Ca^{2+}]. In normal conditions, ER Ca^{2+}-release and -refilling mechanisms are coordinated to minimize the reduction of the free luminal [Ca^{2+}] and to avoid triggering ER stress [4]. The resting free luminal ER [Ca^{2+}] ($[Ca^{2+}]_L$) is in the submillimolar range whereas the cytoplasmic free [Ca^{2+}] ($[Ca^{2+}]_i$) is around 100 nM. This large Ca^{2+} gradient between cytoplasm and the ER requires both the action of sarco-endoplasmic reticulum Ca^{2+} ATPase (SERCA pump) and a reduced activity of leak and release Ca^{2+} channels present in the membrane of ER. Using ratiometric genetically encoded luminal ER Ca^{2+} indicators has been observed a large variability in the resting $[Ca^{2+}]_L$ [5,6]. Since this is more evident in the upper end of the $[Ca^{2+}]_L$ determinations, it has been argued that this is artificial due to saturation of the ratiometric indicators [7]. Although this might be the case for erGAP1 which is of high affinity (12 μM); this cannot be true for GEM-CEPIA1er because it has a much lower affinity for Ca^{2+} (558 μM). Indeed, bradykinin (after the initial reduction of the $[Ca^{2+}]_L$) induces elevation of $[Ca^{2+}]_L$ well above resting level in HeLa cells, arguing against the indicator being saturated *in situ* [6]. These data suggest a large variability in the activity of SERCA pumps and ER Ca^{2+} channels in resting, unstimulated cells. It is important to explain this difference because it could be the reason behind different propensity among cells in the induction of ER stress.

2.1. SERCA pump, the ER Ca^{2+} refilling mechanism

The main mechanism loading ER with Ca^{2+} is the sarco endoplasmic reticulum Ca^{2+} ATPase or SERCA pump. SERCA1a from skeletal muscle has been crystalized in different conformational states providing further support to the proposed catalytic cycle [8]. This membrane protein of ER contains 10 transmembrane alpha helices and a bulky cytoplasmic part formed by three sections named A, N and P [8]. This protein is responsible for the high $[Ca^{2+}]_L$ (in the submillimolar range for free and tens of mM for total) detected in the ER [9]. The transport of Ca^{2+} from cytoplasm to the ER requires hydrolysis of ATP to move Ca^{2+} against its electrochemical gradient. This can be achieved by cycling between two different conformations, E1 of high affinity and E2 of low affinity for Ca^{2+}. ATP is bound in the N region while Ca^{2+} is recognized by the transmembrane region [8]. There are three main inhibitors of SERCA pump: thapsigargin, cyclopiazonic acid and ter-butyl hydroquinone [10]. Thaspigargin is the most potent and practically irreversible inhibitor that binds to the conformation E2 and stops SERCA pump cycle [8]. Any chemical or physical condition that inhibits cycling of SERCA pump results in its inhibition and eventually could lead to depletion of Ca^{2+} store due to the presence of a yet to be identified Ca^{2+} leak channel. There are three different genes and alternative splicing of these genes codify for at least 11 different SERCA pump isoforms (for a review see [180]). Apparently, SERCA pump works in dimers [11] but it is not clear whether only homodimers are formed or there are also heterodimers. ECs express two different isoforms of SERCA pump; SERCA3 and SERCA2b with the former in higher levels than the latter. SERCA2b is more sensitive to oxidative stress than SERCA3 [12]. This in principle would protect ER Ca^{2+} store of ECs from the depleting action of ROS. Indeed, peroxynitrite (200 μM) inhibited the CPA-induced Ca^{2+} response only in pig coronary artery smooth muscle cells (rich in SERCA2) while did not reduce CPA-mediated response in ECs from the same vasculature [13]. However, in ECs from heart of streptozotocin-induced diabetic rats displayed a reduced internal Ca^{2+} store due to decreased activity of SERCA pump [14]. Direct measurement of $[Ca^{2+}]_L$ with Magfura-2 demonstrated that streptozotocin-induced diabetes is associated with a reduced $[Ca^{2+}]_L$ in mouse coronary endothelial cells. This situation results from both a reduced expression of SERCA 3 and also a decreased Ca^{2+} entry at the plasma membrane. The latter was fixed by overexpression of STIM1 that restored $[Ca^{2+}]_L$ [15]. These data suggest that diabetes is associated with a reduced $[Ca^{2+}]_L$ in ECs due both to decrease level of SERCA pump and to reduce Ca^{2+} influx that limits Ca^{2+} access to the pump.

2.2. Luminal ER Ca^{2+} binding proteins

The calcium buffer capacity of endoplasmic reticulum depends on the expression of Ca^{2+}-binding proteins of low affinity and high capacity, for instance calreticulin [16,17]. The distribution of these proteins within the ER appears not to be homogenous based on the observation of regions of high Ca using electron microprobe that are in contact with regions of low Ca^{2+} inside the ER without any obvious diffusion barriers [18]. Actually, Ca^{2+} diffusion inside the ER is rather fast suggesting the absence of diffusion barriers and in agreement with the idea that these Ca^{2+}-binding proteins are of low affinity and fast equilibration times [19]. ECs express calreticulin and calnexin and they are involved in both increasing the buffering capacity of ER and regulating the release activity of IP_3Rs [20]. The absence of calreticulin strongly increases Akt activation by insulin via the PI3K pathway [21]. These data indicate that luminal ER Ca^{2+}-binding proteins generate two different compartments in the ER, one of the free $[Ca^{2+}]_L$ (that is homogenous within the lumen of the ER) and the other of Ca^{2+} bound to proteins (limited by the localization of these proteins within the ER lumen).

2.3. ER Ca^{2+} release channels

There are two main Ca^{2+} release channels; these are the IP_3 receptors (IP_3Rs) and ryanodine receptors (RyRs). These two release channels although are quite different in size, they appear to have a common ancestor [22], there are three genes for IP_3Rs [23] and three other for RyRs. RyR1 is characteristic of skeletal muscle, RyR2 of cardiac muscle and RyR3 was identified as a protein responding to TGF-β in mink lung epithelial cells [24] but is constitutively expressed in skeletal muscle, neurons, smooth muscle cells and some other non-excitable cells [25]. The ER of ECs expresses both IP_3Rs and RyRs. However, of the three isoforms of RyRs, ECs express only type 3 [26,27]. Interestingly, it appears that RyRs are segregated within the ER of ECs because they are localized in regions that are in close apposition to the plasma membrane. Indeed, application of caffeine to activate RyR3 diminished the Acetylcholine-induced $[Ca^{2+}]_i$ response but caffeine *per se* did not induce any $[Ca^{2+}]_i$ response [28]. Indeed, histamine appears to activate this peripheral RyR3s and participate in the activation of Ca^{2+}-dependent potassium channels [29]. Interestingly, Ca^{2+} depletion of the ER with thapsigargin induces a slow process (slower than the activation of capacitative Ca^{2+} entry) of translocating RyRs from the ER to the plasma membrane. Indeed, caffeine application now produces $[Ca^{2+}]_i$ response that depends completely of the presence of external Ca^{2+} and occurs in a Ca^{2+} depleted ER [30]. Moreover, removal of FKBP12/12.6, which are inhibitory proteins of RyRs,

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