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Mini Review

Role of the Na^+/Ca^{2+} exchanger on the development of diabetes mellitus and its chronic complications

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ABSTRACT

Diabetes mellitus (DM) is a serious metabolic disorder with micro- and macrovascular complications that results in significant morbidity and mortality. It is well established that cytosolic Ca^{2+} play an important role in controlling insulin secretion in pancreatic β-cells. The Na^+/Ca^{2+} exchanger (NCX), an ion transport protein, is expressed in the plasma membrane of virtually all animal cells. NCX is a reversible carrier that can mediate the transport of Ca^{2+} across the plasma membrane in both directions. Therefore, great efforts have been made to identify NCX associated with DM. NCX is expressed in several tissues, and acts in the protection against intracellular calcium overload; in the regulation of insulin secretion by beta cells, and in improving vascular endothelium-dependent relaxation. All these mechanisms are associated with DM pathogenesis and its chronic complications. Therefore, NCX is a candidate protein for the development of these disorders. Only a few studies investigated NCX in relation to chronic complications of diabetes, with inconclusive results.

1. Introduction

Ca^{2+} is a very important signaling molecule within cells. Many cellular functions are directly or indirectly regulated by the free cytosolic Ca^{2+} concentration ($[Ca^{2+}]_i$) [1]. The $[Ca^{2+}]_i$ must be very tightly regulated in time, in space and in amplitude because cells manage to extract specific information from these three parameters. Because Ca^{2+} is such an important signaling molecule, mutations causing drastic functional changes in intracellular Ca^{2+} homeostasis are most likely not compatible with life [1]. Activator Ca^{2+} from the extracellular space enters the cell through various types of Ca^{2+} channels and sometimes the Na^+/Ca^{2+} exchanger (NCX), and is actively extruded from the cell by Ca^{2+} pumps and NCX [2]. In general, Ca^{2+} concentration is about 1000 times higher outside than inside the cells. Therefore, it is not possible for Ca^{2+} to exit from the cells on its own, and a driving force is necessary for Ca^{2+} to be extruded from the cell. NCX is a membrane transporter which carries one Ca^{2+} efflux in exchange for 3 Na^+ influx. NCX easily reverses its direction and brings Ca^{2+} into the cells, if the Na^+ concentration gradient decreases and/or the membrane potential becomes less negative [2]. The following equation is used for the calculation of equilibrium potential of NCX: $E_{NCX} = 3E_{Na} - 2E_{Ca}$ where E_{NCX} is the equilibrium potential for NCX, E_{Na} is the equilibrium potential for Na and E_{Ca} is the equilibrium potential for Ca^{2+} [2].

NCX is comprised of 9 transmembrane segments with a long internal loop between the 5th and 6th transmembrane segments [3]. There are three isoforms of NCX, namely NCX1, NCX2 and NCX3 [4]. NCX1 is the ubiquitous type and the one most abundantly expressed in the heart. NCX2 is expressed in the brain and NCX3 in the skeletal muscle [4]. Ni^{2+} was used as a nonselective inhibitor of NCX until the first relatively selective NCX inhibitor, KB-R7943, was developed, and subsequently SEA0400 as a more selective NCX inhibitor [5–7]. Some antiarrythmic drugs listed in the Sicilian gambit, including aprindine, azimilide, bepridil, cibenzoline, amiodarone and its derivative dronedarone, inhibited cardiac NCX current at a concentration range overlapping or slightly higher than the therapeutic concentrations [8–10]. More recently, YM-244769 and SN-6 were developed as new NCX inhibitors [11,12].

2. NCX and diabetes mellitus

It is now widely accepted that decreased β-cell function, resulting in inadequate insulin secretion, is a key component of type 2 diabetes pathophysiology [13]. Indeed, pharmacological agents such as sulfonylureas are used clinically to stimulate insulin secretion in type 2 diabetes. However, there is no absolute requirement for elevated glucose in order for sulfonylureas to stimulate insulin secretion via inhibition of β-cell ATP-sensitive K^+ channels (K_{ATP} channels). Consequently, hypoglycemia is a significant concern with sulfonylurea therapy [13], and there is much interest in the

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development of insulinotropic drugs with improved glucose sensitivity.

In the pancreatic β-cell, cytoplasmic calcium (Ca_c^{2+}) levels rise as a direct consequence of glucose metabolism, via closure of K_{ATP} channels, triggering Ca^{2+} entry and subsequent Ca^{2+}-mediated exocytosis of insulin granules [14]. Therefore, partial inhibition of any protein involved in the removal of Ca_c^{2+} during β-cell excitation should augment insulin secretion only when β-cells are stimulated. One potential candidate protein is NCX1, which is a membrane protein involved in the extrusion of Ca_c^{2+} in many tissues, including the pancreatic β-cell [15–17]. NCX1 is a bidirectional ion exchanger that predominately extrudes Ca_c^{2+} during forward-mode (FM) operation when Ca_c^{2+} is elevated. NCX1 may also operate in Ca^{2+} influx mode (reverse mode; RM) that contributes to the pathophysiological increases in Ca_c^{2+} and Ca_c^{2+} overload that occurs during cardiac ischemia/reperfusion injury [18–20]. In this regard, pharmacological inhibitors have been developed as putative cardioprotective agents to reduce RM NCX1 activity and ameliorate the deleterious Ca_c^{2+} overload in cardiac tissue [21–23]. While such NCX inhibitors favor pathophysiological cardiac RM NCX1 inhibition, their effects on the physiological Ca_c^{2+} extrusion via FM NCX1 activity in β-cells have not been determined. Theoretically, partial pharmacological inhibition of FM NCX1 activity in β-cells should delay Ca_c^{2+} clearance, leading to an increased Ca_c^{2+} exocytotic signal and enhanced insulin secretion that is sensitive to glucose. Kevin results confirm that the major role for NCX1 is the facilitation of Ca_c^{2+} efflux during periods of increased β-cell excitability, namely that partial inhibition of β-cell NCX1 with KB-R7943 further increases Ca_c^{2+} only when Ca_c^{2+} is already elevated by either tolbutamide, glucose, or KCl, leading to increased exocytosis and enhanced insulin secretion only in the presence of such a stimulus. While these results have been attributed to KB-R7943 inhibiting FM NCX1 activity and directly verified by shRNA, possible effects of KB-R7943 on other calcium-handling proteins cannot be ruled out [24].

3. NCX and diabetic nephropathy

Ca^{2+} release from intracellular stores requires stimulation of vasoconstrictive hormones, angiotensin II, arginine vasopressin or thromboxane mimetics which act as stimulators. Binding of these molecules to phospholipase C-coupling receptor induces the release of equimolar water-soluble $InsP_3$ and diacylglycerol from membrane phosphoinositides. Consequently, $InsP_3$ mobilizes Ca^{2+} from the intracellular stores, resulting in an explosive elevation in $[Ca^{2+}]_i$ and subsequent influx of Ca^{2+} through SOCI. SOCI, also called 'capacitative' or Ca^{2+} release-activated Ca^{2+} channel influx, sustains Ca^{2+} influx following $InsP_3$-mediated Ca^{2+} release [25,26]. Recent investigations revealed that the $[Ca^{2+}]_i$ response of MCs to vasoactive hormones is blunted in high-glucose conditions including the function of SOCI [27]. These changes contribute to the loss of contractility of MCs in response to vasoactive hormones and are relevant to hyperfiltration and microalbuminuria in early diabetic nephropathy. As diabetic nephropathy progresses, the pathophysiological features other than contractile abnormality appear, such as phenotypic changes, deranged proliferative rate, apoptosis and death. These Ca^{2+}-dependent cellular dysfunctions are related to a sustained 'tonic' elevation, rather than a responsive increase in stimulators of $[Ca^{2+}]_i$. The adverse role of elevated basal $[Ca^{2+}]_i$ have already been reported in many other cells in various pathophysiological conditions [28,29]. Two recent studies report that intracellular Ca^{2+} signals are related to the regulation of proliferation in MCs [30]. Therefore, we focused on the effect of high glucose on basal $[Ca^{2+}]_i$ and its regulation in MCs that are not stimulated.

The most recently discovered that the activity of NCX was depressed in MCs cultured in the high-glucose condition and the peak $[Ca^{2+}]_i$ following NCX stimulation was significantly decreased by high glucose [31]. The change in NCX function may relate to a number of pathophysiological changes that depend on the intracellular Ca^{2+} signal. In Western Blot analysis, the depression in NCX by high glucose was revealed to occur at the level of protein expression. The investigation on the pathophysiological role of altered NCX in MCs will be an interesting subject in the field of diabetic nephropathy.

4. NCX and diabetic cardiomyopathy

Diabetic cardiomyopathy is an important clinical entity predisposing individuals to ventricular dysfunction and arrhythmogenesis. Calcium cycling is disturbed in the diabetic heart and understanding the involvement of calcium cycling in the cardiomyocyte will give insight into the pathogenesis of diabetic cardiomyopathy [32]. Diabetic cardiomyopathy is defined in part by diastolic and systolic impairment, myocardial remodeling, and inflammation absent from other independent risk factors such as hypertension and coronary artery disease [33]. Diabetic cardiomyopathy is characterized, in part, by calcium handling imbalances associated with ventricular dysfunction. Myocardium exposed to hyperglycemia not only alters the energetic efficiency of the cardiac myocyte, which relies heavily on fatty acid oxidation in the diabetic state, but also leads to significant alterations in activity and expression of Ca^{2+} transporters including cardiac sarco(endo)plasmic reticulum Ca^{2+}-ATPase (SERCA2a), L-type Ca^{2+} channel (LTCC), and cardiac NCX1 [34].

The molecular mechanisms of diabetic cardiomyopathy are not well understood; however, impairment of Ca^{2+} homeostasis is a significant feature of type 1 and type 2 diabetic cardiomyopathies [35,36]. In normal excitation–contraction (EC) coupling, Ca^{2+} entry via LTCC triggers the release of approximately two-thirds of Ca^{2+} stored in sarcoplasmic reticulum (SR), thereby acutely raising cytosolic Ca^{2+}, which activates the contractile apparatus [37]. During diastole, ~95% of cytosolic Ca^{2+} in murine myocytes is resequestered into the SR by SERCA2a, thereby lowering $[Ca^{2+}]_i$ and allowing myocyte relaxation [37]. To maintain beat-to-beat Ca^{2+} balance, Ca^{2+} that has entered via LTCC is extruded by NCX1, with minor contributions from the plasmalemmal Ca^{2+}-ATPase [38]. The exact role of NCX1 in disease and whether it participates as a compensatory or maladaptive mechanism remain controversial. In the initial stages of clinical and experimental heart failure, SERCA2a Ca^{2+} reuptake activity and expression are decreased leading to reduced SR Ca^{2+} load and increased diastolic $[Ca^{2+}]_i$ [39]. Increased NCX1 expression and forward NCX current (Incx) is thought to contribute up to 50% of cytoplasmic calcium efflux to maintain diastolic $[Ca^{2+}]_i$ levels as a compensatory mechanism to decreased SERCA2a activity [40]. In addition, reverse Incx may contribute to Ca^{2+}-induced Ca^{2+} release (CICR) by directly contributing to local Ca^{2+} for CICR and through refilling SR Ca^{2+} content [41]. However, this may come at the cost of increased arrhythmogenesis at the cellular level [42].

In conclusion, DM and its chronic complications are multifactorial diseases associated with both genetic and environmental risk factors. Knowledge on factors associated with DM will allow us to better understand the disease and its chronic complications, and may provide us with more effective approaches to treatment and prevention. NCX plays important roles in regulation of insulin secretion by beta cells and protection against intracellular calcium overload. These mechanisms are associated with the pathogenesis of DM or its micro- and macrovascular complications. Previous work from our laboratory suggests that KB-R7943 can restore im-

paired endothelium-dependent relaxation induced by high glucose in isolated rat aorta and KB-R7943 exerted its beneficial effect by both inhibiting adhesion of monocytes to endothelial cells and the expression of Intercellular adhesion molecule-1 in endothelial cells [43,44]. Therefore, further studies characterizing the molecular basis and regulatory mechanisms of NCX will enable better understanding of the physiological role of this protein on the pathogenesis of DM. Development of drugs that modulate the activity of NCX could, in the future, become new strategies for the treatment of NCX or its chronic complications.

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