Role of Protein Kinase C in Diabetic Complications

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ARTICLE INFORMATION

ABSTRACT

Diabetes is the most common and systemic disorder associated with hyperglycemia which is the significant factor in the development of micro- and macrovascular changes. Many mechanistic approaches i.e. activation of Protein kinase C, glycation end products production, hexosamine pathway and polyol pathway induce cellular damage and lead to the development of diabetic complications like nephropathy, neuropathy, retinopathy, and myopathy. One of the adverse effects of long-lasting hyperglycemia is activation of PKC (intracellular signaling enzyme) and has become a field of great research interest. Hence, in this review special emphasis is placed on microvascular complications which are due to activation of PKC. Clinical trials have also been conducted using selective PKC inhibitors and have shown positive results against hyperglycemia.

1. Introduction

Diabetes, a chronic metabolic disorder, is a major threat nowadays worldwide (Shaw et al., 2010). The resultant hyperglycemia has been shown to be responsible for major diabetic complications like myopathy, retinopathy, nephropathy, and neuropathy which occur after a few years of onset of diabetes (Geraldes and King, 2010). It is believed that intra and extracellular changes by hyperglycemia can induce the signal transduction pathways which lead to the dysfunction of gene expression and proteins (Peppa et al., 2002). One of the most studied pathways; the diacylglycerol-Protein kinase C (DAG-PKC) pathway is activated by hyperglycemia in diabetes (Giacco and Brownlee, 2010). In this review, the functions of PKC and interconnected signaling changes in the growth of diabetic complications have been demonstrated.

Protein Kinase C (PKC)

Serine/threonine kinases are ancestors of Protein kinase C that include 12 isoforms and are differentiated according to their domains that connect calcium or DAG; mutually they control the kinase activity (Schramm et al., 2012). On the basis of biochemical properties, PKC is divided into three types: conventional PKC, novel PKC, atypical PKC (Spiegel et al., 1996). Conventional PKC connects Ca^{2+} and DAG, novel PKC binds only DAG but not Ca^{2+}, and atypical PKC binds none of them (Spiegel et al., 1996). For phosphorylation, the correct isoforms are required

for the activation of conventional and novel PKC and the existence of cofactors such as DAG and Ca^{2+} (Schramm et al., 2012). Conventional and novel PKC are elevated by diacylglycerol (DAG), which in turn is amplified by the hyperglycemia in diabetes (Spiegel et al., 1996). When they are correctly phosphorylated, an increase in Ca^{2+} or DAG will rapidly allow cells to translocate (Gonçalves, 2013). Quick and temporary increases of Ca^{2+} levels and DAG levels are frequently induced by cytokines during the activation of phospholipase C. Activation of PKC requires a sustained decrease of DAG, which involves the activated phospholipase D/C or DAGs de novo synthesis. All the above-mentioned pathways possibly participate in the activation of the DAG-PKC cascade in hyperglycemic and diabetic conditions (Michael et al., 2017).

Hyperglycemia Activates PKC

Diabetic state or hyperglycemia is responsible for the synthesis of a higher level of DAG via an elevation in the formation of glycolytic intermediate (dihydroxyacetone phosphate), which activates PKC (Tripathi and Srivastav, 2006). The most studied pathway via which PKC induces diabetes is the DAG-PKC pathway (Nilsson, 2016). DAG is induced by hyperglycemia and leads to activation of different isoforms of PKC (Tripathi and Srivastav, 2006). de novo DAG synthesis can also be increased when glucose concentration is high during different metabolic pathways (Noh and King, 2007). Another mechanism by which DAG

synthesis can be increased is by inhibiting the glyceraldehyde-3-phosphate dehydrogenase which is a glycolytic enzyme and results in upregulation of dihydroxyacetone phosphate to DAG by triggering higher metabolites from glycolysis into pathways of glucose (Nilsson, 2016). In diabetes, no changes in DAG levels were seen in a peripheral nervous system and central nervous system, but the disturbance in DAG levels was reported in vascular tissues and nonvascular tissues (Adibhatla et al., 2008).
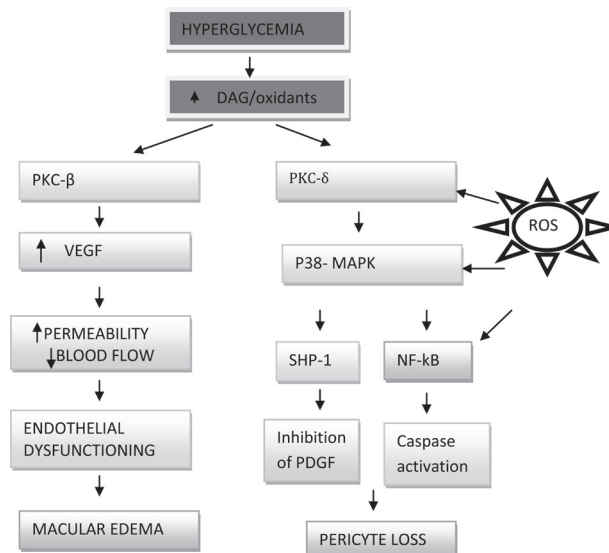
Activation of PKC Leads to Microvascular Complications

Hyperglycemia leads to diabetic complications and shows harmful effects on the human body. These complications are also due to higher levels of DAG-PKC, oxidative stress and an increased amount of glycation. Microvascular complications include retinopathy, nephropathy, neuropathy, and myopathy (Sheetz and King, 2002).

2. Retinopathy

Nowadays, many mechanistic approaches have been found by which vascular tissue damage is induced by hyperglycemia. But the major pathway which leads to microvascular changes is due to elevation in levels of DAG-PKC (Karasu, 2010). The most significant regulatory system for activation and deactivation of the receptor pathway is pursued by adding or subtracting the phosphate group in intracellular protein, via phosphatases and kinases (Carri, 2014). Phosphorylation of many proteins at threonine or serine activates the physiological responses of the cascade which are mediated by PKC. Activation of PKC induces some changes i.e retinal leakage, permeability in endothelial, loss of capillary pericytes (Carri, 2014). In the initial stages of diabetic retinopathy, there is a loss of pericyte in retina around the capillaries followed by the weakening of capillary walls and which cause the leakage of fluid due to the high permeability of walls (Nassar et al., 2007). Recent studies demonstrate that two isoforms of PKC were activated i.e PKCβ and PKCδ through hyperglycemia. Further, these isoforms follow two different approaches; PKCβ will lead to cellular growth whereas PKCδ will give rise to cellular apoptosis (Nagpal et al., 2007). PKCβ after activation affects the vascular endothelial growth factor due to which the permeability of capillary walls increases and blood flow decreases which leads to the dysfunctioning of endothelial and cause macular edema (Dirks et al., 2006). But PKCδ after activation shows two distinct pathways which ultimately lead to cellular apoptosis: 1) increase in production of reactive oxygen species and NF-κB activity which in turn activate the caspase 2) by upregulating the

SHP-1 (protein tyrosine phosphatase) which will decrease the survival signaling pathway of platelet-derived growth factor both of these different approaches results in loss of pericyte as shown below in (Nassar et al., 2007) (Figure1).

Figure 1: Hyperglycemia leads to cellular changes and retinopathy via activation of PKC.
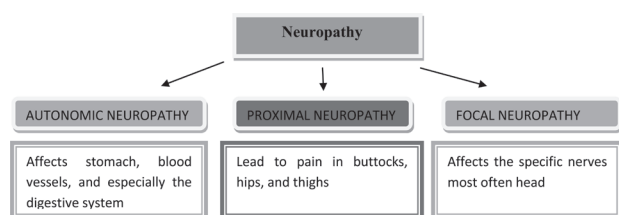
3. Nephropathy

All the causes for risk factor and cardiovascular mortality rate worldwide are due to diabetic nephropathy which is the foremost reason for the end-stage renal disease (Dirks et al., 2006). Due to hyperglycemia, there is an increase in glomerular filtration rate in the kidney which elevates the glomerular filtration pressure (Tonneijck et al., 2017). Several approaches have been studied about the elevation of glomerular rate & pressure together with improved production of prostaglandin and angiotensin II. But the most important pathway leading to an increase in angiotensin II and in vasodilatory prostaglandin is via the DAG-PKC (Kaschina and Unger, 2003). In diabetes, hyperglycemia results in the formation of prostaglandin II which could be a cause of the activation of PKC. Another factor that results in the enhancement of the filtration rate is a higher level of nitric oxide. In diabetes, high amount of nitric oxide metabolites i.e. NO_2 and NO_3 is excreted through urine due to a high level of nitric oxide present in mesangial cell and in inducible nitric oxide synthase (Williamson et al., 1993). But in hyperglycemia both i.e. formation of nitric oxide and inducible nitric oxide synthase can be initiated by an agonist of PKC and blocked by its inhibitor which shows that in PKC induced diabetes there is an increase in levels of NO synthase (Caldwell *et al* ., 2003). Previous studies

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demonstrated that there was a decrease in the production of nitric oxide and glomerular cGMP in glomeruli of diabetic rats which was restored by PKC inhibitor. Thus, this shows that possibly it might be due to an increase in the level of glucose-induced activated PKC which may supervise renal hemodynamics by elevating or declining the levels of nitric oxide production based on the sort of cells and period of hyperglycemia (Kaschina and Unger, 2003). Nephropathic studies also show that in glomerular mesangium there was an accumulation of extracellular matrix. This showed that there was an elevation in the oxidative stress due to hyperglycemia. In renal glomeruli, PKC activities were increased due to hyperglycemia which in turn upregulates many isoforms of the NADPH oxidases to generate too many oxidants (Marsigliante et al., 2001). This increased level of PKC leading to the activation of MAPK which upregulates the fibrotic growth factors. Several studies show that growth factors play a major function in the accumulation of ECM (Khera, 2006).

Current studies have shown that there is an increase in vascular endothelial growth factor (VEGF) in the glomerulus. PKC is known to regulate activator protein-1 (AP-1), which promotes the binding of AP-1 to the promoter region of the VEGF gene. AGEs are also able to activate PKC, which further increase the expression of VEGF and this activated PKC is also responsible for many natural effects of VEGF (Prabhakar, 2004).

4. Neuropathy

Diabetes can cause nerve injury. Burning, numbness, pain in the feets all are the symptoms of diabetic neuropathy (Figure 2) (Argoff et al., 2006).

Figure 2: Neuropathy: Types & effects on various Organs.

It has been demonstrated that in nerves there is an existence of PKC-α, PKC-β1, PKC-β2, PKC-γ, PKC-δ and PKC-ε isoforms which were confirmed by immunochemical analysis (Cameron et al., 2005). Whereas the exact mechanisms of their action are not clear, but currently it is believed that these factors lead to reduced Na$^+$–K$^+$–ATPase activity and vasoconstriction, reduced endoneural blood flow (Martin *et al.*, 2003). Diabetic rats have shown a decline in the activity of PKC in sciatic nerve tissue. There was also a reduction of Na$^+$–K$^+$–ATPase levels due to the involvement

of PKC which could be due to a decline in nerve regeneration and conduction (Evcimen and King, 2007). It was also demonstrated that in diabetic mice there was a reduction in membrane-associated PKC activity and when treated with PKC inhibitor sustained Na$^+$–K$^+$–ATPase action was observed (Marsigliante et al., 2001). Preclinical study also suggested that specific PKC inhibitors were used to recover the neural function i.e inhibition of PKC in nerves boost the blood flow (Brooks et al., 2008) (Figure 2).

5. Cardiovascular Disease

The diabetic patient suffers from diastolic dysfunction, interstitial fibrosis, hypertension, and congestive heart failure (Naito et al., 2001). In hyperglycemia, activated PKC gives rise to cardiomyopathy via inhibiting metabolic actions of insulin. In the myocardium, insulin loss is coupled with lower basal expression factor-1 of hypoxia, which strikes VEGF actions in the myocardium (Valko et al., 2007). In comparison to normal patients other than diabetes, diabetic patients with cardiomyopathy have shown declined expression of VEGF. Immunoblotting showed an increase in levels of PKC-β1 and PKC-β2 in the failed heart of humans as compared to a healthy live heart (Geraldes and King, 2010). Previous studies show that when the human heart was treated with LY333531 which is a PKC-β inhibitor then it leads to the inactivation of PKC (Sakata et al., 2015). In hyperglycemic condition, there is an increase in levels of PKC-α, PKC-β1 and PKC-β2 isoforms in the heart (Arimura et al., 2004). In diabetic heart, both PKC–β inhibitor and ACE improve the gene profile & PKC activity (Naito et al., 2001).The isoforms of PKC i.e. PKC-α and PKC-ε also have important functions in cardiomyopathy and elevate the contractility of the heart leading to less vulnerability to heart attacks (Arimura et al., 2004).

PKC Inhibitors

The role of PKC in the development of diabetic complications has become an area of interest for research (Gennas et al., 2009). There are many specific and non-specific compounds that have inhibitory action for PKC (Khera, 2006). Non-specific inhibitors are not in use because clinically they have been proven as toxic while specific inhibitors have shown great therapeutic use (Khera, 2006). The function of different PKC isoforms was demonstrated by observing the binding of proteins to specific sites after activation and translocation (Aielleo, 2002). Several PKC inhibitors that are being studied are Midostaurin (PKC412, CGS41251, N-benzoyl staurosporine), UCN-01 (KW-2401, NSC-638850), Lestaurtinib (CEP-701, KT-5555), Ro-31-8220 and Go6976 (Shen et al., 2003; Wang et al., 2008; Wang et al., 2009. Ro-32-0432, PKC-α inhibitor, was

found to be effective in AGE mediated damage in diabetic nephropathy. Ruboxistaurin mesylate (LY333531), a potent PKCβII inhibitor, has been evaluated in clinical studies for diabetic complications (Vinik, 2005; Joy et al., 2005; Aiello, et al., 2006). Several clinical benefits such as reduced retinal vascular leakage and improved visual acuity in diabetic macular edema, however, phase III clinical endpoints did not reproduce the desired results (American Diabetes Association, 2005). Vitamin E, a selective inhibitor, also has an inhibitory effect on the DAG–PKC but does not inhibit PKC directly (Aielleo, 2002). Vitamin E has shown a great effect in nephropathy and retinopathy (Kizub et al., 2014).

Preclinical Studies Exploring The Role of PKC in Diabetes (Table 1)

Modulation of PKC activity for clinical drug development is vital as isozyme specific disruptions in PKC activity have been identified in human disease states such as diabetes (Nishikawa et al., 2000, Geraldes et al., 2010). Therefore, understanding the basic biology of the disease and multiple pathways involved in the progression of the disease is essential for therapeutic progress in this field. As shown in table 1, various preclinical studies conducted on PKC inhibitors in diabetes and related complications have been summarised.

Table 1: Preclinical Studies Exploring the role of PKC in Diabetes.

S. No	TITLE	SUMMARY
1	Protein kinase C inhibition and diabetic retinopathy: a shot in the dark at translational research	Donnelly et al studied that activated PKC leads to diabetic retinopathy is one of the major complications of hyperglycemia can be treated with drugs that can lower the cholesterol levels combined with ACE inhibitors (Donnelly et al., 2014).
2	The role of protein kinase C activation and the vascular complications of diabetes.	Evcimen and King studied that activated PKC results in diabetic retinopathy, nephropathy, and cardiovascular disease. So, to cure these complications, use of PKC inhibitors has been introduced with great therapeutics approaches (Evcimen and King, 2007).
3	The role of protein kinase C activation in diabetic nephropathy	Noh and king concluded that PKC plays a major role in diabetes nephropathy (Noh and king, 2007)
4	Ruboxistaurin: PKC-β inhibition for complications of diabetes	Danis and Sheetz demonstrated that activated PKC plays a major role in the development of diabetic complications and they concluded the beneficial effect of PKC-β inhibitor against complications (Danis and Sheetz, 2009).
5	Activation of Protein Kinase C Isoforms and Its Impact on Diabetic Complications	Geraldes and King presented that one of the chronic adverse effects of hyperglycemia is the activation of PKC which cause vascular dysfunction and ultimately worsen the diabetic complications (Geraldes and King, 2010).
6	Old Suspect-New Evidence The Role of PKCβ in Diabetes Mellitus–Accelerated Atherosclerosis	Butcher and Galkina suggested the potential effects of hyperglycemia-induced atherosclerosis via PKCβ signaling pathway (Butcher and Galkina, 2013).
7	Hyperglycemia-induced Oxidative Stress and its Role in Diabetes Mellitus related cardiovascular diseases	Vanessa et al demonstrated that hyperglycemia is associated with many intercellular pathways which can induce cardiovascular changes and exploring many beneficial antioxidant therapies to prevent complications (Vanessa et al., 2013).
8	Protein kinase C in enhanced vascular tone in diabetes mellitus	Kizub et al studied that the microvascular complications of diabetes are mainly due to hyperglycemia which ultimately activate protein kinase C (Kizub et al., 2014).
9	Role of protein kinase C in podocytes and development of glomerular damage in diabetic nephropathy	Teng et al suggested that in diabetes the glomerular injury is due to the activation of PKC (Teng et al., 2014).
10	Increases in PKC gamma expression in the trigeminal spinal nucleus is associated with orofacial thermal hyperalgesia in streptozotocin-induced diabetic mice	Xie et al studied that in diabetes the isoform PKCγ is involved and can be dealt with early insulin management (Xie et al., 2015).
11	PKC-α triggers EGFR ubiquitination, endocytosis and ERK activation in podocytes stimulated with high glucose	Lei et al demonstrated that hyperglycemia leads to activation of PKC-α which contributes to podocyte damage (Lei et al., 2017).
12	Berberine ameliorates diabetic neuropathy: TRPV1 Modulation by PKC pathway	Zan et al demonstrated that diabetic pain can be cured by berberine which suppresses and blocks the activation of the PKC pathway (Zan et al., 2017)

| 13 | Impairment of neurovascular coupling in Type 1 diabetes mellitus in rats is prevented by pancreatic islet transplantation and reversed by a semi selective PKC inhibitor | Vetri et al concluded that DM can be prevented by PKC-α/β/γ inhibitor or via transplantation of pancreatic islet (Vetri et al., 2017). |
| 14 | Pueraria tuberosa extract inhibits iNOS and IL-6 through suppression of PKC-α and NF-kB pathway in diabetes-induced nephropathy | Shukla et al demonstrated that in diabetic nephropathy PTY-2r shows the nephroprotective effect via the down-regulation of PKC-α pathway (Shukla et al., 2018). |

Other Therapeutic Implications and Role of PKC

Current studies have shown that in cardiac patients there is an elevation in levels of PKCα which leads to many heart diseases like heart attack and atherosclerosis. Ro 32–0432 and Ro 31–8220 are the PKC inhibitors which are used to reduce the levels of PKCα as also observed with the reduced the levels of PKCα in left ventricle tissues which have lowered the risk of cardiac diseases (Weeks and McMullen, 2018). In manic and bipolar disorder patients, the levels of PKC are elevated so to reduce the manic symptoms the PKC inhibitors are used. Recent findings have shown that PKC inhibitors i.e tamoxifen have the same effects as compared to valproate and lithium (Zarat and Manji, 2009). As data obtained from preclinical studies showed that Phorbol ester and Bryostatin-1 are the potent PKC activator which helps in the reduction of tumor growth and is a modulator of many signaling pathways. Many PKC inhibitors are still under preclinical studies like Quercetin, Tamoxifen, Safingol, and LY900003, etc. Some of them are under phase II and III clinical trials (Sherova et al., 2006). In many clinical trial phases, the various PKC inhibitors together with partially specific or specific inhibitors have been applied (Capdeville et al., 2002).

Clinical Perspective of PKC

In leukemia patients, phase I studies were conducted to see the positive outcomes of paramethoxymethyamphetamine (PMA) and additionally PMA in combination with 25-dihydroxy vitamin D3, or sodium butyrate was also tested on patients. The results suggested that drugs given in combination were more effective as compared to PMA alone (Diaz et al., 2015). Bryostatin 1 has been used in clinical trials which is one of the PKC modulators and downregulates some PKC isozymes. The anti-tumour activity was shown by Bryostatin 1 in phase I studies but Phase II studies have not yielded clinically usefull results as it was expected. Phase II studies combining bryrostatin 1 with other cytotoxic agents have not shown any efficacy and so it has failed to move in further trials (Koya, 2014). As the same case with safingol which is a specific PKC inhibitor and has shown cytotoxic effects when given in combination with conventional chemotherapy agents where as safingol alone has a nominal effect on tumor cell growth (Table 2) (Zhang et al., 2014).

Table 2: Clinical Studies Exploring The Role of PKC In Diabetes.

S. No	DRUG & EFFECT	CLASS OF AGENT	PHASES OF CLINICAL TRIALS
1	PMA (TPA) PKC activator	Phorbol esters	Phase I clinical trials, hematologic malignancies (Berger et al., 2008)
2	Staurosporin (PKC inhibitor)	Indolocarbazoles	Preclinical phase II trials in small cell lung carcinoma, melanoma, and lymphomas (Aielleo, 2002).
3	Bryostatin-1 (PKC activator)	Macrocyclic lactones	Phase II trials as a single agent and in combinations (Koya, 2014).
4	Quercetin (PKC and other kinases inhibitor)	Flavonoid	Limited phase I trials (Koya, 2014).
5	Tamoxifen (PKC inhibitor)	Antiestrogens	Treatment of breast cancer (Weeks and McMullen, 2018).
6	Safingol (PKC inhibitor)	Lipid analogs	Phase II LY900003 topical treatment (BOONE. 2013).
7	ISIS 3521 (LY900003) aprinocarsen) (PKC specific inhibitor)	Antisense oligonucleotides	Phase II clinical trials in combination with 5-fluorouracil-leucovorin, cisplatin-gemcitabine, docetaxel, phase III with carboplatin, paclitaxel (Chua et al., 2005)

Conclusion

In this review, we studied hyperglycemia is a key factor responsible for diabetic complications which shows harmful effects on the human body and leads to activation of PKC. Microvascular complications like retinopathy, nephropathy, neuropathy, and myopathy occur due to chronic pathological condition leading to a higher level of DAG-PKC, oxidative stress and an increased amount of glycation. Hence, it is concluded that PKC is a therapeutic approach for treating vascular diabetic complications as clinical trials have shown beneficial effects of selective PKC inhibitors in diabetic complications.

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