Activation of Protein Kinase C in Glomerular Cells in Diabetes
Mechanisms and Potential Links to the Pathogenesis of Diabetic Glomerulopathy

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Protein kinase C (PKC) is activated in rat renal glomerulus within a week of induction of experimental diabetes. Studies in isolated glomeruli and in cultured endothelial and mesangial cells have demonstrated that high ambient concentrations of glucose activate PKC and thus implicate hyperglycemia per se as a mediator of PKC activation in glomerular cells in diabetes. High glucose concentrations activate PKC by increasing cellular levels of diacylglycerol (DAG), the major endogenous modulator of this signalling system. In contrast to physiological extracellular stimuli of PKC that increase cellular DAG levels by receptor-mediated enhancement of membrane inositol phospholipid hydrolysis, in glomerular cells high concentrations of glucose increase DAG by de novo synthesis from glycolytic intermediates. Activation of PKC by glucose or other agonists increases the permeability of endothelial cells to albumin and stimulates matrix protein synthesis in mesangial cells; it thereby may be involved in the pathogenesis of both the functional and structural alterations of the glomerulus in diabetes. Recent studies in isolated glomeruli from diabetic rats have also implicated activation of PKC in suppression of nitric oxide (NO)-mediated increases in glomerular cGMP generation in response to cholinergic stimuli. In mesangial cells, cGMP suppresses PKC-mediated increases in matrix protein synthesis. Thus, impaired NO-mediated cGMP generation in glomeruli of diabetic individuals may amplify matrix protein synthesis in response to hyperglycemia and other stimuli of PKC. These and other observations suggest that activation of the PKC system by hyperglycemia may represent an important pathway by which glucotoxicity is transduced in susceptible cells in diabetes. Diabetes 43:1-8, 1994
cated in the pathogenesis of diabetic complications include activation of the polyol pathway (18), altered cellular redox balance (19), and myoinositol depletion (18), reduced Na⁺-K⁺-ATPase activity (18), formation of advanced glycation end products (20), generation of reactive products of glycoxidation including superoxide and oxidized lipoproteins (19,21), enhanced eicosanoid generation (22), and activation of the protein kinase C (PKC) system (23–25). Several of these cellular sequelae of hyperglycemia may be interdependent. Thus, glucose activation of the polyol pathway may result in altered cell redox balance (19), myoinositol depletion (18), reduced Na⁺-K⁺-ATPase activity (18), and also may contribute to PKC activation (19) and increased eicosanoid synthesis (26). This discussion will focus on the biochemical pathways mediating activation of PKC in glomerular cells in diabetes in response to hyperglycemia and enhanced glomerular synthesis of eicosanoids, and the evidence that activation of PKC may signal increased extracellular matrix protein synthesis by the mesangial cell.

ALTERATIONS IN PKC IN GLOMERULAR CELLS IN DIABETES: MECHANISMS AND MEDIATORS

The PKC system consists of a family of at least nine distinct isozymes (27). It is ubiquitously distributed in cells and is involved in the transduction of numerous extracellular signals, including those of growth factors, hormones, paracrines, and autacoids (28). PKC is regulated intracellularly by three principle co-factors: calcium, phospholipids, especially phosphatidylerine, and diacylglycerol (DAG) (29). The major endogenous cellular mediator of PKC activation is DAG, which binds to a specific domain on the regulatory subunit of the enzyme (30). Physiological activation of PKC by extracellular signals that are transduced via specific cell membrane receptors is mediated by activation of membrane phospholipase C with resultant hydrolysis of phosphoinositol bisphosphate (PIP₂) to inositol trisphosphate (IP₃) and DAG (27). The DAG formed by this pathway contains arachidonate in the 2-position and is a potent activator of PKC (27). An increase in cytosolic calcium induced by IP₃, which releases calcium from intracellular sites, facilitates activation of at least the calcium-dependent isozymes of PKC (27).

Both increases (23,24,31,32) and decreases (33) in PKC activity have been reported in different tissues in experimental models of diabetes. The observation of a decrease in myo-inositol content of peripheral nerve from diabetic individuals led to the proposal that activation of PKC might be impaired because of reduced DAG formation secondary to depletion of a pool of membrane inositol phospholipids that serve as the source of DAG (18,33). This hypothesis is supported by some studies in peripheral nerve tissue from diabetic rabbits and rats that have suggested that the defect in nerve conduction and Na⁺-K⁺-ATPase activity observed in these preparations is linked to decreased PKC activity. Specifically, exposure of peripheral nerve from streptozotocin (STZ)-induced diabetic rats in vitro to phorbol ester enhanced Na⁺-K⁺-ATPase (34). In peripheral nerve from the STZ-induced diabetic rats, soluble PKC activity was reported to be decreased, whereas particulate PKC activity was not different from control (33). By contrast, treatment of alloxa diabetic mice in vivo with inhibitors of PKC was reported to restore Na⁺-K⁺-ATPase activity in peripheral nerve (35). A reduction in particulate, but not soluble, PKC in response to the PKC inhibitors was found (36). Thus, the impact of diabetes on the state of activation of PKC and the relationship, if any, of changes in the PKC system to neural injury induced by diabetes remain to be clarified.

In several other tissues from experimental diabetic models, including the glomerulus (23), retinal cells (31), proximal tubule (32), aorta (24), and heart (24,37), there is considerable evidence that PKC is activated. In aorta and heart from STZ-induced diabetic rats, selective activation of the βII isozyme of PKC has recently been reported (24). In glomeruli isolated from STZ-induced diabetic rats, activation of PKC is supported by the finding of both significant translocation of cytosolic PKC activity to the membrane fraction (23) and enhanced in situ phosphorylation of myristoylated alanine-rich C kinase substrate (MARCKS), a family of specific endogenous protein substrates for PKC (38). In glomeruli from STZ-induced diabetic rats, activation of PKC was evident within a week of induction of diabetes and occurred despite a concurrent decrease in glomerular myoinositol content (23), a change postulated to impair PKC activation in peripheral nerve of diabetic rats (18). The role of activation of PKC in the pathogenesis of the changes induced in the kidney by diabetes remains to be defined. However, some evidence indicates that PKC may be involved in the regulation of several general cellular functions highly relevant to the alterations seen in diabetic nephropathy. These include proposed roles for PKC to signal renal hypertrophy (32), increase endothelial permeability to macromolecules (19,39,40), and stimulate the synthesis of mesangial cell matrix proteins as discussed below.

ACTION OF GLUCOSE TO ACTIVATE PKC

Multiple factors may mediate activation of PKC in glomeruli and other tissues in diabetes. Prominent among these is hyperglycemia per se. An action of high ambient concentrations of glucose to activate PKC in vitro has been observed in isolated glomeruli (23), cultured mesangial cells (25,41), endothelial cells (24), vascular smooth muscle cells (42,43), adipocytes (44), and by some laboratories but not others in pancreatic islets (45). In glomeruli (46) and other tissues (24,25,45,47) the action of high ambient glucose concentration to activate PKC is linked to enhanced generation of DAG. There is evidence from several studies (25,44,46) that the increased DAG in cells exposed to high concentrations of glucose is derived from de novo synthesis of DAG from glucose. Thus, in response to high concentrations of glucose, DAG is generated from glycolytic intermediates that are acylated stepwise to phosphatidic acid and DAG (46). The DAG species derived by this pathway will be determined by the fatty acids available in the cell for
incorporation into the 1 and 2 positions. Thus, unlike DAG derived from PIP₂ hydrolysis, which exclusively results in formation of 1-stearoyl-2-arachidonyl DAG, more heterogeneous species are likely formed when DAG is derived from de novo synthesis from glucose. However, in vitro studies of purified rat brain PKC indicate that a variety of naturally occurring DAG species containing different unsaturated fatty acids in the 2, position are as potent as 1-stearoyl-2-arachidonyl DAG with respect to PKC activation (48). The fact that glucose increases DAG levels and activates PKC without a change in inositol phospholipid turnover in some tissues (44,46) implies that sufficient quantities of arachidonyl DAG or other unsaturated DAG species are generated by de novo synthesis from glucose to mediate PKC activation. Glucose-induced activation of PKC may also be related to glucose activation of the polyol pathway. An increase in the cytosolic NADH/NAD⁺ ratio induced by activation of the polyol pathway may favor increased de novo synthesis of DAG from glucose (19). Nevertheless, treatment of diabetic rats with the aldose reductase inhibitor sorbinil at doses that restored glomerular myoinositol content to that of glomeruli from nondiabetic rats did not prevent activation of glomerular PKC in the diabetic rats (23). These data suggested that in the glomerulus, factors other than increased polyol pathway activity were central to activation of PKC. However, they do not exclude an interaction between activation of the polyol pathway and DAG formation from glucose.

ROLE OF INCREASED GLOMERULAR PRODUCTION OF TXA₂ IN PKC ACTIVATION IN DIABETES

Stable analogues of TXA₂/prostaglandin (PG) endoperoxide activate PKC in isolated glomeruli (38), mesangial cells (49,50), and other cells including platelets (51) and endothelial cells (52). Other eicosanoids including PGF₂α may also signal cellular actions through PKC (49). In glomeruli isolated from the STZ-induced diabetic rats, enhanced synthesis of eicosanoids, including TXA₂, is evident within one week of induction of diabetes and has been linked to increased availability of free arachidonate, which is often the rate-limiting step in cellular eicosanoid synthesis (53). The increase in glomerular eicosanoid synthesis in diabetes has been further linked to activation of membrane bound, calcium-dependent phospholipase A₂, a major mediator of release of arachidonate from membrane phospholipids (54). Observations in cultured mesangial cells (55,56) have indicated that activation of PKC by glucose enhances calcium-dependent phospholipase A₂ activity. Accordingly, in diabetes increased glomerular eicosanoid generation may be linked at least in part to activation of PKC by glucose, which in turn mediates activation of phospholipase A₂. Thus, hyperglycemia per se may lead to release of membrane-bound arachidonate and the resultant increase in glomerular eicosanoid generation in diabetes (55).

Early in diabetes in the STZ-induced diabetic rats, glomerular generation of both vasodilatory prostanoids (PGE₃, PGI₂) and the vasoconstrictor TXA₂ are increased, with more prominent enhancement of the former products (53,57,58,59). This early profile of increased glomerular eicosanoid production may contribute to glomerular hyperfiltration (53,60–62). Later, glomerular generation of TXA₂ is preferentially increased (59,63–65), possibly attributable to preferential enhancement of glomerular TX synthetase activity. Accordingly, in STZ-induced diabetic rats increased glomerular generation of TXA₂ occurs from the onset of diabetes and persists, while the initial increase in vasodilatory prostanois generation by glomeruli is not sustained (59). The increase in glomerular TXA₂ generation seen after several months of diabetes in STZ-induced diabetic rats is associated with increased urinary excretion of TXA₂ (59,63–65). The latter correlates temporally with the development of albuminuria in the diabetic rats (59,63–65). Treatment of STZ-induced diabetic rats with a selective inhibitor of TX synthesis, begun at the time of induction of diabetes and given at a dose that suppresses glomerular TX generation and urinary TX excretion toward control values, markedly attenuates albuminuria in STZ-induced diabetic rats (64–66). In addition, inhibitors of TX synthesis also significantly suppress the increases in glomerular basement membrane width or mesangial volume that otherwise occur in STZ-induced diabetic rats after several months of diabetes (65,66). Analogous effects of a TX synthetase inhibitor to prevent the development of albuminuria have been reported by Ledbetter et al. (68) in a genetic diabetic mouse model. These authors found that TX synthesis inhibition prevented the increase in collagen IV mRNA level, which is observed in renal cortex of diabetic mice (68). The mechanisms by which TX may contribute to glomerular injury in diabetes and other renal diseases are not established. The actions of TX as a vasoconstrictor and platelet aggregator are frequently invoked. However, as discussed below, recent studies in cultured mesangial cells have indicated that TX can directly alter matrix protein synthesis by a PKC-dependent mechanism.

EFFECTS OF PKC ACTIVATION IN ENDOTHELIAL AND MESANGIAL CELLS

There is as yet no in situ data to indicate the cell types within the glomerulus in which PKC is activated in diabetes. However, PKC of both cultured mesangial and endothelial cells is activated by exposure to high ambient concentrations of glucose (24,25,41) and by TX/PG endoperoxide analogues (49,52). Thus, the increase in PKC activity detected in intact glomeruli from diabetic rats likely reflects activation of PKC in at least these two glomerular cells. The effects of glucose and TX on PKC activity of glomerular epithelial cells have not been examined.

Endothelial cells. Studies in both cultured endothelial cells and in the microvascular model of rat skin chamber granulation tissue have indicated that activation of PKC alters endothelial cell barrier function and leads to increased permeability to albumin and other macromolecules (19,39,40). Activation of PKC also increased endothelial permeability and edema formation in perfused lung preparations (69). The precise mechanisms by which activation of PKC induces these permeability changes are not clear. However, studies have indicated
that activation of PKC leads to the development of intercellular gaps in endothelial cell monolayers with reorganization of vinculin and F-actin filaments (39,40). Whatever the precise mechanism, activation of PKC in glomerular endothelial cells in diabetes may be an important determinant of the reduction of permselectivity of the glomerulus to albumin. In endothelial cells, a role for activation of PKC in the stimulation of extracellular matrix protein synthesis by glucose is not established (70–72). The finding that L-glucose mimics the stimulatory effects of D-glucose on matrix protein synthesis in cultured endothelial cells (70) but not in mesangial cells (41) suggests that mechanisms that do not require glucose metabolism, such as nonenzymatic glycosylation, may contribute to expression of glucose actions on matrix protein synthesis in endothelial cells.

Mesangial cells. In mesangial cells, PKC activation has been linked to the modulation of cell contraction, eicosanoid synthesis, and matrix protein production. With respect to mesangial cell contraction, PKC has complex effects on the expression of the actions of vasoconstrictor hormones (73–75). Activation of PKC has been implicated in both the mediation of renal vasoconstriction caused by angiotensin II (73) and in mesangial cell contraction (74). Conversely, in mesangial cells, down-regulation of PKC has been reported to enhance contraction in response to angiotensin II (75). These findings may reflect biphasic actions of PKC on the contractile response in mesangial cells, with a PKC-mediated secondary desensitization of these cells to pressor hormone actions that is expressed either at the level of receptor binding or more distally (42,59,75,76). As noted above, activation of PKC has also been linked to increased synthesis of eicosanoids in mesangial cells (75), possibly via activation of phospholipase A2 with release of arachidonate (55–56).

Perhaps more relevant to the pathogenesis of the histopathological change seen in the glomerulus in diabetes, several laboratories have now demonstrated that in cultured mesangial cells both high ambient concentrations of glucose (25,41,72,77) and TXA2/PG endoperoxide analogues (78–80) increase the accumulation and synthesis of several extracellular matrix proteins. Stimulation of the synthesis of matrix proteins by high concentrations of glucose or TXA2/PG endoperoxide analogues in mesangial cells has been supported by both pulse/chase experiments with labeled precursors and/or by increased levels of mRNA levels for fibronectin, laminin, and type IV collagen (15,41,77–80). Both glucose and TX analogues activate PKC in mesangial cells (25,41,50,80).

A number of observations indicate that this may signal an increase in synthesis of mesangial cell matrix proteins. Thus, other agents that activate PKC also increase matrix protein synthesis in mesangial cells, including phorbol esters (41), stable analogues of DAG (25), angiotensin II (81,82), and low-density lipoproteins (83). Moreover, the actions of high concentrations of glucose and the TXA2/PG endoperoxide analogue U46619 to stimulate matrix protein synthesis in mesangial cells are blocked by inhibitors of PKC or by prior downregulation of PKC induced by exposure to a high concentration of phorbol ester (41,80). Of interest, the actions of high concentrations of glucose and U46619 on fibronectin in mesangial cells are additive (unpublished observations). This may reflect activation of PKC in mesangial cells by these two agents via independent metabolic pathways, namely, formation of DAG by de novo synthesis in response to glucose (25) and by receptor mediated inositol phospholipid turnover in response to TXA2/PG endoperoxide (49).

In view of the fact that DAG species with differing fatty acid substituents may be formed through the de novo synthesis pathway versus the inositol phospholipid pathway (48), it is also possible that glucose and TXA2 activate different isozymes of PKC with differing co-factor preferences in mesangial cells. In mesangial cells exposed to high concentration of glucose, there is evidence for selective membrane translocation of two of the four isozymes of PKC identified in these cells by immunoblot analysis (84). The isozyme profile translocated in mesangial cells by U46619 has not been examined. Although the molecular mechanisms involved remain to be determined, current data strongly suggest that activation of PKC in mesangial cells in diabetes induced by hyperglycemia, TX/PG endoperoxide, and possibly other stimuli may signal increased mesangial cell synthesis of matrix protein.

**EFFECTS OF PKC ACTIVATION ON NITRIC OXIDE (NO) ACTIONS**

Complex and still poorly understood changes may occur in endothelial dependent responses of vascular smooth muscle cells and mesangial cells in diabetes. These at least in part may reflect interactions between the PKC and cGMP cellular signalling systems. Endothelial-dependent relaxation factor (NO) has been implicated in the pathogenesis of vasodilation and increased vascular permeability of diabetes (85,86). It has also been suggested that increased NO production may participate in the pathogenesis of glomerular hyperfiltration in diabetes (87). Thus, Bank and Ayedjian (87) reported higher levels of stable products of NO (NO2−/NO3−) in urine and plasma of STZ-induced diabetic rats compared with controls, and a blunted vasoconstrictor response in the diabetic rats to an inhibitor of NO synthetase. However, the inhibitor of NO synthesis failed to abolish the difference in the glomerular filtration rate between control and STZ-induced diabetic rats (87), suggesting that factors other than NO were involved in the pathogenesis of glomerular hyperfiltration in STZ-induced diabetic rats. In studies of skin granulation tissue, Corbett et al. (85) found that NG-monomethyl-L-arginine and amino-guanidine, both of which inhibit NO synthesis, reduce glucose-induced increases in albumin clearance, consistent with a role for NO in expression of the vascular actions of glucose to induce vasodilation and increased permeability. Although cGMP mediates the vasodilatory action of NO, it has not been demonstrated that cGMP mediates any action of NO to increase vascular permeability. Rather, cGMP has been reported to decrease permeability in endothelial cell monolayers (40). Accordingly, NO-mediated increases in cGMP may not account for all of the vascular actions of glucose reported (85).
Conversely, several laboratories have observed impaired NO-dependent relaxation in aorta and cerebral microvessels isolated from experimental models of diabetes and exposed to cholinergic agents in vitro (88–91). Similarly, attenuation of the NO-dependent vasodilatory action of cholinergic agents has been reported in vivo in experimental diabetes (92–94) and in diabetic patients (95). From studies of diabetic rat aorta, Cohen et al. (88) have suggested a role for glucose-induced increases in endothelial production of vasoconstrictor prostanoids and TXA2/PG endoperoxide in attenuation of NO-mediated vasodilation in diabetes. These actions of glucose may be at least in part be expressed through activation of PKC (96). However, a role for either reduced NO generation or for suppression of the action of NO to increase cGMP in the pathogenesis of impaired vasodilation to cholinergic stimuli in diabetes has not been clearly established. Three laboratories have reported decreased macrovascular cGMP responses to cholinergic stimuli from diabetic rats (92,97,98), whereas two other laboratories have reported no change in the macrovascular cGMP response (99,100). The explanation for these apparently discordant findings in NO-mediated cGMP responses of large vessels in diabetes is at present unresolved. However, analogous to the reduction in NO-responsive cGMP observed by some investigators in large vessels in diabetes (92,97,98), two groups have recently observed impairment of the cGMP responses to carbachol in nitroprusside in glomeruli isolated from STZ-induced diabetic rats (38,94). In one study, a significant reduction in NO-dependent basal cGMP generation was also observed in glomeruli from the STZ-induced diabetic rats (38). Neither arginine depletion, which might impair endogenous NO generation, nor an alteration in the NO responsiveness of soluble guanylate cyclase accounted for the impaired cGMP responses to carbachol in nitroprusside observed in glomeruli from STZ-induced diabetic rats (38). Defective NO generation, enhanced quenching of NO, or both, may have participated in the impairment of cGMP responses to NO-dependent stimuli (38). Because the cGMP but not the soluble guanylate cyclase response to nitroprusside was impaired in glomeruli from diabetic rats and because this agent generates NO nonenzymatically, NO quenching was strongly implicated as one mechanism for attenuation of the cGMP response. Moieties increased in diabetes and capable of quenching NO include end products of glycosylation (93), reactive oxygen species (101), oxidized lipoproteins, and lipid peroxides (102). Of interest, NO-dependent cGMP is reduced in glomeruli isolated from diabetic rats within 1 to 2 weeks of induction of diabetes (38,94) at which time glomerular hyperfiltration is well-established (53). This finding does not support a role for NO-mediated changes in NO synthesis with the glomerulus in the pathogenesis of hyperfiltration. However, it does not exclude a role for increases in NO production and actions at other key sites within the nephron in the pathogenesis of hyperfiltration. These sites include the afferent arteriole where recent studies with NO-synthetase inhibitors have implicated basal NO production as an important determinant of preglomerular resistance (103).

Of note, both inhibitors of PKC and a TXA2/PG endoperoxide receptor blocker partially restored the cGMP response to carbachol in glomeruli from the diabetic rats (38). Conversely, U46619, which activated PKC in glomeruli from nondiabetic rats, significantly attenuated the cGMP response to carbachol in these glomeruli. Both actions of U46619 on the glomerulus were blocked by PKC inhibitors (38). These data suggested that activation of PKC in glomerular cells in diabetes may lead to attenuation of cGMP responses to NO. Consistent with a role for PKC in the suppression of NO synthesis, Bredt et al. (104) have previously reported that PKC stoichiometrically phosphorylates the purified constitutive NO synthetase from brain, an action that suppresses NO-synthetase activity. Moreover, phorbol esters have been shown to suppress NO-dependent cGMP production in cells transfected with the cDNA for NO synthetase (104) and to suppress NO production by cultured endothelial cells in response to bradykinin and A23187 (105). The mechanism by which activation of PKC attenuates NO-mediated cGMP generation in the glomerulus in diabetes and the role, if any, of this change in the pathogenesis of diabetic glomerulopathy remain uncertain. However, cGMP has been shown to inhibit several functions of the mesangial cell, including contraction, proliferation, and matrix protein production (80,106). In recent studies, we have found that both activation of PKC and stimulation of fibronectin synthesis induced by U46619 in mesangial cells were suppressed by exogenous cGMP (80) as well as by agonists of endogenous cGMP generation (unpublished observations). Thus, it is possible that impaired NO-dependent cGMP generation in glomeruli in diabetes amplifies the PKC signal in response to TXA2, hyperglycemia, and other agonists of PKC. An attenuation of cGMP generation may, in turn, enhance the stimulatory effects of PKC activators on matrix protein production. This and other potential interactions between these two cellular signalling systems in diabetes requires further study.

CONCLUSIONS

In diabetes, at least some of the cellular actions of hyperglycemia on glomerular endothelial cells and mesangial cells are likely transduced by activation of the PKC system. These include increased endothelial permeability to albumin and other macromolecules and increased matrix protein synthesis by mesangial cells. In contrast to extracellular stimuli of PKC, including TXA2, which increases cellular levels of DAG through receptor-mediated enhancement of membrane inositol phospholipid hydrolysis, increases in DAG induced by high concentrations of glucose occur via de novo synthesis. Activation of PKC by these two independent metabolic pathways provide a possible basis for the additive stimulatory effects of TXA2/PG endoperoxide and glucose on mesangial cell matrix protein synthesis. Complex interactions also likely exist between the PKC and cGMP cellular signalling systems and these may be
altered in diabetes. In glomerular cells in diabetes, activation of PKC impairs NO-responsive cGMP generation induced by cholergeric stimuli. Studies in cultured mesangial cells indicate that cGMP suppresses PKC activity and several PKC-mediated actions in the mesangial cells, including matrix protein production. Thus, an impairment of NO-mediated cGMP generation in mesangial cells in diabetes may amplify the PKC signal to activation.

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