Regulation of Protein Kinase C\(\mu\) by Basic Peptides and Heparin

PUTATIVE ROLE OF AN ACIDIC DOMAIN IN THE ACTIVATION OF THE KINASE*

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Protein kinase \(C\mu\) (PKC\(\mu\))\(^1\) is a novel member of the protein kinase \(C\) (PKC) family that differs from the other isoenzymes in structural and enzymatic properties. No substrate proteins of PKC\(\mu\) have been identified as yet. Moreover, the regulation of PKC\(\mu\) activity remains obscure, since a structural region corresponding to the pseudosubstrate domains of other PKC isoenzymes has not been found for PKC\(\mu\).

Here we show that aldolase is phosphorylated by PKC\(\mu\) in vitro. Phosphorylation of aldolase and of two substrate peptides by PKC\(\mu\) is inhibited by various proteins and peptides, including typical PKC substrates such as histone H1, myelin basic protein, and p53. This inhibitory activity seems to depend on clusters of basic amino acids in the protein/peptide structures. Moreover, in contrast to other PKC isoenzymes PKC\(\mu\) is activated by heparin and dextran sulfate. Maximal activation by heparin is about twice and that by dextran sulfate four times as effective as maximal activation by phosphatidylserine plus 12-O-tetradecanoylphorbol-13-acetate, the conventional activators of c- and nPKC isoforms.

We postulate that PKC\(\mu\) contains an acidic domain, which is involved in the formation and stabilization of an active state and which, in the inactive enzyme, is blocked by an intramolecular interaction with a basic domain. This intramolecular block is thought to be released by heparin and possibly also by 12-O-tetradecanoylphorbol-13-acetate/phosphatidylserine, whereas basic peptides and proteins inhibit PKC\(\mu\) activity by binding to the acidic domain of the active enzyme.

Protein kinase \(C\mu\) (PKC\(\mu\))\(^2\) is a serine/threonine protein kinase that is phospholipid-dependent and activated by diacylglycerol and the phorbol ester TPA (1–3). In this respect, PKC\(\mu\) behaves similarly as most PKC isoenzymes (cPKCs and nPKCs, for reviews see Refs. 4 and 5) of the PKC family. However, PKC\(\mu\) is a novel member of the protein kinase C (PKC) family that differs from the other isoenzymes in structural and enzymatic properties. No substrate proteins of PKC\(\mu\) have been identified as yet. Moreover, the regulation of PKC\(\mu\) activity remains obscure, since a structural region corresponding to the pseudosubstrate domains of other PKC isoenzymes has not been found for PKC\(\mu\).

PKC\(\mu\) is inhibited by various proteins and peptides, most likely due to clusters of basic residues in their structure, and is activated by heparin and dextran sulfate. Based on these results, the putative role of an acidic domain in the activation of PKC\(\mu\) is discussed.

EXPERIMENTAL PROCEDURES

Materials—TPA was supplied by Prof. Dr. E. Hecker, German Cancer Research Center, Heidelberg, Germany. Go\(\ddagger\)6976 and Go\(\ddagger\)6983 were kindly provided by Gödecke, A.G., Freiburg, Germany. The tumor suppressor protein p53 was given by Dr. M. Frey, German Cancer Research Center, Heidelberg, Germany. Syntide 2, \(\mu\)-peptide 1, \(\mu\)-peptide 2, \(\nu\)-peptide, \(\tau\)-peptide, \(\xi\), and \(\eta\) were synthesized by Dr. R. Pipkorn, German Cancer Research Center, Heidelberg, Germany.

Other materials were bought from companies as indicated: \(\gamma\)-[\(\beta\)]\(^3\)P-ATP (specific activity, 5000 Ci/mmol), Hartman Analytic (Braunschweig, Germany); aldolase, Boehringer (Mannheim, Germany); heparin, phosphatidylserine (PS), protamine sulfate, dextran sulfate, histone H1 (III-S), myelin basic protein, poly-L-lysine (M\(_r\) 15,000–60,000), poly-L-lysine (M\(_r\) 1,000–4,000) poly-L-arginine (M\(_r\) 15,000–60,000), t-Lysine, histamine, quinine, Sigma (Munich, Germany).

Recombinant PKC\(\mu\)—SF 158 cells were infected with recombinant PKC\(\mu\) baculovirus, and cell extracts were prepared and used as source for PKC\(\mu\) as described previously (3, 7).

Protein Kinase \(C\mu\) Assay—Phosphorylation reactions were carried out in a total volume of 100 \(\mu\)l containing buffer I (50 mM Tris-HCl, pH 7.5, 10 mM \(\beta\)-mercaptoethanol), 4 mM MgCl\(_2\), 5 \(\mu\)l of a SF 158 cell extract containing recombinant PKC\(\mu\), 35 \(\mu\)M ATP containing 1 \(\mu\)Ci of \(\gamma\)-[\(\beta\)]\(^3\)P-ATP and 5 \(\mu\)g of syntide 2 or \(\mu\)-peptide 1 as substrates. PS, TPA, heparin, Go\(\ddagger\)6976, or various other compounds (see Table I) were added at concentrations indicated in the legends of the figures and Table I. After incubation for 7 min at 30 °C, the reaction was terminated by transferring 50 \(\mu\)l of the assay mixture onto a 20-mm square piece of phosphocellulose paper (Whatman \(p\)81), which was washed three times in deionized water and twice in acetone. The radioactivity

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\(\ddagger\) The abbreviations used are: PKC, protein kinase C; TPA, 12-O-tetradecanoylphorbol-13-acetate; PS, phosphatidylserine.

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on each paper was determined by liquid scintillation counting. Phosphate incorporated into the substrate peptide was obtained by subtracting values determined in the absence of kinase.

Autophosphorylation and Phosphorylation of Aldolase or Histone H1—These phosphorylations were carried out essentially as described for the protein kinase Cε assay. However, no substrate was added for the autophosphorylation, and for the phosphorylation of aldolase or histone H1, these proteins instead of the substrate peptides were added, at the concentrations indicated in the text. The assay contained 7 μCi of [γ-32P]ATP. Proteins of the reaction mixture were separated by SDS-polyacrylamide gel electrophoresis and visualized by autoradiography.

RESULTS AND DISCUSSION

No substrate protein of PKCε, neither in vitro nor in vivo, has been found so far. In accordance with previous reports (3, 9), we observed that typical PKC substrates, such as histone H1, myelin basic protein, and protamine sulfate, were phosphorylated very weakly by PKCε and, therefore, cannot be considered as PKCε substrates. Recently, the tyrosine kinase Syk and the phospholipase Cγ1 were claimed to be substrates of PKCε. However, phosphorylation by PKCε in vitro of these proteins was even weaker than that of myelin basic protein (10). Here we show that aldolase can serve as a substrate for PKCε in vitro. Aldolase was phosphorylated by PKCε much more effectively than histone H1 (Fig. 1). To our surprise, when aldolase (5 μg) and histone H1 (5 or 10 μg) were both present in the kinase assay, histone H1 suppressed the phosphorylation of aldolase almost completely and also autophosphorylation of PKCε was inhibited (Fig. 1).

To determine the dose dependence of the inhibitory effect of histone H1 on PKCε, we used syntide 2 as well as a novel synthetic peptide that we termed μ-peptide 1 as substrates for PKCε. The μ-peptide 1 with the amino acid sequence RKRRSMRRRH/V corresponding to the sequence 825–839 of human PKCε, proved to be a potent PKCε substrate. It incorporated around 30% more phosphate than syntide 2 on phosphorylation with PKCε.2 Phosphorylation of syntide 2 and μ-peptide 1 by PKCε were determined from standard proteins, as indicated.

FIG. 1. Phosphorylation of aldolase and histone H1 by PKCε and inhibition of aldolase phosphorylation by histone H1. Aldolase (A) and histone H1 (H) alone or together (the concentration is given as μg/100 μl in brackets) were phosphorylated by recombinant PKCε as described under “Experimental Procedures.” Proteins were separated by polyacrylamide gel electrophoresis (10% gel) and phosphorylated proteins visualized by autoradiography. Molecular masses (kilodaltons) were determined from standard proteins, as indicated.

FIG. 2. Inhibition by histone H1 of phosphorylation of syntide 2 and μ-peptide 1 by PKCε. Phosphorylation of the peptides (5 μg each) in the presence of various concentrations of histone H1 and determination of incorporated phosphate were performed as described under “Experimental Procedures.”

TABLE I

| Compound (5 μg) | Inhibition of syntide 2 phosphorylation |
|----------------|----------------------------------------|
|                | %                                      |
| Protamine sulfate | 95                                      |
| Histone H1       | 94                                      |
| Myelin basic protein | 78                                      |
| p53             | 68                                      |
| EF-1α           | 6                                       |
| p53-peptide, SHLKSKKGQPTSRHKK | 58                                      |
| MARCKS-peptide, KKKKRRRFKSKSFGLSFPSKKSK | 92                                      |
| Ser-pseudosubstrate (c-peptide), YIRRGRWRWKL | 62                                      |
| Ser-pseudosubstrate (c-1, c-peptide-1), YIRRGRWRWKL | 48                                      |
| Ser-pseudosubstrate (c-2, c-peptide-2), YIRRGRWRWKL | 29                                      |
| Ser-pseudosubstrate (c, c-peptide), RKRRRSRRRH/V | 51                                      |
| Ser-pseudosubstrate (d, d-peptide), MNNRRSQAK | 15                                      |
| μ-Peptide 2, GVRRL | 5                                       |
| Poly-L-arginine, M, 15,000–60,000 | 90                                      |
| Poly-L-lysine, M, 15,000–60,000 | 76                                      |
| Poly-L-lysine, M, 1,000–4,000 | 64                                      |
| l-Lysine, histamine, quinine (free base) | 0                                       |

2 M. Gschwendt, F.-J. Johannes, W. Kittstein, and F. Marks, unpublished results.
the pseudosubstrate domain of PKCζ (IYRRGSRRWRKLF) and η (RKRRQSMRRRVH), which contain serine instead of alanine and therefore serve as substrates for several PKC isoenzymes, were also found to effectively inhibit PKCζ. However, the respective peptide derived from the pseudosubstrate of PKCζ (MNRRGSKQAKI) as well as the μ-peptide 2 (GVRERRRL), corresponding to the amino acid sequence 198–204 of human PKCζ, did not show such an inhibitory effect. A major difference between the two peptides and the inhibitory peptides (ζ-peptide, η-peptide, myristoylated alanine-rich protein kinase C substrate-peptide, and p38 peptide) exists in the total number and clustering of basic amino acids (Arg/Lys). The δ-peptide and the μ-peptide 2 contain four basic amino acids and one cluster of two or four basic amino acids, respectively, whereas the inhibitory peptides have at least six basic amino acids arranged in two or three clusters. The myristoylated alanine-rich protein kinase C substrate-peptide (KKKKKRFSDKKKSK) with 12 basic residues and three clusters was the most effective inhibitor peptide. Thus, a peptide might require a minimal positive net charge and/or specific clusters of basic amino acids to be able to inhibit PKCζ. In fact, an exchange of one or two basic amino acids in the ζ-peptide for neutral residues resulting in ζ-peptide-1 (IYRRGSRRWRKL) and ζ-peptide-2 (IYRRGSRRWRKL for causing a gradual loss of inhibitory activity (Table 1). ζ-peptide-2 has a similar arrangement of basic amino acids as the δ-peptide. EF-1α protein, which does not contain any cluster of basic amino acids even though it is basic (pI = 9), did not inhibit PKCζ thus further supporting our notion. The strongly basic polypeptides poly-L-arginine and poly-L-lysine (molecular weights of 15–60 kDa), and even the smaller poly-L-lysine (molecular mass of 1–4 kDa) inhibited PKCζ effectively. L-Lysine and other basic low molecular weight compounds, such as histamine and quinine, were on the other hand unable to inhibit PKCζ activity. This indicates that structural features, such as the above mentioned clusters of basic amino acids, rather than a positive net charge, determine the suitability of a compound to act as PKCζ inhibitor, thus pointing to some specificity of the interaction with the kinase. Most of the proteins and peptides inhibiting PKCζ are substrates rather than inhibitors of the other PKC isoenzymes, and some of them, such as protamine and poly-L-arginine, have been found to activate other PKC isoenzymes (13). On the other hand, none of the inhibitory proteins and peptides was significantly phosphorylated by PKCζ. Thus, inhibition of PKCζ was not likely to be due to a competition of the inhibitory compound with the substrate syntide 2 for ATP. Inhibition was not reduced by increasing substrate concentrations, as demonstrated in Fig. 3 for the inhibition by protamine sulfate of syntide 2 phosphorylation by PKCζ. For comparative purposes, Fig. 3 shows also the inhibition of PKCζ by the pseudosubstrate peptide. In this case, inhibition decreased upon increasing the concentration of the substrate syntide 2. This clearly demonstrates that the PKCζ-inhibiting peptides do not act like the well known pseudosubstrate peptides that inhibit other PKC isoenzymes by competing with the PKC substrate for its binding site (14). Therefore, we postulate that PKCζ contains an acidic domain, different from the acidic substrate-binding motif of other PKCs (see Ref. 15), which is involved in enzyme activation or stabilization of the active state of the kinase. In the active state PKCζ is inhibited by proteins and peptides containing clusters of basic residues probably due to an interaction with this “activating” domain. In the inactive state the acidic domain might not be accessible, due to an interaction with an autoregulatory basic domain of the enzyme. Indeed, PKCζ exhibits a highly acidic domain (amino acid sequence 336–391 of human PKCζ) in the regulatory part close to the C terminus of the cysteine-rich regions. This domain contains 40% acidic and just 2% basic residues and, in a smaller region (342–362), even 48% acidic residues. It is intriguing that the other PKC isoenzymes lack a comparable domain.

Our hypothesis would imply that polyanions are able to break up the autoinhibitory interaction between the acidic and...
the basic domain. In fact, the highly sulfated polysaccharides heparin and dextran sulfate were found to function as potent activators of PKC\(\mu\). Maximal activation of PKC\(\mu\) by heparin alone, i.e. in the absence of any other cofactor, was about twice and that by dextran sulfate four times as effective as maximal activation by PS/TPA (Fig. 4). Dextran sulfate contains more sulfate groups than heparin and is, therefore probably, more active than heparin in stimulating PKC\(\mu\). Application of PS/TPA together with heparin or dextran sulfate did not further increase the activity of PKC\(\mu\). Activation of PKC\(\mu\) by heparin or dextran sulfate was saturable at low concentrations (Fig. 5). The \(K_a\) values for heparin and dextran sulfate, as determined by a Lineweaver-Burk plot, were approximately 0.36 and 0.05 \(\mu\)M (based on an average molecular weight of 20,000 and 500,000, respectively, as given by the supplier). Thus, heparin and dextran sulfate are very effective activators as compared for instance with diacylglycerol (e.g. the \(K_a\) value of dioctanoyl-glycerol for PKC\(\delta\) is 10 \(\mu\)M, see Ref. 16). As shown in Fig. 6, A and B, the maximal velocities (\(V_{max}\)) of the heparin- and dextran sulfate-activated syntide 2 phosphorylations (23.3 pmol/min and 41.7 pmol/min, respectively) were much higher than that of the PS/TPA-activated phosphorylation (9.5 pmol/min). On the other hand, the affinity of the enzyme for the substrate was rather lower upon activation with the two polyanions (same \(K_m\) for both: 9.5) than with PS/TPA (\(K_m\): 4.8 \(\mu\)M). Thus, the much more effective incorporation of phosphate into syntide 2 by the polyanion-activated PKC\(\mu\) than by the PS/TPA-activated kinase is due to an increase in the maximal velocity of the phosphorylation reaction. As the mechanisms of action of heparin and dextran sulfate are likely to be identical, we will in the following just deal with heparin. Autophosphorylation of PKC\(\mu\) was also more efficiently stimulated by heparin alone than by PS/TPA (Fig. 7). Both, heparin- and PS/TPA-activated (7) autophosphorylation could be strongly suppressed by 1 \(\mu\)M of the PKC inhibitor G66976, but not at all by 1 \(\mu\)M of G66983, an effective inhibitor of the other PKC isoenzymes. These inhibitors are known to interact with the ATP binding site of PKC.

TPA is generally thought to activate PKC by a conformational change that results from its binding to the zinc finger regions of the enzymes (4). As a consequence, an inhibitory pseudosubstrate domain is removed from the substrate binding site. Whether this mechanism can explain the activation by TPA/PS of PKC\(\mu\) remains an open question, since a domain corresponding to the pseudosubstrate regions of other PKC isoenzymes has not been found in the PKC\(\mu\) structure (7). This does not exclude, however, that upon identification of bona fide in vivo substrates of PKC\(\mu\), a specific pseudosubstrate sequence will be identified in the future. Within the PKC family the activation by heparin may, on the other hand, turn out to be a specific feature of PKC\(\mu\), since PKC\(\delta\) activity was not affected by heparin (data not shown) and a PKC preparation from rat brain (containing mainly PKC \(\alpha\), \(\beta\), \(\gamma\)) was even inhibited by

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**Fig. 5.** Activation of PKC\(\mu\) by heparin and by dextran sulfate. PKC\(\mu\) activity was determined in the presence of various concentrations of heparin or dextran sulfate as described in the legend to Fig. 4.

**Fig. 6.** Dependence of PKC\(\mu\) activation by PS/TPA, heparin, and dextran sulfate on substrate kinetics. A, phosphorylation of syntide 2 (concentrations as indicated) was performed as described in the legend to Fig. 4 and under “Experimental Procedures.” B, Lineweaver-Burk plots of the data shown in A. The intercepts of the double-reciprocal plots with the \(x\) axis give the \(K_m\) values and those with the \(y\) axis the \(V_{max}\) values.
heparin (17). The latter result is in agreement with the finding that heparin might block smooth muscle cell proliferation by inhibition of PKCα (18). Several other protein kinases, such as casein kinase 1 and 2, nuclear kinases, the tyrosine kinase Syk, and G-protein-coupled receptor kinases are inhibited by heparin (17, 19, 20, and references in Ref. 17). On the other hand, activation by heparin was reported for instance for a RNA-activated protein kinase (21) and a Lyn-related tyrosine protein kinase (22). Activation of each of the two kinases by heparin was shown to occur through mechanisms different from those of other known activators of these kinases, thus resembling the activation of PKCµ by heparin. Moreover, many growth factors are known to bear specific heparin-binding sites that contain a cluster of basic amino acid residues (23, 24).

The activation by heparin or dextran sulfate of PKCµ appears to be rather specific, as other acidic compounds, such as chondroitin sulfate, cholesterol sulfate, double-stranded polynucleotidic acid, DNA (calf thymus), poly-L-aspartic acid, and poly-L-glutamic acid, did not or just very weakly activate PKCµ (data not shown). This supports the notion that heparin and dextran sulfate specifically break up the intramolecular interaction of basic residues with an acidic domain of PKCµ. The apparent specificity of the stimulatory effect may be taken as an indication for a physiological function of heparin or heparin-like compounds in the control of PKCµ activity. Heparin has been shown to affect various intracellular signaling pathways, including PKC-dependent pathways, and to be a potent proliferation inhibitor of several cell types (Refs. 25 and 26 and references therein). However, these effects are thought to be mediated by binding of heparin to cell surface binding sites or growth factors (23, 24, 27). Little is known about possibly direct actions of heparin on signaling pathways inside the cell. As heparin is synthesized in the Golgi complex and PKCµ has recently been shown to be localized there (11), a direct action of heparin on PKCµ in this cellular compartment is conceivable. Alternatively, heparin might mimic the effects of heparin-like factors in vivo. Such factors are produced, for instance, by endothelial and smooth muscle cells and are growth-inhibitory for these cells (28, 29).

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