Cyclic Nucleotide Phosphodiesterases: New Role in the Pathogenesis of Glomerulonephritis?

Adenosine and guanosine 3',5'-cyclic monophosphate (cAMP and cGMP, respectively) are archetypal second messengers that regulate numerous cellular functions. One of the most exciting and novel developments in studies of cAMP and cGMP is a wealth of new information about the enzymes that metabolize these cyclic nucleotides, namely, the cyclic nucleotide phosphodiesterases (PDEs) (1). Although PDEs were discovered some 35 years ago, the elucidation of their diverse biochemical nature had to await much more recent studies, conducted with new methodologies; the PDEs comprise an enormously complex superfamily of isozymes consisting of at least seven gene families, also called “types” and designated as PDE type 1 through PDE-type 7 (PDE1 through PDE7).

The various PDEs differ in structure, catalytic properties, intracellular regulation and location, and expression in different cells. A number of type-specific PDE inhibitors have now been developed, and these inhibitors have become powerful experimental tools as well as a new class of pharmacologic agents (1). It is now clear that PDEs not only inactivate cAMP and cGMP when they are no longer needed in a given intracellular function, but they also play an active regulatory role by interacting with other intracellular signaling pathways (1).

Interactions of PDE3 and PDE4 with other signaling systems appear to be responsible for certain pathological processes in renal glomeruli, in particular of glomerular mesangial cells (2, 3). The latter are often focal points for immune-inflammatory injury. Of particular relevance is the observation that the cAMP-PDE3-protein kinase A (PKA) pathway, via “negative cross talk,” can inhibit the mitogen-activated protein kinase (MAPK) cascade (Fig. 1). This pathway carries signals initiated at the cell surface by growth factors and cytokines, through the cytoplasm to the cell nucleus where activation of genes is triggered (2).

In rat mesangial cells grown in culture, inhibitors of PDE3 caused activation of PKA and suppressed mitogenesis, both in the quiescent state and when stimulated by epithelial or platelet-derived growth factors (EGF or PDGF, respectively). In contrast, inhibitors of PDE4 had little or no effect on mitogenesis but selectively (compared with inhibitors of PDE3) suppressed generation of reactive oxygen metabolites, also via PKA (Fig. 1) (2). Activation of PKA by PDE3 and PDE4 inhibitors was additive, indicating that two distinct PKA entities or compartments were activat-

FIGURE 1. Bifurcation of the adenosine 3',5'-cyclic monophosphate (cAMP) signaling pathways in renal mesangial cells. Mitogenic growth factors bind to receptors to activate the mitogen-activated protein kinase (MAPK) cascade, which is inhibited by a pool of cAMP that is metabolized by cyclic nucleotide phosphodiesterase isozyme (PDE) type 3. Reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase catalyzes the formation of reactive oxygen metabolites (superoxide anion-free radical, O_2^-); this reaction can be inhibited by a pool of cAMP that is metabolized by PDE4.
ed. Thus cAMP can follow two distinct signaling pathways within glomerular mesangial cells, depending on whether the nucleotide is metabolized by PDE3 or PDE4.

Given the central pathogenic role of mesangial cell proliferation and generation of oxygen metabolites in glomerular injury, the above in vitro studies suggested that inhibitors of PDE3 and PDE4 might modify such injury. This suggestion was tested through in vivo experiments using a model of mesangioproliferative nephritis in rats (3). Administration of both PDE3 and PDE4 inhibitors (together) prevented proteinuria, abated proliferation of mesangial cells, and decreased infiltration by macrophages (3). Inhibitors of PDE3 alone had similar effects, indicating the important role of mesangial cell proliferation in the pathogenesis of this type of glomerulonephritis. Clearly, the effects of these inhibitors (alone or in combination as well as in different doses) on different types of nephritides need to be tested. Not only that, but it would now seem worthwhile to ascertain the possible role of the many PDE isozymes on mesangial cells and on other types of renal cells. Specific inhibitors of PDE isozymes will be of immeasurable value in such studies, and further positive results with these inhibitors could lead to novel “signal transduction pharmacotherapies” of glomerulonephritides and other diseases.

References


Thomas P. Dousa