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Phospholipid derived mediators and glomerulonephritis

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THE contributions made by the various eicosanoids, PAF, the HETES and the lipoxins to the pathophysiology of glomerulonephritis is reviewed. A case can be made for clinical trials of PAF, leukotriene and thromboxane antagonists. Combined thromboxane synthetase and thromboxane receptor antagonism would seem to be the more efficacious approach for the various disease entities.

Key words: Eicosanoids, Glomerulonephritis, 15 HETE, Leukotrienes, Lipoxins, PAF acether, Thromboxane A_2.

Introduction

Glomerulonephritis is inflammation of the glomerular filtering units of the kidneys, that is caused either by deposition of immune complexes following infections or by formation of an antibody that interacts with the basement membranes of the capillaries of the glomeruli. Such inflammation will be accompanied by immediate deposition of platelet aggregates in the capillaries and a rapid infiltration with polymorphonuclear leucocytes (PMNs), and a slower infiltration of monocytes and macrophages. Thus filtration is impaired, so that the blood urea rises, and leakage of protein through permable capillaries results in a variable loss of protein in the urine called proteinuria.

We are now in a position to define the several roles of the phospholipid derived mediators, such as the various eicosanoids, PAF, the HETES and the lipoxins in glomerulonephritides. This has entailed examining their actions on the intrinsic cells of the glomeruli, like the capillary endothelial cells, the central stalk mesangial cells and the epithelial cells that lie on the urinary side of the filtration surface, which is the glomerular basement membrane (GBM). Their effects on the cells that become lodged in or that infiltrate the glomeruli, namely the platelets, PMNs and the monocyte-macrophages must also be accounted for.

As with inflammation at any site, vascular permeability that results in the leakage of protein rich fluid into the extravascular space is mediated by the combined action of vasodilator prostaglandins, that promote increased blood flow through arterioles and capillaries, and the peptidoleukotrienes that cause postcapillary venular constriction.[1] Leukotriene D_4 is a principal mediator,[2] and PAF[3] and the HETE molecules act synergistically, since they cause contraction of vascular endothelial cells,[4,5] and they will add to the effects of other agents like histamine, bradykinin and the anaphylatoxins that arise during the activation of complement. Loss of negatively charged heparan sulphate molecules from the walls of the glomerular capillaries is an important accessory process which means that albumin molecules are no longer subjected to 'charge repulsion' and so there is leakage of albumin. Heparitinases produced by platelets, and the lysosomal neutral proteinases of white cells that include proteoglycanases, aid such losses. At any rate involvement of platelets in the various forms of glomerulonephritis,[6] and the recruitment of PMNs followed soon by monocyte-macrophages[7] is an integral part of the process. Involvement of these phagocytic cells in free radical generating reactions is then accompanied by formation of leukotrienes,[8] as does damage to cells by complement mediated reactions.[8] Table 1 emphasizes the various roles of the phospholipid derived mediators in the complex pathophysiology of glomerulonephritides that have been deduced from animal experiments.

Survey of Table 1 reveals that the phospholipid derivatives have vascular effects that account for modulation of blood flow through the inflamed glomeruli in nephritis and that all have some effect on vascular permeability and hence proteinuria. Additionally the mediators control the responses of platelets, PMNs and infiltrating macrophages, and they alter the responses of mesangial stalk cells and thus modulate glomerular blood flow and filtration of urine. The thromboxanes even determine protein synthesis by the mesangial cells,[22] and the formation of extracellular matrix proteins like

Table 1. Pharmacological actions of phospholipid-derived mediators

Mediator	Vascular effect	Cellular action
PGI_2	Vasodilatation	Inhibits platelet aggregation
PGE_1	Vasodilatation	Inhibits platelet aggregation
PGE_2	Vasodilatation, proteinuria[9]	Causes platelet aggregation
$PGF_{2\alpha}$	Vasoconstriction	Mesangial cell proliferation[10]
TxA_2	Vasoconstriction Lowers GFR and plasma flow,[11] Causes proteinuria,[12] Salt and water retention.[13]	Causes platelet aggregation, Mesangial matrix formation,[14] Enhances T-cell responses.[15]
LTB_4	Vascular permeability[16]	Chemotaxis for white cells,[16] Activation of PMNs and macrophages.
LTC_4-D_4	Vascular permeability proteinuria[2]	Contraction of mesangial cells, so lowering the GFR.[17]
HETES	Vascular permeability[18]	5HETE—PAF synthesis[18] 12HETE—chemotaxis[18] 15HETE—endothelial proliferation 15HETE—inhibition of LTB_4 synthesis.[17]
Lipoxins	LXA_4 vasodilator[7,20] counteracts leukotrienes. LXB_4 lowers the GFR[20]	Reduce PMN reactivity[19]
PAF	Vascular permeability and proteinuria[3] Loss of anionic charges.[21]	Mesangial cell contraction and reduction of the GFR[3]

fibronectin that determine the onset of the fibrosis that leads to glomerulosclerosis and ultimate destruction.

Specific role of the mediators in nephritides

Culture of whole glomeruli or isolated mesangial cells[23] has been used to study biochemical pharmacology. So it was shown that $PGF_{2\alpha}$[10] will act synergistically with growth factors to cause mesangial cell proliferation, and studies have been done on the interaction of cytokines and eicosanoids.[24] In the study of the various animal models of glomerulonephritis, one has to examine the effect of pharmacological mediators on physiological responses by using micropuncture studies,[25,26] and studies of the porosity of the glomerular capillary walls to dextrans of defined size and charge. In nephritides one will expect an increase in renal cortical plasma flow and yet a reduction of the glomerular filtration rate (GFR), and a marked reduction of the glomerular capillary ultrafiltration coefficient, K_f.[26]

In all types of nephritis there is complement activation and increased leukotriene synthesis,[1] and hence vascular permeability and a fall of GFR and an infiltration of PMNs. There is an important role for thromboxane A_2 in mediating the increase of renal vascular resistance during this early phase.[27,28] However soon this will be counteracted by the production of vasodilators like nitric oxide originating from endothelial cells,[29,30] increased production of PGE_2,[26] and the formation of lipoxin A_4 that causes arteriolar dilatation.[31] So then there will be increased blood flow and yet low GFR and K_f.

There is an early burst of glomerular synthesis of leukotrienes, following which they are suppressed.[7,8] Early production of PAF-acether contributes to the formation of leukotrienes.[32] LTB_4 accounts for the attraction of PMNs into the glomeruli[16] along with cytokines like interleukin-8. LTB4 accounts for attraction of monocyte-macrophages along with chemokines like monocyte chemoattractant protein, MCP-1. Leukotrienes C_4-D_4 cause deterioration of glomerular function and in the ultrafiltration coefficient,[33] K_f, as proven by the improvement that is achieved with a leukotriene D_4 antagonist.[33] Indeed it has been known for a long time that nephritis is ameliorated by rendering animals neutropenic.

There is also a free radical catalysed lipid peroxidation product 8 epi-$PGF_{2\alpha}$ (an eight isoprostane), which turns out to cause mesangial cell contraction and reduction of glomerular blood flow and filtration.[34] This mediator was discovered whilst pursuing the fact that short term cholesterol feeding to rats causes renal vasoconstriction that is overcome by a thromboxane receptor antagonist.[35]

At any rate the appearance of macrophages within the glomeruli means that there is now local production of 15HETE. 15HETE abolishes the chemotactic response of PMNs (certainly in the rat). It is converted to lipoxin A_4[7,36] which is antagonistic to LTB_4.[36,37] Hence, according to Badr,[7] the GFR is now improved. Even more significantly 15HETE synthesis is thought to account for the disappearance of PMNs from the glomeruli.[7] Its production increases progressively over days and even weeks, since there are now many local macrophages. Unfortunately it is known that their presence portends glomerulo-fibrosis.

All this means that in the later stage of nephritis poor glomerular function is more likely to be mediated by thromboxane A_2.[7,26] Thromboxane production also accounts for proteinuria.[36] PAF is yet another factor,[39] but we should note that many actions of PAF are probably mediated via thromboxane.[40] Selective antagonism of thromboxane will certainly improve the GFR in all the models of nephritis,[41–43] and usually proteinuria is lessened.

Much interest is now centred on the fact that thromboxanes that are released during glomerular injury lead to proliferation of mesangial cells,[41] and they promote formation of extracellular matrix proteins.[14,22,45] They also will be produced by macrophages. Concurrent lipid peroxidation leads to collagen formation.[46,47] Now it is recognized that the cytokine transforming growth factor beta leads to collagen formation and glomerulosclerosis, since TGFβ also inhibits local metalloproteinases.[48] The inter-relationships between these factors have not been explored as yet. Often mesangial cells produce type I collagen and epithelial cells produce type IV collagen.

There is ample evidence that renal perfusion is maintained during glomerulonephritis by the vasodilator action of prostaglandins,[7] albeit they also facilitate leakage of protein[27–28] through the glomeruli. It is salutary to reflect that production of prostaglandins PGE_2, $PGF_{2\alpha}$ and PGI_2 is increased as a consequence of complement mediated damage to glomerular cells,[49] as a result of local production of oxygen radicals,[50] and in response to the proinflammatory cytokines like IL-1 and TNFα,[51] and that their ultimate role is likely to be 'cytoprotective'.

The question will arise as to whether all of these proinflammatory mediators are involved in the same way in each different histological form of nephritis. Generally this discussion applies to all forms of proliferative nephritis. In these there is infiltration of PMNs followed by monocyte-macrophages, and there is throughout an overriding role for the thromboxanes,[41–43] for thromboxane antagonists lessen the cellular proliferation and extracellular matrix deposition that leads to glomerulosclerosis and the proteinuria.

Similar mediators are certainly involved in 'membranous nephropathy' in which the capillary loop basement membranes appear thickened. This is not surprizing because involvement of the underlying epithelial cells elicits the same type of mediator response as does involvement of either endothelial or mesangial cells. A recent study has shown that PAF excretion is increased in proportion to the degree of proteinuria in membranous nephropathy in man.[52] Since it is well established that PAF excretion is increased in lupus nephritis in mice,[53] which is a proliferative cellular nephritis this again emphasizes that general statements can appertain.

Therapy of glomerulonephritis with anti-inflammatory drugs

Owing to its ability to induce lipocortin,[54] cortisone is our most powerful anti-inflammatory and anti-allergic drug. It stops formation of the eicosanoids and of PAF and the release of cytokines like IL-1 and TNFα. Yet effective usage is often accompanied by serious side-effects. Indeed, corticosteroids are only now used with specific intent in the nephritis of SLE (systemic lupus erythematosus) in which various lymphocyte driven auto-immune mechanisms are involved. Lymphocytes are easily suppressed by cortisone. In other forms of proliferative nephritis steroids are of little benefit.

The NSAIDs have been used to reduce proteinuria in nephrotic syndrome. Yet there is always the risk of allergic reaction and thus superimposed interstitial nephritis and acute renal failure. Hence currently the ACE inhibitors[55] are more likely to be used for reduction of proteinuria. The glomerular effects of angiotensin II are actually mediated through the thromboxanes.[56]

There is now great interest in the use of thromboxane synthetase and thromboxane receptor antagonists, for reasons that have been discussed. Increased thromboxane formation has been demonstrated in all human glomerulopathies e.g. in minimal change nephrotic syndrome, in the various proliferative nephritides and in diabetic nephropathy. In animal experiments thromboxane antagonism is successful in controlling hypertension, proteinuria and declining renal function.[41–44,57–59] The time for clinical trials has come, albeit the remark could apply also to PAF and leukotriene antagonists.

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