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Pathogenesis of ascites and hepatorenal syndrome

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Ascites is one of the most common complications of cirrhosis and has a one year mortality of up to 50%. For fluid to accumulate in any clinical situation the amount of sodium ingested must exceed that excreted by the kidneys and the virtual absence of sodium from the urine of ascitic patients was first documented by Farnsworth and Krakusin in 1948.[1] Five years later Chart and Shipley showed such patients to have an excess of a sodium retaining hormone in their urine (later identified as aldosterone).[2] Four decades after these discoveries the inter-relationship between renal function, hormonal changes and ascites formation remains controversial. At the other extreme of functional renal changes up to 85% of patients dying with cirrhosis have renal failure and, where there is no apparent cause other than the liver disease, is termed 'hepatorenal syndrome.' In 1863 Flint noted that proteinuria was uncommon and kidney morphology often normal, but some patients showed a variety of renal parenchymal changes.[3] Hecker and Sherlock confirmed the absence of proteinuria and normal histology in many patients and reported very low urine sodium concentrations – findings of a prerenal type of uraemia.[4]

Ascites

Renal function varies enormously in patients with ascites, values for glomerular filtration rate and renal plasma flow showing a complete spectrum from twice normal down to those found with significant renal impairment. When renal failure is present, the markedly reduced filtration of sodium may be sufficient alone to explain the fluid retention, but for those with well preserved renal function other factors acting on the renal tubules must be implicated. It is possible to determine the nephron site for abnormal sodium retention under conditions of a maximum water diuresis. Although the increased sodium reabsorption has been shown to occur throughout the nephron the greatest difference between patients with and without sodium retention is in the distal segment (distal convulted tubule or collecting tubule) (Fig 1).[5] Hormonal and neural factors affecting this part of the nephron include aldosterone, atrial natriuretic hormone and the sympathetic nervous system.

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RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

The concept has developed that cirrhosis is a high renin high aldosterone state. This has not, however, been confirmed in many studies in which only 35–50% of patients accumulating ascites have increased values (Fig 2)[5-8] Furthermore, before there is clinical evidence for fluid retention the renin-angiotensin-aldosterone system has been reported to be suppressed.[5 6]

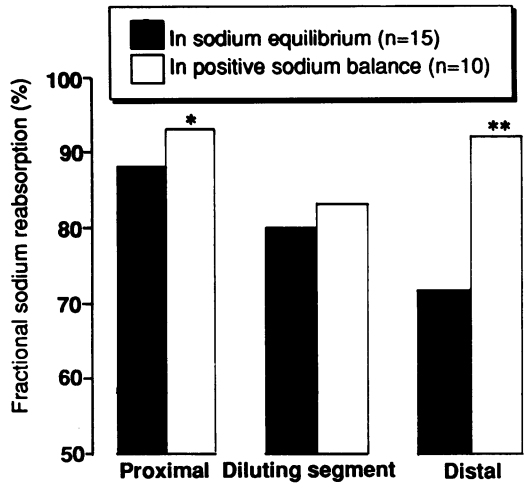

Figure 1: Comparison of the role of the different nephron segments in the pathogenesis of abnormal sodium retention in cirrhosis. These studies were carried out during a water diuresis and all patients diluted their urine to <75 mosmol/kg. From Wilkinson et al *(ref 228). Reprinted with permission from* Clinical Science. *Copyright @ 1979 The Biochemical Society, London.*

In view of the normal values for aldosterone in a number of patients actively retaining sodium its pathogenic importance has been questioned. Evidence in favour of a dominant role for aldosterone include: (a) renal sodium excretion is closely related to plasma concentration and the renal excretion of aldosterone whatever the state of sodium balance[5]; (b) blood volume, and expression of renal sodium retention, correlates well with the plasma aldosterone concentration[9]; (c) the aldosterone antagonist spironolactone or adrenalectomy will almost invariably reverse the sodium retention, provided renal failure is not already present[10 11]; (d) during β-adrenergic blockade it was observed that the renal sodium excretion increased or decreased exactly as predicted by the changes in aldosterone.[12] Thus if aldosterone is of major importance one must implicate an increase in renal tubular sensitivity to this hormone. It is of further interest that the abnormal aldosterone/sodium excretion relationship is 'shifted to the left' compared with control subjects and this becomes more marked with advanced disease.[9]

ATRIAL NATRIURETIC PEPTIDE

It is now established that a 28 amino acid peptide (atrial natriuretic peptide) synthesised by the atrial wall has a major role in the regulation of sodium excretion. It is released in response to central volume expansion. Atrial natriuretic peptide concentrations in cirrhosis are variable, but most studies have shown plasma values to be increased or normal when ascites is present.[13 14] Furthermore, in contrast with aldosterone, there appears to be a reduced renal sensitivity to its

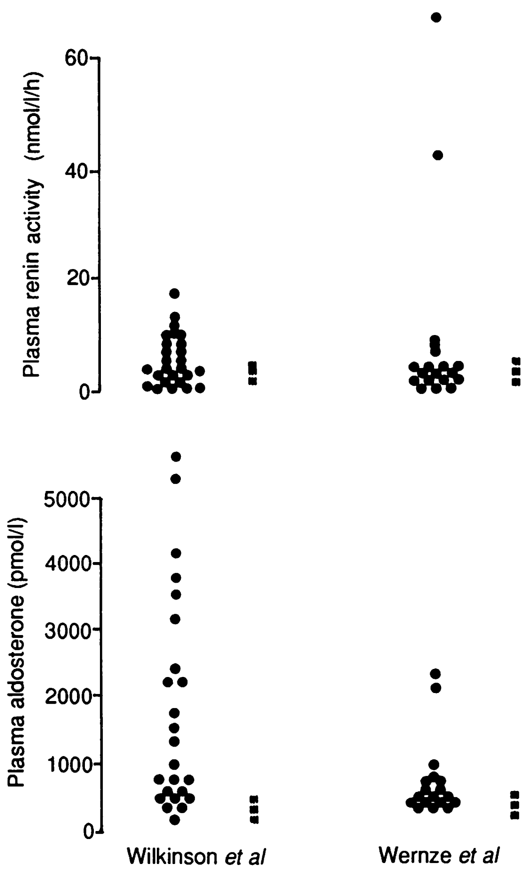

Figure 2: Plasma renin activity and aldosterone concentration in patients with cirrhosis and without clinical evidence of fluid retention. Stippled areas indicate the normal range. Modified from Wilkinson et al *[216, 223, 228] (1977–79).*

natriuretic effects.[15 16] Whether this is true insensitivity or down regulation of receptors remains to be determined.

SYMPATHETIC ACTIVITY

Increased renal sympathetic activity promotes sodium reabsorption. Plasma noradrenaline concentrations (an indirect index of sympathetic activity) are raised in cirrhotics with ascites, and are inversely related to sodium excretion.[17] More recent studies in cirrhotic animal models have shown marked amelioration of sodium retention when the renal sympathetic system is denervated.[18]

WATER RETENTION

The kidney retains water secondary to sodium in order to maintain osmotic equilibrium. With ascites, however, excess water is sometimes retained resulting in hyponatraemia. Most studies point to increased antidiuretic hormone levels as the dominant pathogenic factors.[19] Recent studies using a thromboxane A_2 synthase inhibitor have suggested that this compound may also affect renal water excretion in cirrhotics with ascites.[20]

Synthesis of available data relating to the pathogenesis of ascites

Ascitic fluid is derived from hepatic and splanchnic lymph, the formation of which increases consequent to portal hypertension, and accentuated by hypoalbuminaemia. Traditionally renal sodium and water retention is thought of as a homeostatic mechanism to restore 'effective' extracellular fluid volume and blood volumes (the components available to the intrathoracic volume receptors). The initial deficits were said to arise as a result of loss of extracellular fluid into the peritoneal compartment as ascites, and from sequestration of blood in the splanchnic circulation secondary to portal hypertension. It is now realised, however, that sodium retention *precedes* ascites formation.[21] This concept has therefore been modified with peripheral vasodilatation, characteristic of many patients with cirrhosis, as the initiating factor causing a low effective arterial blood volume.[22] The site of vasodilatation is likely to be the splanchnic circulation and/or that supplying the skin and muscles. Although this 'underfill' concept may indeed be valid for the one-third of patients with a stimulated renin-angiotensin-aldosterone system it is incompatible with the findings of normal values for those with normal plasma aldosterone, and with increased plasma atrial natriuretic peptide. In order to explain the mechanisms involved in the other patients a number of findings must be taken into account. These include suppression of the renin-angiotensin system before clinical evidence of fluid retention, and possible altered renal tubular sensitivity to aldosterone and atrial natriuretic peptide.

Consideration of patients before ascites has developed may help interpretation. Whatever its explanation the aldosterone/sodium excretion relationship is abnormal at this stage of the disease and sodium excretion appears to be related to aldosterone. Presumably, as the abnormality develops the previously normal aldosterone levels result in some degree of fluid retention which account for the expanded plasma volume observed at this stage of the disease. If the fluid remains within the 'effective' compartments this could explain the suppression of the renin-angiotensin-aldosterone system which would result in a return to sodium balance at a higher concentration of total body sodium. The process would be accentuated by reduced renal sensitivity to atrial natriuretic hormone.

An alternative explanation to the traditional concept for ascites formation is 'the overflow theory.'[23] Renal sodium and water retention are said to be the primary abnormalities with the expanded extracellular fluid localising to the peritoneal cavity when factors such as portal hypertension and reduced plasma oncotic pressure favour ascites formation. For the 35% of patients in whom the renin-angiotensin-aldosterone system is not stimulated and natriuretic hormone concentrations are increased the findings fit well with this concept.

There is evidence that splanchnic haemodynamics may be fundamentally different for these two groups of ascitic patients. In one study patients were divided into those readily responding to diuretics without complication and those with resistant ascites is which diuretics readily precipitated renal impairment.[24] Although the components of the renin-angiotensin-aldosterone system were not specifically determined one might predict that the diuretic responsive group are more likely to have ascites forming as an overflow mechanism than those in whom the effective extracellular fluid was already depleted (diuretics in the latter group presumably resulting in further depletion with renal impairment and thus diuretic resistance). Those comprising the latter group had significantly less spontaneous portasystemic shunting and a tendency to a higher postsinusoidal vascular resistance. The authors concluded that collateral vascular resistance must also be higher. Taken together these changes would encourage intrahepatic lymph formation with consequent accumulation of ascites. Thus, ascites would be developing as a primary abnormality independent of the effective extracellular fluid volume which eventually falls.

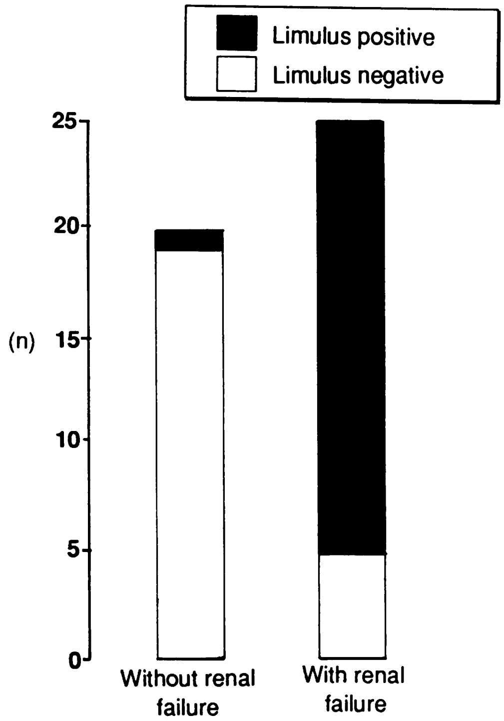

Figure 3: Relationship of hepatorenal syndrome to endotoxaemia as measured by the limulus *assay. From Wilkinson* et al *(ref 220). Reprinted with kind permission from the* British Medical Journal. *Copyright @ 1976.*

Hepatorenal syndrome

The aetiology of hepatorenal syndrome is still incompletely understood. To date most emphasis has centred on the hypothesis that it is caused by severe renal arterial and arteriolar vasoconstriction causing reduced renal blood flow and thence renal failure. This has been based on many studies which have shown reduced renal blood flow, but was given extra impetus by those of Epstein *et al* in which renal angiography showed marked vasoconstriction of the arterial vasculature.[25] Studies by Ring-Larsen and others, however, have shown that many patients with ascites but relatively intact renal function have renal blood flows comparable with those observed in many subjects with hepatorenal syndrome.[26] This suggests that other factors modulating glomerular filtration rate must be important.[27 28] This is likely to involve mesangial cells which have similar properties to smooth muscle. These cells invaginate the glomerular capillary tuft and contract in response to many mediators. Mesangial cells appear to dynamically regulate the surface area available for ultrafiltration, and thus the ultrafiltration coefficient.[25 26]

Renal blood flow is dependent on renal vascular resistance and renal perfusion pressure (mean arterial pressure minus renal venous pressure). Many patients with decompensated liver disease have a moderately low mean arterial pressure, and increased renal venous pressure. Furthermore, liver failure is characterised by increased sympathetic tone which appears to shift the autoregulatory curve such that renal blood flow is more dependent on renal perfusion pressure. Thus, even patients with a modest decrease in renal perfusion pressure may exhibit a significant fall in renal blood flow. No studies constructing a scattergram of the perfusion pressure/renal blood flow relationship in patients with liver disease or hepatorenal syndrome have yet been carried out.

MECHANISMS FOR VASOCONSTRICTION

Most research over the last 10–20 years has focused on identifying increased production of vasoactive mediators of vasoconstriction. Interestingly, many of these mediators also modulate mesangial cell function, causing contraction of this smooth muscle like cell, and may therefore modulate not only renal blood flow through the arterioles but also through the glomerular capillary bed.

PERIPHERAL ARTERIAL VASODILATATION HYPOTHESIS

The most recent proposal to explain renal vasoconstriction is the vasodilatation hypothesis of Schrier *et al*,[22] and suggests that systemic vasodilatation is the initiating event. This, in its extreme form results in a reduction of effective arterial blood volume with moderate hypotension. The cause of systemic vasodilatation is unknown, but recent studies on the role of endothelium derived relaxing factor (nitric oxide) in animal models of cirrhosis have suggested that this may be an important factor.[29] Systemic vasodilatation activates homeostatic mechanisms causing rises in plasma renin, aldosterone, noradrenaline, and vasopressin concentrations which cause sodium retention and renal vasoconstriction. Procedures which augment plasma volume, such as head out of water immersion or plasma expansion, result in a small transient increase in renal blood flow and glomerular filtration rate in many subjects, but this is rapidly offset by redistribution of fluid or enhanced vasodilatation. Fernandez-Seara *et al* have reported an interesting study in which they observed a decrease in systemic vascular resistance, a decrease in renal blood flow, and in patients with ascites there was an initial increase in femoral blood flow (to twice normal), indicative of participation of the extra-splanchnic system in the vasodilatation.[30] On the other hand, patients with hepatorenal syndrome exhibited femoral blood flow close to normal subjects suggesting that splanchnic vasodilatation was extreme causing intense activation of the pressor systems.

There is marked activation of the sympathoadrenal system in advanced liver disease, and the degree of activation follows the degree of decompensation.[31] The kidneys are richly innervated by the sympathetic system which, when activated, increase renal vascular resistance. Early studies of α-adrenergic blockade by phentolamine infusion produced no improvement in renal function, although any beneficial effect was offset by a fall in mean arterial pressure.[32] More recently, a novel approach has used lumbar sympathetic blockade of the sympathetic nerves, which produced an increase in renal blood flow in all eight subjects studied, but only five subjects showed an improvement in glomerular filtration rate, and three showed an actual deterioration.[33] Thirdly, studies in which head out of water immersion have followed serial changes in glomerular filtration rate and plasma noradrenaline concentrations did not observe suppression of noradrenaline in nine out of 15 subjects in whom there was an improvement in glomerular filtration rate.[34] Thus, increased sympathetic activity may be an important factor reducing glomerular filtration rate in some but not all patients with hepatorenal syndrome.

As already discussed the renin-angiotensin system is activated in decompensated liver disease.[6,8] Increased renin formation may be secondary to renal hypoperfusion or a decrease in effective blood volume. Activation of renin formation increases angiotensin II formation within the kidney. Angiotensin II predominantly increases efferent arteriolar tone and thus the filtration fraction. Although this reduces renal blood flow and increases renal vascular resistance, it maintains glomerular filtration rate. Thus, in conditions such as hypovoalemia or shock, it is often regarded as a mechanism protecting glomerular filtration rather than the converse. This important principal was demonstrated by Schroeder *et al* who infused angiotensin II into patients with cirrhosis.[35] This study observed that in four of five patients with the lowest renal blood flow there was an actual increase in glomerular filtration rate despite a further fall in renal blood flow.

CIRCULATING OR INTRARENAL VASOCONSTRICTOR. ROLE OF ENDOTOXINS

Although activation of the above homeostatic mechanisms are undoubtedly responsible for some degree of renal vasoconstriction other factors are likely to be important.

Endotoxins are the lipopolysaccharide components of the cell wall of gram negative bacilli. They are thought to be responsible for many of the manifestations of gram negative septicaemia in man, and are known to be vasoconstrictor in the renal circulation in animals. In advanced liver disease, there appears to be failure of the reticuloendotheliac system to remove endotoxins absorbed from the gut, and direct absorption through portasystemic collaterals into the systemic circulation. Several studies have shown a higher incidence of endotoxaemia in the systemic circulation in hepatorenal syndrome[36,38] (Fig 3). Other toxins such as staphylococcal toxin may act synergistically with endotoxins and may account for some of the discrepant results reported by other groups. Supportive evidence is also provided by more recent studies in which daily culture of blood, urine, sputum, ascites, as well as daily nasopharyngeal/vaginal swabs, have shown a higher incidence of bacterial infection and fungal infection in patients with fulminant hepatic failure developing hepatorenal syndrome.[39]

If endotoxins or indeed other bacterial toxins are important in the pathogenesis of hepatorenal syndrome, what is the mechanism? Several lines of investigation have shown that endotoxins activate formation of the eicosanoids. This is either through a direct effect on circulating monocytes or tissue resident macrophages. Eicosanoids comprise in part the prostaglandins, thromboxane A_2, and the cysteinyl-leukotrienes (LTC_4, LTD_4, and LTE_4). These may be classified into renal vasodilators (PGE_2, and prostacyclin) and renal vasoconstrictors (TXA_2, and LTC_4 and LTD_4), as well as causing relaxation or contraction of the mesangium respectively. The role of thromboxane A_2 is controversial. Some studies have reported increased renal production while others have suggested that there is normal or decreased production of thromboxane A_2 as assessed by urinary excretion rate or concentration of its stable metabolite TXB_2 (40–43). More recent studies have suggested that while there is increased renal and systemic production of thromboxane A_2 in hepatorenal syndrome,[44] this was not significantly greater than that in subjects appropriately controlled for severity of hepatic dysfunction but with relatively normal renal function. Thus, increased production appears to primarily reflect the severity of liver disease.

The vasodilatory prostaglandins are important in maintaining renal function in patients with decompensated liver disease. Renal production of PGE_2 and prostacyclin is increased in patients with ascites,[31,41,43] and several studies have shown that administration of non-steroidal anti-inflammatory drugs to such subjects causes a marked reduction in glomerular filtration rate.[40,45] Studies have shown that urinary excretion of PGE_2 is decreased in hepatorenal syndrome. This may indicate decreased renal production of this prostanoid or may reflect glomerular filtration rate dependent excretion. Recent immunocytochemistry studies suggest, however, that medullary endoperoxide synthase was decreased in renal biopsy samples from subjects with hepatorenal syndrome compatible with decreased production.[44] There is no good evidence, however, to suggest that decreased production of prostacyclin is responsible for hepatorenal syndrome.[44]

Two studies have now shown increased cysteinyl-leukotriene production in hepatorenal syndrome.[28,47] Cysteinyl-leukotrienes are produced by inflammatory cells, lung, vascular tissue, and probably kidney. We recently re-

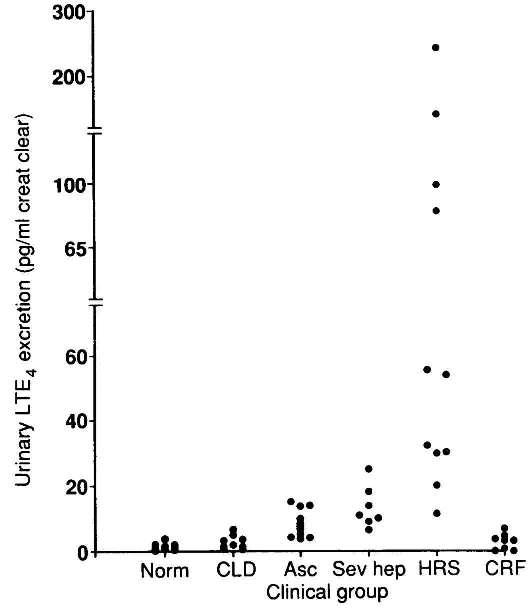

Figure 4: Urinary LTE_4 excretion in decompensated liver disease and hepatorenal syndrome. Highest values were observed in hepatorenal syndrome, indicative of increased production. CLD=compensated liver disease. Asc=Ascites. Sev hep=Severe hepatic failure. CRF=Chronic renal failure. Reprinted by courtesy of J Hepatol *(Ref 44).*

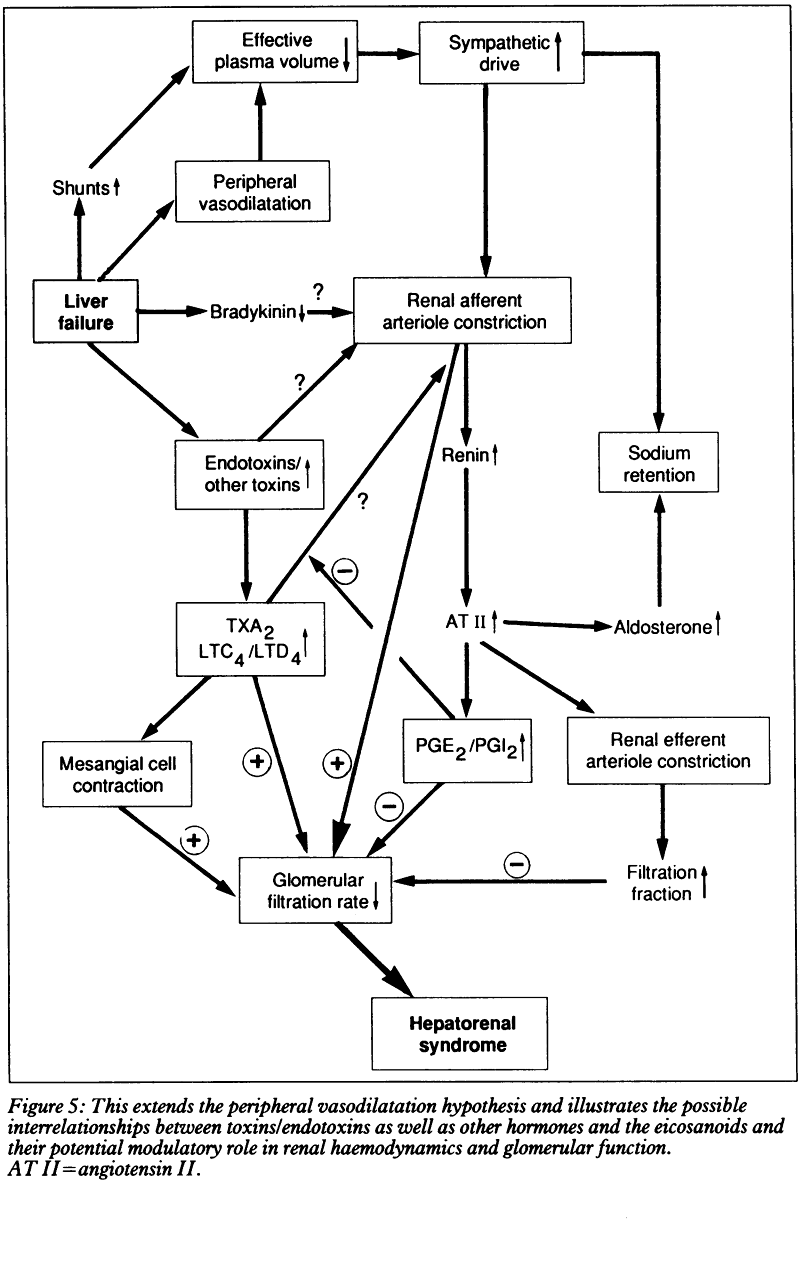

Figure 5: This extends the peripheral vasodilatation hypothesis and illustrates the possible interrelationships between toxins/endotoxins as well as other hormones and the eicosanoids and their potential modulatory role in renal haemodynamics and glomerular function. AT II=angiotensin II.

ported markedly increased cysteinyl-leukotriene production in hepatorenal syndrome compared with appropriate controls suggesting that leukotrienes may be important in the aetiology of this condition[28] (Fig 4).

Other mediators such as adenosine may also be important because this may cause systemic vasodilatation and renal vasoconstriction. Synthesis may be increased by tissue hypoxia which is well recognised in advanced liver failure. Recent studies with dipyridamole (which inhibits adenosine uptake) in cirrhotic patients have shown that this compound produces renal impairment suggesting that this may also be an important mediator.[48] Studies with theophylline (an adenosine antagonist) in cirrhotic patients, however, showed little systemic effect.[49] Trials using the newer and more specific adenosine antagonists are needed. Platelet activating factor and endothelin are also potent modulators of renal function, and studies on these are awaited with interest.

Thus, current concepts on the aetiology of hepatorenal syndrome are that it is a multifactorial condition caused by reduced renal blood flow and altered ultrafiltration coefficient as a result of mesangial cell contraction. Reduced renal blood flow is caused by a moderate decrease in renal perfusion pressure caused by systemic vasodilatation and increased renal venous pressure. This is probably exacerbated by a shift in the renal autoregulatory curve because of increased sympathetic activity. This, together with increased renovascular resistance and mesangial cell contraction induced by a combination of endotoxaemia, altered eicosanoid production, and possibly increased adenosine production gives rise to the functional renal impairment known as hepatorenal syndrome (Fig 5).

Unresolved problems

The most intriguing unresolved issue relating to renal sodium retention is the apparently increased renal tubular sensitivity to aldosterone, apparent resistance to atrial natriuretic hormone, and the mechanisms underlying the peripheral vasodilatation. Clarification of these abnormalities might be fundamental to understanding the initiation of sodium retention. Further clarification of splanchnic haemodynamic changes is also required. In particular whether there really are fundamental differences between patients who might form ascites as an 'overflow' mechanism from those who appear to have effective central hypovolaemia. Longitudinal studies are required to establish whether the former group progresses to the latter or *vice versa*.

With respect to hepatorenal syndrome the role of reduced renal perfusion pressure needs further evaluation, and accurate data on the renal blood flow/pressure relationship in liver disease will be fundamental to this area. More definitive studies on the role of cysteinyl-leucotrienes using specific LTD_4 antagonists are needed, and the role of other mediators of increased vascular tone and mesangial cell function such as endothelin and platelet activating factor may also turn out to be important contributory factors.

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