CHAPTER 2

Background information

Effects of amino acids on renal hemodynamics

The effects of amino acids on renal hemodynamics were studied in both animals and humans using various types of amino acids. Pitts firstly reported that glycine could increase GFR in dogs (Pitts, 1944). Subsequent study demonstrated that intravenous glycine infusion induced acute rise in both GFR and RPF and the effects was due to the renal vasodilatation (Johannesen et al., 1977). In 1982 Lee and summerill reported that various types of amino acids could increase GFR by both oral and intravenous loadings (Lee and summerill, 1982). An increase in GFR was associated with the metabolism of amino acids and did not depend on the concentration of amino acids in plasma. Only metabolized amino acids could augment GFR whereas unmetabolized amino acids did not poss this property. However, subsequent study showed that unmetabolized amino acid could also induced acute rise in GFR (Woods et al., 1986). Until now, there are many studies about the renal hemodynamic effects of amino acids. The common findings from those studies showed that various types of amino acids could increase GFR and RPF. Both GFR and RPF were increased in the same magnitude so

that these increments occurred from the renal vasodilatation. Several mechanisms had been purposed but the exact mechanisms were not established.These mechanisms could be simply divided into three grougs : the role of hormones, role of liver and the role of tubuloglomerular feedback mechanisms.

1. Role of hormones on the renal hemodynamics

Many hormones are repoted to be the mediators of the renal vasodilatation in both animal and human models. Meyer et al. reported that intravenous infusion of amino acids in rats resulted in renal vasodilatation. The renal vasodilatation did not occur from solute load and it should be mediated by hormones because the vasodilatation was inhibited by somatostatin (Meyer et al., 1983). The study of Castellino et al. also confirmed the role of hormones. They reported that intravenous infusion of amino acid mixtures in normal subjects induced the renal vasodilatation and this effect was also inhibited by somatostatin (Castellino et al., 1986). Somatostatin was the hormone that could inhibit other hormones. Subsequent studies by Castellino et al demonstrated that the renal vasodilatation were attributed to hyperaminoacidemia, insulin, glucagon and growth hormone (Castellino et al., 1987 ; Castellino et al., 1988). Hyperaminoacidemia in the absence of increased levels of insulin, glucagon and

growth hormone or increased levels of these hormones in the absence of hyperaminoacidemia could not induce renal vasodilatation. The role of glucagon on the renal hemodymamics was also reported. Hirschberg et al. demonstrated that renal vasodilatation from amino acid infusion was mediated by glucagon and prostaglandin (Hirschberg et al., 1988). They previously demonstrated that the renal vasodilatation was not mediated by growth hormone (Hirschberg et al., 1987). The role of prestaglandin was supported by other investigator (Ruilope et al., 1987) whereas this role was also debated (Herrera et al., 1988 ; Hostetter, 1986).

2. Role of liver

The role of liver was suggested by Alvestrand and Bergstrom. They proposed that a transient increase in GFR after ingestion of a protein meal or during intravenous infusion of amino acids was mediated by glomerulopressin (Alvestrand and Bergstrom, 1984). This hormone was isolated from venous blood of liver from toads, rabbits and dogs. This hormone enhances GFR in rats and dogs. They proposed that secretion of this hormone was stimulated by an increased uptake of free amino acids by the liver. Free amino acids uptake of liver was increased after protein intake, during amino acid infusion and during glucagon infusion. The important role of liver was later supported by the studies of Premen. Intrarenal

infusion of glucagon in dogs had no effect on GFR and RPF but intraportal infusion of glucagon could cnhance GFR and RPF (Premen, 1985). On the contrary, the role of liver was debated by Woods et al. They demonstrated that intravenous infusion of a mixture of amino acids in normal anesthetized dogs and in a group of dogs after ligating all blood vessels supplying the liver and inserting a hepatic portal-femoral venous shunt had the same result. Both routes could induce acute rise in GFR and RBF (Woods et al., 1987).

3. Role of tubuloglomerular feedback

Tubuloglomerular feedback is the other possible mechanism in amino acid-induced renal vasodilatation. Stimulation of this feedback mechanism results in renal vasoconstriction and on the other hand, renal vasodilatation is obtained from inhibition of this feedback mechanism. This hypothesis was firstly supported by the work of Woods et al. They showed that elevation ofplasma amino acids increased GFR and RBF in dogs by a mechanism that required an intact macula densa (Woods et al., 1986). This work indicated that there was some relationship between renal vasodilatation and tubuloglomerular feedback. Subsequent study showed that amino acids infusion in man induced renal vasodilatation through inhibition of tubuloglomerular feedback mechanism (Appiani et al., 1988). Amino acid increased proximal

sodium reabsorption so distal sodium delivery was reduced. A decrease in distal sodium delivery to macula densa modulated the tone of glomerular arterioles and renal vasodilatation occurred.

Physiology of prostagladins

Prostaglandins are series of endogenous hormones derived from arachidonic acids. The biosynthesis of these hormones occursin almost all mammalian tissues including the kidneys. There is no evidence that prostaglandins are stored ; thus, release into extracellular fluid reflects de novo synthesis (Piper and Vane, 1969). Renal prostaglandins are synthesized in both renal cortex (Thurau, 1964) and renal medulla (Bohman, 1977 ; Crowshaw, 1971 ; Muirhead et al., 1972 ; Zusman and Kaiser, 1977). Prostaglandins could modulate renal vascular tone so they are capable of altering renal blood flow (Feigen et al., 1976 ; Herbaczynska - Cedro and Vane, 1973 ; Lonigro et al., 1973 ; Venuto et al., 1975), glomerular filtration rate (Levenson et al., 1982), tubular transport of electrolytes especially sodium (Bolger, 1978 ; Chang et al., 1975 ; Lee et al., 1971 ; Weber et al., 1975) and excretion of water (Anderson et al., 1975 ; Fejes - Toth, Magger, and Walter, 1977 ; Grantham and Ordoff, 1986 ; Martinez - Maldonado et al., 1972). Intrarenal artery infusion of various types of prostaglandins in dogs could increase renal blood flow in dose dependent manner

(Lifschitz, 1981). Several investigators showed that in awake trained animals inhibition of prostaglandin biosynthesis had no elfect on resting renal blood flow (Swain et al., 1975 ; Zin, 1975). When animals were studied under anesthesia and acute surgical trauma, conditions that would be expected to activate the renin - angiotensin and adrenergic nervous systems, then indomethacin did reduce total renal blood flow in the dog (Feigen et al., 1976 ; Herbaczynska - Cedro and Vane,1973; Lonigro et al., 1973 ; Venuto et al., 1975). These experiments suggest that under resting conditions the basal synthesis of prostaglandins is low and does not contribute significantly to renal vascular resistance. When the system is perturbed or stressed, however, prostaglandin biosynthesis may be critical to the modulation of renal vascular resistance.

Most prostaglandins synthesized in the kidney are natriuretic, both in humans and in animals. The most potent natriuretic prostaglandins are PGE_2 and PGI_2 (Bolger 1978 ; Fulgraff, Brandenbusch, and Heintze, 1974 ; Lee et al., 1971) whereas PGF_2 is natriuretic only at dosages threefold to fivefold higher (Fulgraff and Bradenbusch, 1974). Unfortunately, it is still unclear that natriuretic effect of prostaglandins occurs from the renal vasodilatation or direct tubular inhibitory action (Hart and Lifschitz, 1987).

Prostaglandins have been shown to reduce vasopressin - stimulated water transport (Grantham and Orloff, 1968 ; Orloff, Handler, and Bergstrom, 1965) and prostaglandin cyclooxygenase inhibitors enhance ADH stimulation of water reabsorption (Anderson et al., 1975 ; Berl et al., 1977, Leyssac et al., 1975 ; Lum et al., 1977). The antagonism appears to occur at the adenylate cyclase level (Beck et al., 1971 ; Lipson and sharp, 1971).

Indomethacin, an prostaglandin cyclooxygenase inhibitor, is widely employed as a pharmacologic agent to investigate the renal actions of prostaglandins. Inhibition of renal prostaglandins synthesis has been documented by demonstrating a reduction of prostaglandin level in renal venous blood or urine (Roman et al., 1978).