Chapter II

Background Information

Prostaglandins and acute renal failure

Arachidonic acid, the precursor for PGs synthesis presents in phospholipid of cell membrane. In response to various stimuli (mechanical, hormonal and coagulating factors) it is released from cell phospholipid by the action of phospholipase and metabolized via the cyclooxygenase pathway to prostanoids characteristic of the given type of cell and biological response. The cyclooxygenase enzymes oxygenates arachidonic acid to form the prostaglandin endoperoxides, PGG_2 and PGH_2 which are then converted to 5 prostanoid (primary prostanoid) such as PGD_2, PGF_2, PGI_2 and thromboxane (Cannon, 1984). Among these cyclooxygenase products, prostacyclin (PGI_2) and thromboxane A_2 (TXA_2) are the most of interest. PGI_2 synthetized in the wall of blood vessel by the action of prostacyclin synthetase (Cannon, 1984; Russo-Marie, 1985), is a potent vasodilator and an inhibitor of platelet aggregation. PGI_2 is unstable, in blood at 37°C it has a half-life of 2-3 min (Dusting, Moneada & Vane, 1977). In the kidney it produces an increased renal blood flow and decreased renal vascular resistance (Dunne, 1983). Synthesis of PGI_2 is prominent in microdissected cortical arteries and arterioles (Schlondroff & Ardaillon, 1986), rat glomeruli (Shlondroft, Roczniak, Satriano & Folkert, 1980) human mesengial cells and isolated human glomerulus (Schlondroff & Ardaillon, 1986). Thromboxane A_2 synthetized by

platelet and in a minor extent by adventitia layer of vessel wall via thromboxane synthetase pathway. It has a very short half-life of 30 sec in aqueous media at 37°C (Canon, 1984). Thromboxane A_2 is a powerful vasoconstrictor and proaggregator and also contracts isolated glomeruli (Schlondroff & Ardaillon, 1986).

Because of the counteraction of the two PGs, PGI_2 and TXA_2, the primer is potent vasodilator and the latter is powerful constrictor, they play a contributory role in renal autoregulation as modulators of renal vascular tone and mesangial contraction (Schlondroff & Ardaillon, 1986). Imbalance between the vasodilator and vasoconstrictor prostaglandin or abnormal production of TXA_2 found in various form of kidney insults. TXA_2 is an important mediator of vasoconstriction in obstructive nephropathy in rat (Yarger et al, 1980; Klotman, Smith & Volpp, 1986) dog (Cadnapaphornchai et al 1982; Balint et al, 1985). In nephrotoxic serum nephritis (Lianoss et al, 1983) and autoimmune mice lupus nephritis (Kelley, Sneve & Musinski, 1986) found that the increased intrarenal biosynthesis of TXA_2 mediated deterioration of renal hemodynamic. A direct linear relation between the percent of TXB_2 produced by renal microsome preparation and serum creatinine was found in glycerol-induced ARF (Benebe et al, 1980). Thromboxane synthetase inhibitor (TSI) relieved renal vasoconstriction (Balint et al, 1985), improved renal hemodynamic (Yarger et al, 1980; Lianoss et al, 1983) and concentrating ability of the postobstructed kidney (Cadnapaphornchai et al, 1982). Additional data suggested that vasodilatory PGs and TXB_2 modulate glomerular filtration rate in rat with reduced renal mass (Stahl, Kudellka,

Pararicini & Schollmeyer, 1986).

Renal effects of Russell's viper venom

Kidney is one of the organ frequently involved in snake bite patients who survived from the early effects of a severe viper bite oftens die of ARF (Aung-Khin, 1978). In patients bitten by Russell's viper, ARF with tubular necrosis was noted by Sitprija et al (1974) and Chugh et al (1975). Renal pathologic changes are variable. Diffuse fine glomerular deposition of IgM and third component of complement (C_3) in mesengial area with extensive along the capillary wall is detected. Vascular lesions in the kidney, the most obvious alteration is necrotizing arteritis of the interlobular arteries. Thrombophlebitis of the arcuate vien is also present (Sitprija et al, 1985). It is probable that vascular necrosis, due to the absorption of the venom from the site of bite into blood streams and a very high concentration being achieved in the kidney (Varaguman & Panabokke, 1970). Tubulointerstitial lesion demonstrated by the Puchtler-Sweat method show hemoglobbin casts in the lumen of distal convoluted tubules and collecting tubules (Sitprija et al, 1985). Inflamatory cells always locate around the necrotic collecting tubule. Snake venoms as the membrane toxin may exert the toxicity by changing the permeability of membrane in various cells and tissue inducing cytotoxicity necrosis, blood coagulation and hemolysis. The study has been shown more informations about pathogenesis of tubulotoxicity of Russell's viper venom with a change in depolarization of the proximal tubule of triturus kidney. The pattern of change was same as those

of DNP which indicated that the venom may act as metabolic inhibitor to abolish the energy supply for ionic transport mechanism (Chaiyabutr et al, 1985).

It is believed that extrarenal factor, hypotension due to the cardiovascular effects of Russell's viper venom may responsible for the kidney insults. In many experimental data showed that after envenomation, blood pressure dropped markedly which associated with increasing of renal vascular resistance, falling of glomerular filtration rate and renal blood flow, prompt oliguria presented. (Tongvonchai, 1984; Tungthanathanich, 1983). Therefore ARF induced by Russell's viper venom may be ischemic type. However alteration in renal function of envenomated animal are due to changes of both extrarenal and intrarenal factors confirmed by Chaiyasest (1986).

ARF induced by Russell's viper venom may be due to nonspecific effects of hormonal changes such as prostaglandins, renin- angiotensin system (RAS), kallikrein-kinin system, catecholamine, histamine or serotonin. Some changes may be secondary to hypotensive effect of the venom. It is known that hypotension is the potent stimulus for RAS to sustain blood pressure. This may be the compensation for survival in envenomated victim since converting enzyme inhibitor (CEI) aggravated hypotensive effect of Russell's viper venom inspite of administration of CEI alone did not give any significant change in blood pressure (Chaiyabutr et al, 1985). Furthermore, Huang (1984 b) demonstrated that phospholipase A_2 (PLA_2) from vipers russelli snake venom induced an increased in plasma PGI_2 and TXA_2 level in normotensive rats.

Plasma renin activity was reduced in hypertensive rats. Both PGs and RAS are vasoactive hormone which produced in the kidney to regulate renal hemodynamic and renal function. It is believed that these substances may contribute to the alteration in envenomated kidney. The mechanism of Russell's viper venom-induced deterioration of renal function was proved to be mediated by prostaglandin synthesis. Since the envenomated animal showed a decreased in renal hemodynamic and renal function while the animal pretreated with indomethacin exhibited the improvement of these changes (Tongvongchai, 1984).