Chapter II

Background and Information

The catecholamines: epinephrine, norepinephrine and dopamine are located in the biosynthetic pathway in the following order; tyrosine-->dopa--dopamine--norepinephrine--epinephrine. Norepinephrine is generally contained in the sympathetic nerves and sympathetically innervated as well as in kidney and the adrenal medulla. In the brain, norepinephrine is concentrated in the hypothalamus and can synthesize from tyrosine in the heart

Origin and Storage of Transmitter

1. Synthesis:

The postganglionic neurons activity take up tyrosine from the extracellular fluid and by successive enzymatic reactions transform it in the neuroplasm to dopamine. The dopamine is taken up by the storage vesicles and converted to norepinephrine by dopamine hydroxylase. An increase in the neuroplasmic concentration of norepinephrine exerts a negative feedback on the activity of the enzyme tyrosine hydroxylase (end-product inhibition) where as increased activity of the adrenergic neuron or depletion of the catecholamine stores has the opposite effect. (Vanhoutte et al., 1981).

2. Neuronal uptake:

The cell membrane of the adrenergic neuron can take up norepinephrine and a number of other substances that can interact with adrenergic sites (neuronal uptake). Part of norepinephrine is taken up by the neuronal membrane and enzymatically destroyed by the neuronal monoamine oxidase (MAO) to 3, 4-dihydroxyphenylgylcol (DOPEG) before it reaches the storage sites; the DOPEG the diffuses to the extracellular space. The norepinephrine taken up by nerve ending originates either from the adrenergic terminal itself or from the blood circulation.

Release of Transmitter

1. Leakage:

Part of the norepinephrine containing in the storage sites continuously diffuses to the neuroplasm and towards the extracellular space. Most of it is deaminated by the intraneuronal monoamine oxidase and the concentration of intact norepinephrine reaching the junctional cleft to activate the postjunctional adrenergic receptor. Organic solvents such as propylene glycol and acetaldehyde and high concentrations of drugs such as reserpine, the local anesthetic agent, etidocaine, the α_1-adrenolytic drugs prozosin and yohimbine and the combined and β-adrenergic blocker labelalol cause an increase in the efflux of [^{3}H] norepinephrine and [^{3}H] DOPEG in unstimulated isolated blood vessels. Inhibitors of monoamine oxidase converts the overflow of deaminated metabolites into intact [^{3}H] norepinephrine. Theses results suggest that these agents increase the permeability of the storage vesicles and favor the leakage of stored transmitter; in particular, if

monoamine oxidase is inhibited, enough intact norepinephrine reaches the synaptic cleft to activate the postjunctional adrenergic receptor (Anderson et al., 1979).

2. Pharmacological displacement:

A number of substances, including amphetamine, butalamine, ephedrine, guanethidine and tyramine have a greater affinity for the storage proteins than the adrenergic transmitter itself. They displace norepinephrine to the neuroplasm and extracellular space (indirect sympathomimetic effect). Because large amounts of transmitters are displaced and the indirect sympathomimetic amine (in particular tyramine) competes for monoamine oxidase, the junctional concentration of norepinephrine can increase so that the postjunctional adrenergic receptor are activated. Unlike the exocytosis process, the pharmacological displacement of stored norepinephrine does not require an increase in neuroplasmic Ca^{++} (George & Leach, 1973). The effects of indirect sympathomimetic amines are depressed by any procedures that cause denervation or catecholamine depletion. Those can inhibit the neuronal uptake process, by contrast, they are augmented by procedures that reduce the activity of monoamine oxidase. Since the neuronal uptake carrier has a higher affinity for indirect sympathomimetic amines than for norepinephrine, the former inhibit the neuronal uptake of the latter (Hedqvist et al., 1968). Part of the response to indirect sympathomimetic amines can be ascribed the direct influences on postjunctional α-adrenergic receptors on the smooth muscle cells (Campbell & Farmer, 1968; Furchgott et al., 1963; Krishnamurty & Grollman, 1972).

3. Exocytotic release:

The active release of norepinephrine is initiated by the active potentials generated in the ganglionic cell body. The storage vesicles are fused with neuronal membrane by Na^{+} and Ca^{++} activation. When the site of fusion ruptures, norepinephrine and dopamine-hydroxylase in the vesicular contents are released in the junctional cleft. Stimulation of the sympathetic nerves serving peripheral venous effluent from the vascular bed; the vasomotor response and evoked release of norepinephrine disappear after degeneration of the adrenergic nerve ending, after catecholamine depletion, and after administration of inhibitors of postganglionic conduction. Similar results have been obtained in isolated perfused organ such as the kidney, the pancrease and the spleen (Bacq et al., 1974; Garcia et al., 1976; Hedqvist, 1979).

Adrenergic receptors

Adrenergic receptors are classified to alpha and beta according to hemodynamic effects of different catecholamines (Londs et al., 1967). For α-adrenergic receptors, α_1 receptors are generally postsynaptic and α_2 receptors are generally presynaptic sites that inhibit norepinephrine release (Berthelsen & Pettinger, 1977; Starke, 1977). In addition to postsynaptic β_1 and β_2-adrenergic receptors, some β_2 presynaptic receptors may act to facilitate norepinephrine release (Starke, 1977) Thus, the net effect of infusing epinephrine, for example, into the renal artery may involve the summation of α_1, α_2, β_1 and β_2 components at various sites in the kidney. This multiplicity of receptors and their

subtypes-contributes to the currently imprecise definition of the physiological role of catecholamines in regulating renal function.

Interrelationship between norepinephrine, prostaglandins and renin-angiotensin system in controlling of renal hemodynamics.

Because the renal circulation receives about 25% of the total cardiac output, renal vascular resistance can be modulated as a means of controlling arterial blood pressure. The administration of lethal dose of endotoxin in the intact dogs results in impaired renal functions which may be attributed to the effects of systemic hypotension, renal vasoconstriction and a possible action of endotoxin on renal tubular activity (Hinshaw et al., 1961). The response of the dogs was characterized by an immediate sustained rise in angiotensin levels and a latter variable rise in catecholamine levels (Hall and Hodge, 1971). Infusion of prostacyclin (PGI_2) after injection lethal endotoxemic dogs marked a reduction in plasma norepinephrine level to the base line at 4 hours and caused an improving of systemic and renal hemodynamics (Krausz et al., 1981). In addition, administation of indomethacin was found to lower plasma renin activity in the dog, rabbit and man (Data et al., 1978; Larsson et al., 1974; Fralich et al., 1972). The results have been suggested that the prostaglandins may be mediators of renin release secondary to stimulate of renal baroreceptor and macula densa (Gerber et al., 1981).

However, Fluorescent histochemical studies indicate the presence of norepinephrine containing fibers associated with the renal,

arcuate and interlobular arteries as well as in peritubular and juxtaglomerular locations (Barajas, 1978; Dinnerstein et al., 1979) In experiment found that renal nerve stimulation (RNS) caused vasoconstriction in both cortex and medulla, this constriction was abolished or reduced by prazosin (Chapman et al., 1981) This results indicated that the catecholamines regulate renal hemodynamics predominantly via α_1-adrenergic mediated vasoconstriction and increase renal vascular resistance (Drew and Whiting, 1979). The activation of intrarenal baroreceptor, macula densa and sympathetic nerve via α_1-adrenergic results in renin release and mediated by prostaglandins (Gerber et al., 1981).

Renal effects of Russell's viper venom

Acute renal failure (ARF) is also a serious complication and an important cause of death in patients who survived the early effects of a severe viper bite (Aung-Khin, 1978) A broad spectrum of renal lesions including tubular necrosis (Sitprija et al., 1974; Sitprija and Boonpucknavig, 1977), cortical necrosis (Chugh et al., 1973), glomerulonephritis (Sitprija and Boonpucknavig, 1980), interstitial inflammation, edema and hemorrhage (Sarangi et al., 1980), and acute interstitial nephritis (Sitprija et al., 1982) have been reported. The clinical syndromes in viperine bite are variable, while minor reactions consist only of local pain and swelling, severe reaction may include hemorrhage, hypotension, shock, ARF and death. Diffuse fine granular deposition of IgM and the third component of complement (C_3) in mesangial areas with extension along the capillary wall is

detected. By electron microscopy, occasional narrowing of the glomerular capillary lumen is observed. This is due to mesangial hyperplasia with an increase in the amount of basement membrane like matrix and the swelling of the attenuate portion of the endothelial cytoplasm. The arterial lesions are seen strikingly in Russell's viper bite. The most obvious alteration is necrotizing arteritis of the interlobular arteries. Tubular necrosis, arteritis and thrombophlebitis of the arcuate vein are present (Sitprija et al., 1974, 1985; Chugh et al., 1978). Tubulointerstitial lesions are demonstrated by the Puchtler-Sweat method, there are hemoglobin casts in the lumen of distal convoluted tubules and collecting tubule (Sitprija et al., 1985). Necrosis of the renal cortex has been observed following the Russell's viper bite (Chugh et al., 1975).

By immunofluorescent study, deposition of β-1C globulin was noted in the arterial lesion, the glomerular mesangium and the arteriolar wall. No immunoglobulines were noted in the lesion. Deposition of complement in the arterial lesion without immunoglobulins suggests that the nonimmunologic activation of the complement system through the alternate pathway and the viper venom might be the activator. The venom might have the injurious effect to the artery, and this injurious effect was mediated through complement activation (Sitprija et al., 1974).

Sarangi et al., (1980) indicated that after Russell's viper bite the most common type of renal function was a reduction in urinary output with an incidence of hematuria. It is generally accepted that

changes in renal functions are associated with changes on cardiovascular system. Circulatory shock may lead to ARF which is caused by filtration failure due to reduced renal circulation. Many investigators have been studied the effect of Russell's viper venom on renal hemodynamic and cardiovascular system (Chaiyabutr et al., 1984; Tongvonchai, 1984; Tungthanathanich et al., 1983). They explained that the venom caused an obviously decrease in general circulation and renal hemodynamic following envenomation. Thereafter the blood pressure and heart rate gradually increase and approach the control level within 2 hours. However the rate of blood flow through the kidney, glomerular filtration rate and renal fraction (% C.O.) were decreased throughout the period of 2 to 48 hours after given a minimal lethal dose of 0.1 mg/kg. of Russell's viper venom (Tungthanathanich et al., 1986). This is due to local vasoconstriction in the kidney which is associated with an increase in renal vascular resistance. The mechanism of renal hormonal interactions involved in intrarenal vasoconstriction are probably complex.

According to current concepts, renal circulation is regulated by two hormones system: prostagnlandins and kallikrein-kinin system act as vasodilators while vasoconstriction mediated by norepinephrine and/or renin-angiotensin system (RAS). Previous experiment demonstrated that phospholipase A_2 (PLA_2) from Russell's viper venom induced an increase in plasma prostaglandin (PGI_2) and thromboxane A_2 (TXA_2) level in normotensive rats (Huang, 1984). Administration of indomethacin, a prostaglandin inhibitor, 40 minutes before envenomated dogs caused a disturbance of renal function (Thamaree et al., 1987). Direct evidence for the involvement of renin-angiotensin system in response to

renal vasoconstriction after envenomation has been proposed by Chaiyabutr et al (1985) in pretreated envenomated rats with intrarenal angiotensin II blockage (MK-422, enalapril maleate). Enalapril was found to increase renal blood flow, glomerular filtration rate and decrease the renal vascular resistance in animals given Russell's viper venom as well as prazosin, an α_1-adrenergic blocker. The pretreated dogs with enalapril and imidazole associated with left renal artery continuous infusion of prazosin in viperine injection produced a beneficial effect on renal circulation (Kidmungtangdee, 1989). In addition, the response of the dog in endotoxic shock shows not only sustained rise in angiotensin levels but also catecholamine levels (Hall and Hodge, 1971).