BAROREFLEX SENSITIVITY AND PRESSOR RESPONSE IN EXPERIMENTAL UREMIA

Thesis

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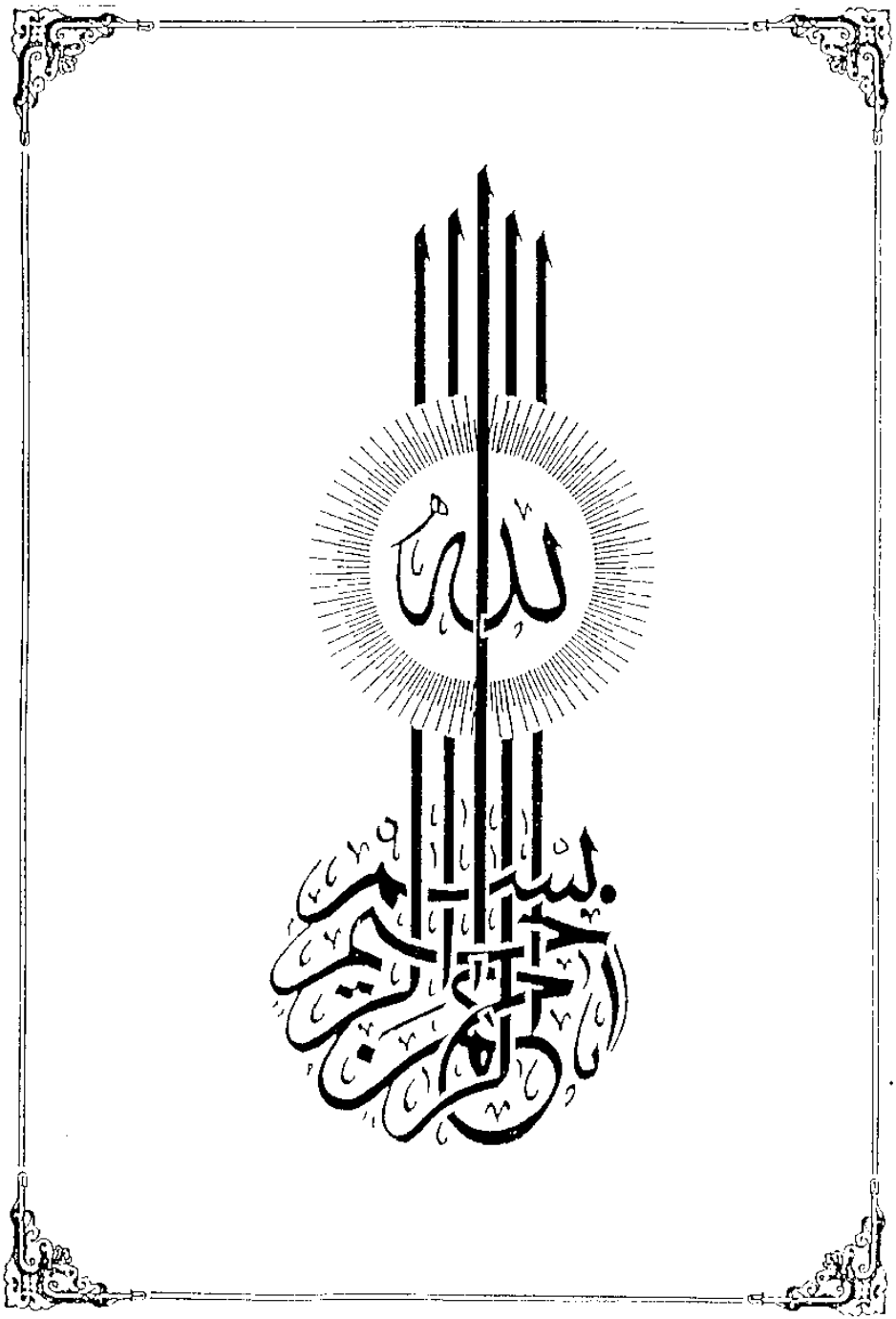

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INtroduction

INTRODUCTION

Hypertension occurs in up to 80 percent of patients with renal insufficiency and is a major risk factor for the excessive cardiovascular morbidity and mortality among these patients ***(Lindner et al., 1974; Rostand et al., 1991; Zucchelli and Zuccala 1992)***.

However, the underlying causes of this hypertension are not fully understood despite extensive investigation into the roles of salt-water volume expansion and inappropriate activity of the renin - angiotensin system.

There are several reports showing involvement of the autonomic nervous system in renal insufficiency ***(Kersh et al., 1974; Campese and Massry 1995)***.

Furthermore, with the recent advent of maintenance hemodyalysis and the consequent increase in longevity of patients with chronic renal failure, nephrologists frequently encounter patients with disturbances of the autonomic nervous system. On the basis of observations of defective autonomic nervous system in uremia, a neurogenic component to the hypertension of renal insufficiency may be postulated. The autonomic nervous system dysfunction in uremia include depressed baroreflex sensitivity ***(Lazarus et al., 1973; Moreira et al., 1990; Agarwal et al., 1991; Kastenbauer et al., 1994)*** and altered catecholamine metabolism ***(McGrath et al., 1978; Darwish et al., 1984; Yuhara et al., 1989; Isaac et al., 1993)***.

In particular, it has recently been suggested that baroreflex dysfunction may be a relatively important contributary factor in blood pressure elevation in uremia. Moreover, in other hypertensive states baroreflex sensitivity has been shown to contribute to the pathogenesis of the hypertension by allowing normal pressor stimuli to be less well buffered.

Regarding vascular responsiveness in renal insufficiency, several reports have demonstrated the change in responsiveness to vasoconstricting agents ***(Nakashima et al., 1987; Fadda et al., 1988; Massry et al., 1995)***. This study reports the effect of uremia on the baroreceptor sensitivity and attempts to determine whether, in uremia, a disturbance of normal cardiovascular reflexes could contribute to the associated hypertension.

Aim Of The Work

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The present study was designed to evaluate the effect of renal insufficiency, in rat models of uremia, on the baroreflex sensitivity and the pressor responsiveness to exogenous pressors : noradrenaline, angiotensin II and arginine vasopressin.

Review Of Literature

REVIEW OF LITERATURE

The prevalence of hypertension increases with decreasing kidney function and reaches over 80% at the stage of terminal renal failure that requires dialysis treatment ***(Schalekamp et al., 1973; Lindner et al., 1974; Ye et al., 1997).*** Hypertension remains a significant clinical issue in these patients and various factors may play a role in its pathogenesis ***(Thomson et al., 1967; Schalekamp et al., 1973; Ye et al., 1997)***. Those include sodium retention and volume expansion, increased activity of the renin-angiotensin system ***(Schalekamp et al., 1973; Lazarus et al., 1974; Weidmann et al., 1976)*** Removal of sodium and water by hemodialysis can usually reduce blood pressure in these patients. The minority of patients with severe hypertension have high renin levels with variable extracellular fluid volumes; this type of hypertension is unresponsive to correction of the sodium and water balance by hemodialysis ***(Davies et al., 1973)*** but does respond to bilateral nephrectomy with a consequent reduction in plasma renin activity. For this reason, abnormality of either the volume or the vasoconstrictor mechanism has been suggested as the most likely pathogenesis of hypertension accompanying chronic renal failure.

Increased activity of the sympathetic nervous system might contribute to hypertension with end stage renal disease ***(Henrich et al., 1977; Campese et al., 1981; Izzo et al., 1982; Cuche et al., 1986; Weidmann et al., 1987)***, and considered as a third mechanism, which operates in patients whose blood pressure cannot be controlled by either volume reduction or bilateral nephrectomy or explained by elevations in plasma renin

activity. Reduced baroreceptor activity had been demonstrated in patients with chronic renal failure ***(Nakashima et al., 1987)***.

Chronic renal failure may be accompanied by reversible sympathetic activation, which is mediated by an afferent signals arising in the failing kidneys ***(Converse et al., 1992; Campese, 1994)***. Thus activation of renal sensory nerves may trigger the onset of a neurogenic form of hypertension ***(Ye et al., 1997)***.

A fourth mechanism that has been proposed is the absence of vasodepressor substances of renal origin, such as prostaglandins, which may play a role in the genesis of essential hypertension or renoprival hypertension ***(Cinotti et al., 1987)***.

Autonomic Nervous System Dysfunction In Uremia

Abnormalities of the autonomic nervous system may play an important role in morbidity and mortality of patients with end stage renal disease ***(Campese et al., 1981; Campese and Massry 1995)***. These disturbances may affect the function of many organs and manifest themselves in a variety of clinical signs and symptoms. Several patients may have reduced baroreceptor sensitivity, which may result in paroxysmal hypertension, postural hypotension, persistent hypotension, and hypotensive episodes during hemodialysis unresponsive to volume repletion. Autonomic dysfunction may also in part responsible for abnormal circadian variations of blood pressure with reduced fall of blood pressure during the night, reduced pressor response to vasoconstrictor agonists ***(Massry et al., 1995)***.

The pathogenesis of autonomic nervous system dysfunction in uremia is complex and most likely