

EFFECT OF VASOACTIVE AGENTS ON CHRONIC SALINE LOADED ANAESTHETISED RATS

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SUMMARY

Male albino rats were chronically loaded with sodium by giving 1% NaCl solution as the sole source of drinking water. Daily fluid intake, daily urinary output and daily Na⁺ and K⁺ excretion rates were compared with control rats receiving tap water for six weeks. At the end of six weeks, sodium loaded animals were found to have raised plasma Na⁺ concentration, lowered plasma K⁺ concentration and lowered haematocrit value. Sodium loaded rats were also significantly more responsive to the pressor effect of submaximal doses of adrenaline, noradrenaline and angiotensin II given intravenously. It is concluded that the increase in sensitivity to adrenaline and noradrenaline may be due to changes in ECF and alterations of plasma electrolytes concentration. For angiotensin II, additionally, it may be due to low circulating endogenous angiotensin II, consequent of reduction in renin release attributed to chronic sodium loading.

INTRODUCTION

The effect of excessive sodium intake on the raised blood pressure has been well documented. The increase in blood pressure is accompanied by a concurrent increase in extracellular fluid volume, and this increase in blood pressure may be due to an increase in total peripheral resistance (Perera & Blood, 1947; Dahl & Love, 1956; Meneely & Dahl,

1961; Phelan & Wong, 1968; Blaustein, 1977). However, there had been relatively few studies involving the effect of vasoactive agents on the pressor effect of the sodium loaded animals. The present study is therefore designed to study the fluid and electrolytes balance during chronic saline loading and the effect of noradrenaline, adrenaline and angiotensin II on the blood pressure of these rats.

MATERIALS AND METHOD

Male albino rats were used for the entire investigation. Treated animals received 1% NaCl solution from graduated drinking bottles as their sole source of fluid, while control animals received tap water from similar bottles. Each rat was housed in a metabolic cage and all rats fed on standard rat pellets.

Daily fluid intake was estimated from graduated drinking bottles, daily urine flow rate obtained from measuring cylinder placed below the metabolic cage. Daily urinary sodium and potassium excretion was determined by flame photometry. These parameters were monitored daily for six weeks, after allowing 12 days for the animals to stabilise.

At the end of six weeks, each rat was anaesthetised by giving pentobarbitone sodium (Nembutal, 40 mg/Kg) intraperitoneally. A polythene trachea cannula was inserted. The right carotid artery and the left jugular vein were cannulated with polythene tubes filled with heparinized saline. Blood collection was made via the carotid artery cannulae for the determination of haematocrit value and plasma electrolytes concentration. Mean systemic arterial pressure was monitored from the carotid cannulae through pressure transducer coupled to a Grass polygraph. All injections of drug were made through the jugular vein cannulae in volumes not exceeding 0.2 ml. Each injection was washed with 0.1 ml 0.9%

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NaCl. Ganglion blockade was induced in all rats by administration of pentolinium (Ansolsen) 2.5 mg (0.5 mg i.v. and 2 mg s.c.) each to give a more stable basal blood pressure (Peart, 1955). Doses for adrenaline, noradrenaline and angiotensin II (Hypertensin, Ciba) used were all submaximal.

RESULTS

Figure 1 shows that saline loaded rats consumed considerably more fluid than control animals (A) and there was a concurrent increase in daily urine flow rate (B). The daily sodium excretion rate in saline loaded rats was increased but the daily urine potassium excretion rate was lowered as shown in Fig. 2 (A & B). Blood analysis at the end of six weeks showed a raised plasma sodium concentration, a lowered plasma potassium concentration and haematocrit value in saline

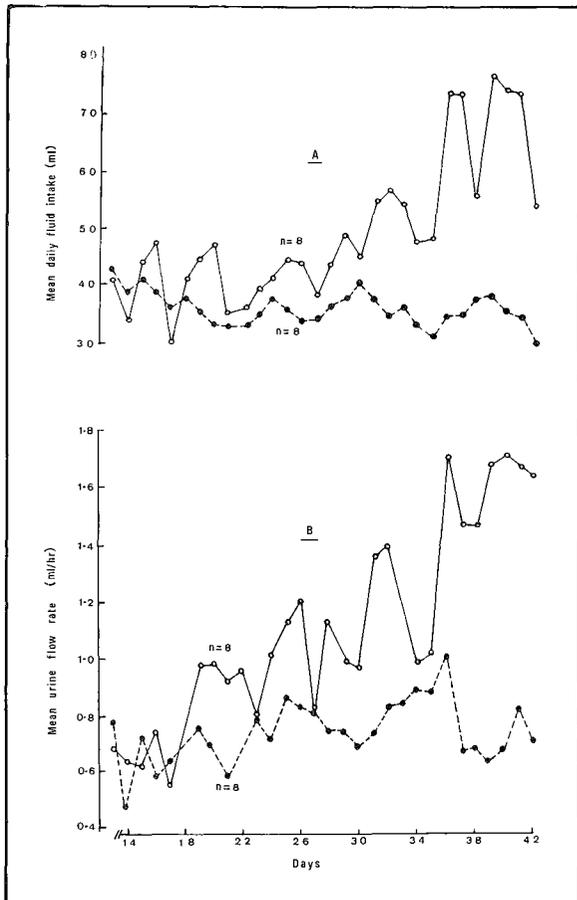


Fig. 1 Mean daily fluid intake (A) and mean urine flow rate (B) for control (closed circle) and saline loaded (open circle) rats. For simplicity standard error bars are omitted.

loaded rats as illustrated in Fig. 3.

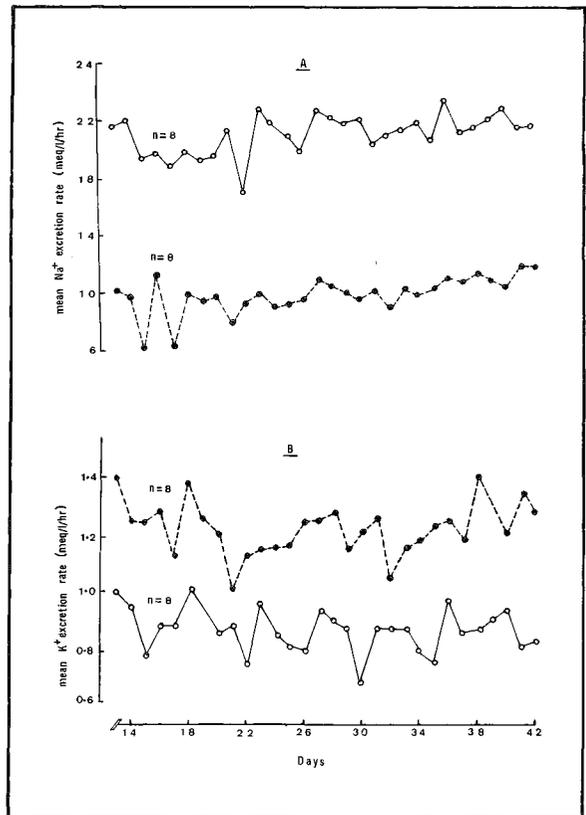


Fig. 2 Mean Na⁺ (A) and mean K⁺ (B) excretion rates for control (closed circle) and saline loaded (open circle) rats. For simplicity standard error bars are omitted.

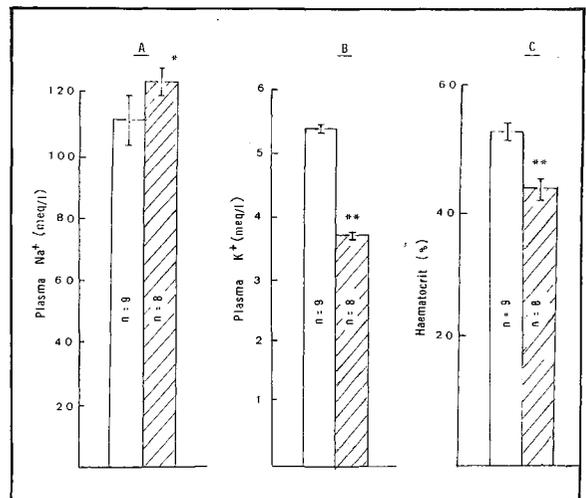


Fig. 3 Plasma sodium (A), potassium (B) and haematocrit value (C) for control (unshaded) and saline loaded (shaded) rats. Values are mean \pm S.E.M. Significance difference was evaluated by Student's t-test, * $P < 0.05$ ** $P < 0.01$

The mean systemic arterial blood pressure of treated rats under pentobarbitone sodium general anaesthesia was raised slightly (though not significantly) and the extent to which the mean systemic arterial pressure decreased by pentolinium-induced ganglion blocking agent did not differ (Fig. 4 A & B).

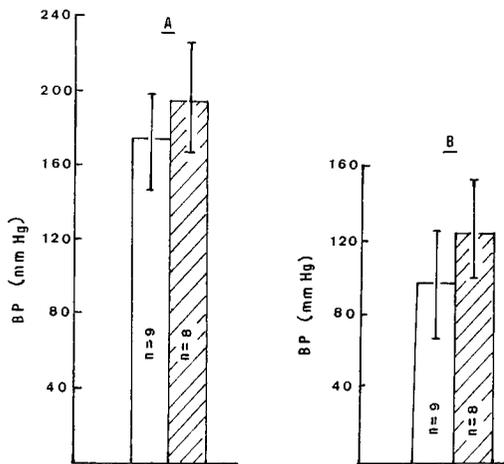


Fig. 4 Mean arterial blood pressure for control (unshaded) and saline loaded (shaded) rats before (A) and after pentolinium-induced ganglion blockade (B).

Noradrenaline in doses 125 and 250 ng induced significant increase in the systemic arterial blood pressure of saline loaded rats. This was shown in Fig 5. Similarly in Fig.6 & Fig. 7, adrenaline in doses 125, 250 and 500 ng and angiotensin II in doses 12.5, 25 and 50 ng all significantly induced a higher increase in the mean systemic arterial blood pressure over that of control animals.

DISCUSSION

The increase in salt and water intake of salt-treated rats exceeds the excretory ability of the kidneys, resulting in extracellular fluid volume expansion and mild hypertension. This observation concurs with all previous findings (Sapirstein *et al.*, 1950; Dahl *et al.*, 1968; Cowley & Lohmeter, 1977). The major feedback mechanism for control of plasma sodium concentration and extracellular osmolality is via the antidiuretic hormone and thirst mechanism. But due to the continuous loading of hypertonic saline in rats for six weeks, it is possible that this feedback mechanism may be deranged and is thus not completely successful in controlling

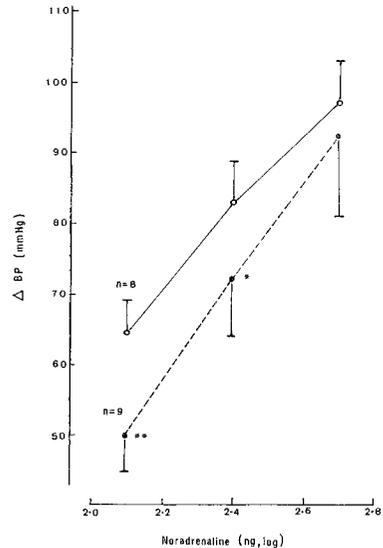


Fig. 5 Effect of noradrenaline on changes made in blood pressure for control (closed circle) and saline loaded (open circle) rats. Values are mean \pm S.E.M. Significance difference was evaluated by Students' t-test, * $P < 0.05$, ** $P < 0.01$

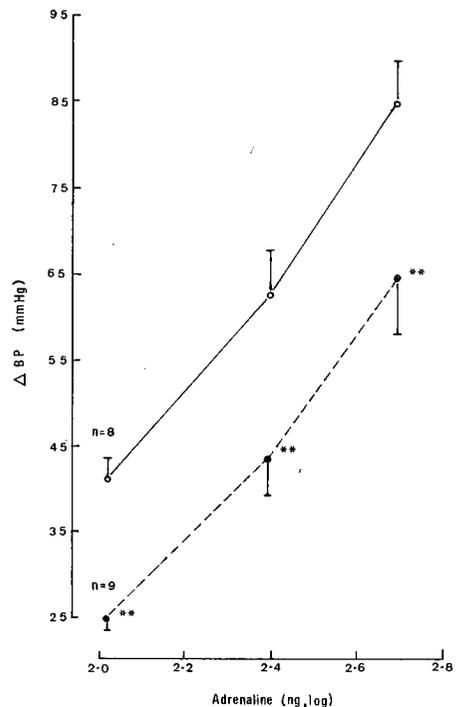


Fig. 6 : Effect of adrenaline on changes made in blood pressure for control (closed circle) and saline loaded (open circle) rats. Values are mean \pm S.E.M. Significance difference was evaluated by Students' t-test, * $P < 0.05$, ** $P < 0.01$

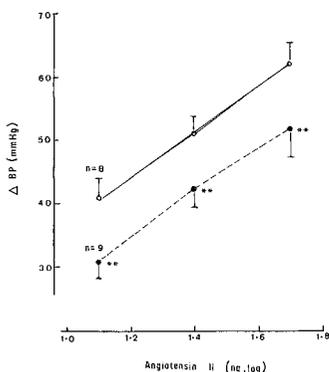


Fig. 7: Effect of angiotensin II on changes made in blood pressure for control (closed circle) and saline loaded (open circle) rats. Values are mean \pm S.E.M. Significance difference was evaluated by Student's t-test, * $P < 0.05$, ** $P < 0.01$

the increased sodium concentration in extracellular fluid (ECF) nor the increased ECF volume.

Salt-treated rats are significantly more reactive to the pressor effect of adrenaline, noradrenaline and angiotensin II in sub-maximal doses. Honore & Gardner (1966) showed that salt-treated male rats were significantly more reactive to the pressor effect of adrenaline than the control animals. Increased sensitivity to noradrenaline has also been reported in anaesthetized spontaneous hypertensive (Phelan *et al.*, 1962) and in DOCA/saline treated rats (Dusting *et al.*, 1973). In the same study, Dusting *et al.* demonstrated positive correlation between increase in mean arterial pressure and plasma sodium. It is therefore likely that the increase in sensitivity to adrenaline and noradrenaline may be attributed to ECF expansion coupled with an increase in ECF sodium and/or decrease in ECF potassium.

Excessive sodium intake has been known to suppress renin secretion (Brown *et al.*, 1964). This will undoubtedly result in the suppression of angiotensin II in the circulation, for angiotensin II is derived from the enzymatic actions of renin on the converting enzyme. Whether the increase in sensitivity to angiotensin II is due to the low level of circulation angiotensin II in the plasma, the raised ECF sodium and/or the decrease in ECF potassium is not known for sure.

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