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THE EFFECT OF CYCLOPHOSPHAMIDE ON ARGININE VASOPRESSIN AND THE ATRIAL NATRIURETIC FACTOR

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The effect of cyclophosphamide (CTX) on the renal handling of water and sodium and on plasma concentrations of vasopressin (AVP) and of the atrial natriuretic factor (ANF) was studied in the rabbit. When compared to controls, animals receiving CTX (100 mg/kg IV) showed an increase in the diuresis and natriuresis. In addition, ANF plasma concentrations increased by 84% between 4 and 8 hours after CTX, while AVP plasma concentrations remained unchanged. It is concluded that in the rabbit CTX has a diuretic and a natriuretic effect that may, at least in part, be related to the increase in ANF plasma concentrations.

Zedeck et al. (1,2) have shown that cyclophosphamide (CTX) induced a natriuretic and diuretic response in the rat and dog animal models. On the other hand, it has been reported that in man CTX might stimulate the secretion of arginine vasopressin (AVP) (3,4,5). As the stimulation of AVP does not explain an increase in diuresis, the present study aimed to investigate the effect of CTX on the circulating level of two hormones greatly involved in water and electrolyte homeostasis: AVP and the atrial natriuretic factor (ANF) (6).

MATERIALS AND METHODS

Protocols - In the first experiment, 4 male New Zealand rabbits (Ferme Cunicole, Mirabel, Quebec, Canada) received IV 100 mg/kg CTX (Procytox, F.W. Horner, Mount-Royal, Quebec, Canada) in a solution of NaCl 0.9%. The same animals were used as controls and received an identical volume of NaCl 0.9%. A solution of

Abbreviations used in this paper: CTX, cyclophosphamide; AVP, arginine-vasopressin; ANF, atrial natriuretic factor; AUC, area under the curve; Cl_{H2O}, free water clearance.

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NaCl 0.9% / dextrose 5% (50/50) was infused at the rate of 12 mL/h in a lateral vein of the ear to compensate physiological losses. Blood samples (5 mL) were drawn through the central ear artery at 0, 90, 120, 135, 150, 165 and 180 minutes to measure APV, Na^+ and osmolality. Urine was collected, via an urinary catheter, for the 0-90 and 90-180 minutes periods, to measure sodium and osmolality. The volume of blood withdrawn was replaced with an equivalent volume of NaCl 0.9%.

In humans, to avoid a CTX-induced hemorrhagic cystitis the intake of fluid is recommended. For this reason, in the second experiment, we induced a slight overhydratation to eleven rabbits by infusing at 20 mL/h of NaCl 0.9% / dextrose 5% (50/50) for 8 hours, starting after an IV administration of 100 mg/kg of CTX. The same animals were used as controls but received saline instead of CTX. Blood samples (5 mL) were drawn at 0, 2, 4, 6 and 8 h and urine was collected for 0-4 h and 4-8 h where AVP, ANF, Na^+ and osmolality were measured. The volume of blood withdrawn was replaced with NaCl 0.9%.

Methods - Plasma AVP and ANF were assayed by radioimmunoassay as described elsewhere (7,8). Plasma and urinary sodium and osmolality were determined by flame photometry (IL 943) and freezing point depression (Osmette A) respectively.

RESULTS

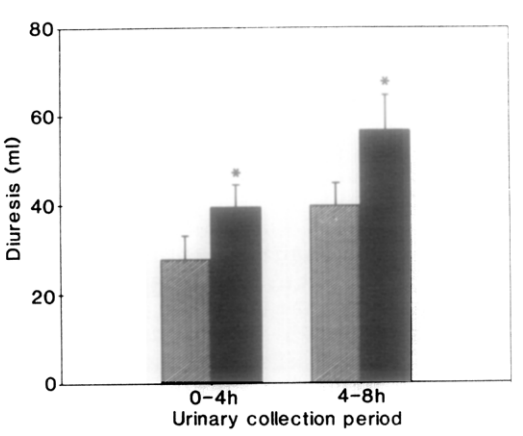
In the first experiment, CTX tended to increase the natriuresis as well as the diuresis and that in both urinary collections (Table 1). In fact, the natriuresis showed an average increase of 32% and the diuresis of 27%, however these trends were not statistically significant. Plasma AVP, sodium and osmolality were not modified. In the second experiment, in animals with a slight overhydration, the diuresis was elevated by 42% ($p < 0.05$) in both collection periods and the natriuresis by 46% ($p < 0.05$) in the first period and by 390% ($p < 0.05$) in the second (Figure 1).

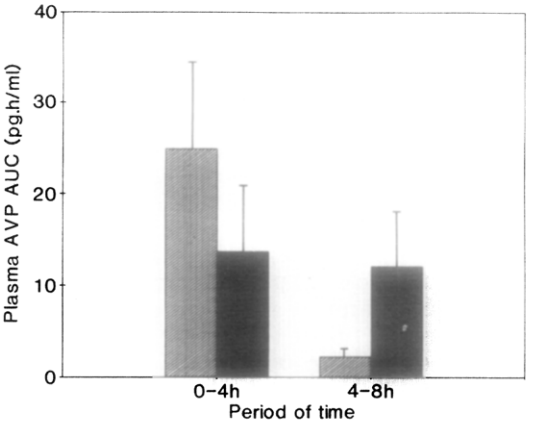
In the first collection period (0-4h) free water clearance (Cl_{H2O}) was lower in animals receiving CTX (-11.4 $\pm$ 1.4 mL/h)

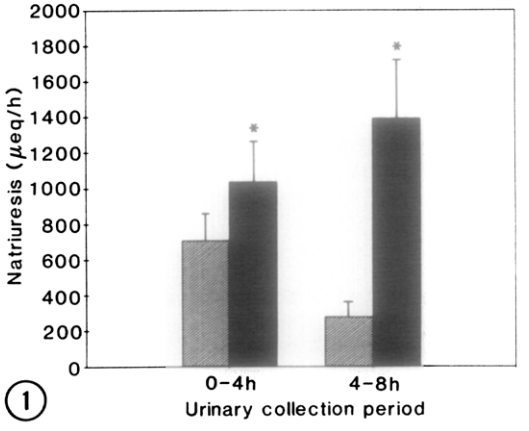
Table 1. Diuresis and natriuresis following the IV administration of 100 mg/kg of cyclophosphamide (CTX)

Collection period		Diuresis (mL/h)	Natriuresis (µEq/h)
0 - 90	Control	2.7 $\pm$ 0.9[a]	243 $\pm$ 30
	CTX	3.5 $\pm$ 0.8	306 $\pm$ 46
90 - 180	Control	3.4 $\pm$ 1.1	249 $\pm$ 27
	CTX	4.9 $\pm$ 1.0	427 $\pm$ 88

[a] Mean $\pm$ S.E.M.







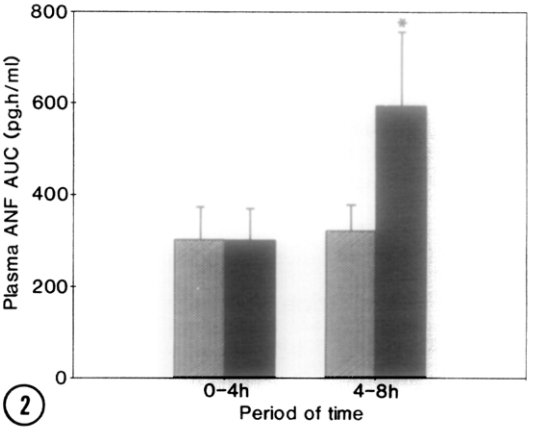


Figure 1. Diuresis and natriuresis for the overhydration experiment. The hatched bars are for control rabbits (saline) and the dark bars for the same rabbits after receiving CTX (100 mg/kg IV). *p < 0.05 versus control.

Figure 2. Plasma AVP and ANF AUC for the overhydration experiment. The hatched bars are for control rabbits (saline) and the dark bars for the same rabbits after receiving CTX (100 mg/kg IV). *p < 0.05 versus control.

than in controls (-6.1 ± 1.0 mL/h) ($p < 0.05$). During the second urinary collection (4-8h) Cl_{H2O}) increased in both treated and control rabbits, however more in the former group, so the difference observed in the first collection period disappeared (-4.2 ± 1.3 versus -3.4 ± 2.6 mL/h). The increase in Cl_{H2O} in treated animals was statistically significant ($p < 0.05$).

Urinary and plasma osmolality as well as plasma sodium remained unchanged. Plasma AVP area under the curve (AUC) was

not changed, but there was a significant increase (84%) in plasma ANF AUC during the second half of the experiment (4-8h)(Fig. 2).

DISCUSSION

Under our experimental conditions, a high dose of CTX raises the natriuresis as well as the diuresis, confirming the results of Zedeck et al. (1,2). The negative and lower Cl_{H2O} in treated rabbits during the first period suggest that salt excretion is relatively more important than water excretion. Interestingly, in the second period, in treated animals the Cl_{H2O} increased significantly despite that it remained negative. These changes can be explained by the increase in ANF plasma concentrations; effectively, it has been demonstrated that an increase in ANF plasma concentrations will increment the natriuresis as well the Cl_{H2O} (6). Supporting this hypothesis is the fact that the timing of CTX-induced changes in ANF plasma concentrations coincides with the changes in renal function. Under our experimental conditions CTX did not influence plasma concentrations of AVP.

These effects of CTX in the rabbit and other animals contrast with the CTX-induced antidiuresis, e.g. increase in urinary osmolality and decrease in Cl_{H2O}, observed in man (3,4,5). These differences could be explained on the basis of interspecies variations concerning CTX metabolism (9) or central nervous system response to CTX. In addition, in man it is of frequent use to concomitantly administer antiemetics (steroids, phenothiazine and metoclopramide), known to affect AVP secretion (10,11).

In conclusion, these results suggest that in the rabbit CTX or its metabolites increase the natriuresis and diuresis through several mechanisms, the increased secretion of ANF being involved only in a late phase.

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