ACUTE EFFECTS OF 2-BROMOETHANAMINE HYDROBROMIDE (BEA) ON RENAL FUNCTION IN RATS

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Chronic interstitial nephritis and renal papillary necrosis are the final stages in analgesic nephropathy (Spuehler et al., 1953). However, up to now the underlying causes of this lesion are not finally established. In animal models various substances have been used to produce lesions which are morphologically similar to those seen in analgesic nephropathy in man (Bach et al., 1982).

One of these chemicals is 2-Bromoethanamine hydrobromide (BEA). It's advantage is that a single dose will produce necrotic changes within 24 hrs of administration in virtually all BEA-treated animals. Changes in renal function have been described for the time 24 hrs following administration (Arruda et al, 1979) but there is virtually no information regarding functional changes earlier than 24 hrs.

The present study was therefore designed to obtain information about the onset of the BEA-induced changes in renal function. We studied possible effects on glomerular function as well as overall renal plasma flow, on tubular function (urea and electrolyte excretion) and on the countercurrent mechanism (urine flow, osmolality).

MATERIALS AND METHODS

Female Wistar rats (mean BW 124g) were anaesthetized and placed on a heated operating table. After catheterization of jugular vein, carotid artery and bladder a prime dose of 0.2 ml Saline/100g BW was given i.v., either with or without BEA (100 mg/kg BW). Maintenance infusion of Saline was kept at 5 µl/min (10 µl in the clearance studies). Urine flow was measured continuously over 3 hrs. Urine samples were collected at 30 or 60 min intervals and analyzed for Na, K, urea and osmolality. Clearance studies were performed with polyfructosan (Inutest^{R}) for measurement of GFR and ^{14}C-PAH for RPF.

RESULTS

Urine flow was increased as early as 30 min after injection of BEA (100mg/kg i.v.) with 2.5 $\pm$ 0.4 µl/min compared to 1.39 $\pm$ 0.24 µl/min in the control animals and showed a linear rise over the 3 hr period up to 6.29 $\pm$ 0.94 µl/min. Osmolality did not decrease until 90 min after injection of BEA (1511 $\pm$ 157 at 30 min, 1419 $\pm$ 118 at 90 min and 742 $\pm$ 158 mosm/kg H_2O at 180 min compared to 1549 $\pm$ 215 at 30 min and 1605 $\pm$ 93 at 180 min in the control group) (Fig.1).

Clearance studies to determine glomerular filtration rate and renal plasma flow were performed at a higher infusion rate (10 µl/min Saline). Table 1 shows that Na-excretion was significantly higher in BEA-treated animals after 3 hrs following injection (1.3 $\pm$ 0.21 µmol/min vs. 0.27 $\pm$ 0.14) while K-excretion was not different in animals treated with 100 mg BEA/kg BW and control animals. Urea-excretion was significantly higher in the BEA-treated animals after 60 min compared to the control group. Polyfructosan clearance decreased from 1.11 $\pm$ 0.10 ml/min/100g at 1 hr following injection of BEA to 0.69 $\pm$ 0.06 at 3 hrs. PAH-clearance was higher in the BEA group after 1 hr (2.95 $\pm$ 0.19 ml/min/100g) and then started to decrease (2.21$\pm$0.22 at 3 hrs).

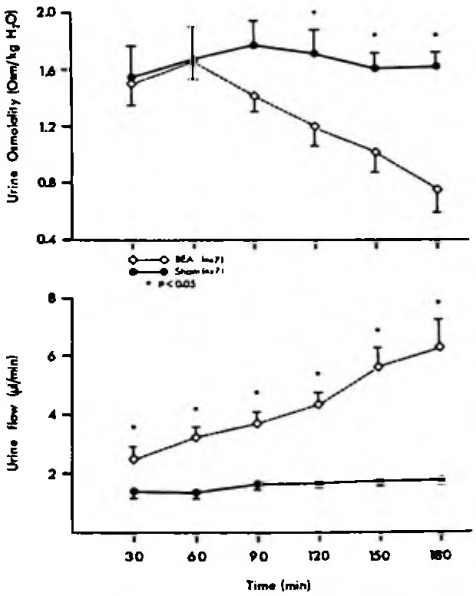

Fig. 1: Urine flow and osmolality

TIME	Na EXCRETION Control n=5	Na EXCRETION BEA n=5	UREA EXCRETION Control n=7	UREA EXCRETION BEA n=7
60	0.14±0.03	0.33±0.13	0.78±0.18	2.06±0.38*
120	0.20±0.11	0.40±0.16	1.00±0.10	1.96±0.22#
180	0.27±0.14	1.30±0.21#	1.06±0.15	1.79±0.29*

TIME	K EXCRETION Control n=5	K EXCRETION BEA n=5
60	0.56±0.11	0.36±0.10
120	0.40±0.19	0.64±0.16
180	0.69±0.10	0.87±0.17

GFR + RPF = ml/min/100g BW
Excr. = µmol/min
TIME = min after injection of BEA or Saline

TIME	GFR Control n=6	GFR BEA n=6	RPF Control n=6	RPF BEA n=6
60	1.05±0.05	1.11±0.10	2.32±0.19	2.95±0.19*
120	1.17±0.04	0.90±0.06#	2.77±0.21	2.72±0.17
180	1.06±0.06	0.69±0.06#	2.51±0.14	2.21±0.22$

* = p<0.05, # = p<0.005, $ = p<0.05 vs BEA 60 min

Table 1: Urine solute excretion, GFR and RPF

DISCUSSION

Our experiments show 1. an involvement of the whole nephron with the glomerulus, the tubular apparatus and the counter-current system in the BEA-induced lesion and 2. an onset of functional changes within minutes following injection of the chemical which may be followed within 24 hrs by morphological lesions, e.g. papillary necrosis.

Urine flow was affected in our experiments as early as 30 min from the time of injection. Together with the decreasing osmolality this may be due to impaired water reabsorption following injection of BEA, an effect which has been shown in studies on the toad bladder (Sabatini et al., 1984). The early rise in urine flow without accompanying drop in urine osmolality may be due to changes in nephron function other than the change in distal water permeability. Na-excretion was increased only in BEA-treated animals subjected to the higher infusion rate. We suggest that this finding is due to a decreased Na uptake in the ascending limb of Henle's loop. Urea excretion rose 60 min following injection of BEA but fraction of filtered urea excreted showed no difference compared to a group of diuretic control animals (Wilks et al., in preparation) suggesting that the high urea excretion is caused indirectly as a result of the increased urine flow which leads to a "wash-out" effect on the medulla and a decreased distal urea reabsorption.

In our experiments BEA caused a decrease in GFR similar to the one seen by other investigators (Reineck et al., 1980) who described a substantial decrease in filtering juxtamedullary nephrons which may also be the case in our study. The decrease in PAH-clearance could be the result of disturbed secretion mechanisms due to damage of the tubular transport system.

In summary our studies show an effect of BEA on the renal concentration capacity, tubular transport mechanisms and glomerular filtration rather than a specific action on the renal papilla. This acute effect seems to precede morphological changes as seen by other investigators (Murray et al., 1972). We suggest that BEA exerts an acute overall nephrotoxic insult which may be more pronounced in the renal medulla because of higher concentration of the substance.

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