ALLEVIATION OF ISCHAEMIC ACUTE RENAL FAILURE BY BETA BLOCKERS: SPECIFIC TUBULAR RECEPTOR BLOCKADE OR MEMBRANE STABILISING EFFECT?

I Iaina, I Serban, S Gavendo, S Kapuler, H E Eliahou

Department of Nephrology, Sheba Medical Centre, Tel-Hashomer, Israel

The administration of beta adrenergic blockers in experimental ischaemic acute renal failure (IARF) was found to alleviate the resulting uraemia [1–9], to prevent the mortality in dogs autotransplanted with kidneys following controlled 30–60 minutes of warm ischaemia [5], and to reduce the severity of the post transplantation IARF [4, 5]. It was suggested that the administration of beta blockers may produce their alleviating effect through a direct tubular action [7–9]. Such an action can be produced by either of two ways: a specific tubular beta adrenergic receptor blockade or a membrane stabilising effect at the tubular cell level. The aim of the present study was to differentiate between these two possible ways of action of the beta adrenergic blockers during the development of IARF.

In one series of experiments, one of three drugs was studied at a time:

(i) dl-propranolol, with both specific beta blockade and membrane stabilising effects;
(ii) d-propranolol with only membrane stabilising effect; and
(iii) practolol with only beta blocking activity.

In a second series of experiments the changes in the number and affinity of specific beta1 adrenergic receptors of tubular cell membrane [10, 11] were studied during the development of IARF untreated and treated with dl-propranolol.

Materials and methods

IARF was produced in Charles River rats (Yokneam, Israel). During ether anaesthesia, immediately after right nephrectomy, the left renal artery was clamped for 70 minutes. Throughout the experiment a total amount of 6ml fluid/hr was infused through a femoral artery [1, 2].

dl-propranolol and d-propranolol were administered in a dose of 1mg/hr/kg bw. Practolol was given in a dose of 6mg/hr/kg bw. The infusions of the drugs were started 15 minutes before clamping and lasted a total period of 100 minutes. Twenty four hours later blood urea and serum creatinine were measured by an autoanalyser.
The number and affinity constant $K_D$ of the extravascular renal tubular plasma cell membrane beta$_1$ adrenergic receptors, were determined by direct tissue binding with (-)($^3$H)dihydro-alprenolol, as previously described [10, 11]. These receptors were studied in the ischaemic kidneys as follows: kidneys clamped for 70 minutes and removed without declamping, kidneys clamped for 70 minutes followed by a period of 30 minutes or 24 hours after declamping. In another group, the rats received dl-propranolol 1mg/hr/kg bw throughout the experiment and the receptors were studied in the kidneys removed 30 minutes after declamping.

The right kidneys in all the groups were used as control for the ischaemic kidneys.

Results

The effect of the administration of dl-propranolol, d-propranolol and practolol on the severity of IARF is given in Table I. Both dl-propranolol (membrane stabilising and beta blocking effects) and practolol (only beta blocking effect) reduced the severity of the uraemia: 24 hours after declamping, the blood urea and serum creatinine were about half of the values obtained in the untreated rats. d-propranolol, with only membrane stabilising effect, did not change the course of the renal failure.

<table>
<thead>
<tr>
<th>Experimental group</th>
<th>Blood urea mg%</th>
<th>Serum creatinine mg%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham operated (n = 10)</td>
<td>64 ± 7 (SE)</td>
<td>1.5 ± 0.1 (SE)</td>
</tr>
<tr>
<td>IARF untreated (n = 11)</td>
<td>275 ± 25 (SE)</td>
<td>4.0 ± 0.3 (SE)</td>
</tr>
<tr>
<td>IARF treated with dl-propranolol (n = 10)</td>
<td>116 ± 16 (SE)</td>
<td>1.3 ± 0.4 (SE)</td>
</tr>
<tr>
<td>IARF treated with d-propranolol (n = 6)</td>
<td>238 ± 23 (SE)</td>
<td>4.1 ± 0.3 (SE)</td>
</tr>
<tr>
<td>IARF treated with practolol (n = 15)</td>
<td>141 ± 18 (SE)</td>
<td>2.3 ± 0.3 (SE)</td>
</tr>
</tbody>
</table>

The changes in the number and affinity constant $K_D$ of the tubular cell beta$_1$ adrenergic receptors during the development of IARF are given in Table II. Neither the number nor the $K_D$ were altered at least 24 hours following 70 minutes of renal ischaemia.

In the ischaemic kidneys of the rats treated with dl-propranolol, no specific alprenolol binding sites could be measured (34 rats).
### TABLE II. Number and affinity of tubular beta adrenergic receptors in different stages of untreated and dl-propranolol treated ischaemic acute renal failure

<table>
<thead>
<tr>
<th>Experimental Group</th>
<th>Ischaemic kidneys</th>
<th>Control kidneys</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of sites</td>
<td>K\textsubscript{D}nM</td>
</tr>
<tr>
<td></td>
<td>fmol/mg prot.</td>
<td></td>
</tr>
<tr>
<td>70 min ischaemia no declamping (20 rats)</td>
<td>43.8</td>
<td>6.7</td>
</tr>
<tr>
<td>70 min ischaemia 30 min declamping (21 rats)</td>
<td>60.1</td>
<td>5.8</td>
</tr>
<tr>
<td>70 min ischaemia 24 hr declamping (23 rats)</td>
<td>62.7</td>
<td>5.1</td>
</tr>
<tr>
<td>Normal rats (89 rats)</td>
<td></td>
<td>69.8 ± 29.1 (SD)</td>
</tr>
<tr>
<td>70 min ischaemia dl-propranolol treatment 30 min after declamping (34 rats)</td>
<td>no detectable (−)(³H)dihydro-alprenolol binding sites</td>
<td></td>
</tr>
</tbody>
</table>

### Discussion

The administration of different beta blockers during the development of IARF demonstrated that the severity of uraemia is reduced when the blocker has a specific beta adrenergic receptor blocking activity. This also occurred in the absence of a membrane stabilising effect (practolol). dl-propranolol, a drug having membrane stabilising activity only, did not influence the development of the renal failure. From the tubular cell receptor studies, it follows that the extra-vascular beta\textsubscript{1} adrenergic receptors are unaltered during renal ischaemia of 70 minutes, and stayed almost unchanged for 24 hours following the ischaemic episode.

The alleviating effect of these beta blockers could not be attributed to the renin-angiotensin system, since it was found to occur under conditions of angiotensin II receptor blockade with saralasin [1, 2]. Furthermore, the reduction of the resulting uraemia could not be explained only by the haemodynamic changes since renal tubular obstruction was demonstrated as the predominant abnormality found in IARF in the rat [12, 13]. The administration of dl-propranolol demonstrated tubular adrenergic blockade to such an extent that no more free receptors were detectable when the kidneys were taken 30 minutes after declamping.

It is concluded that alleviation of ischaemic acute renal failure is by specific tubular beta adrenergic blockade and not by the membrane stabilising effect of the beta adrenergic blocker used.
Acknowledgment

This work was supported by Schreiber grant from Tel-Aviv University, Sackler School of Medicine.

References

1 Iaina A, Solomon S, Eliahou HE. Lancet 1975; ii: 157
6 Klein LE. Invest Urology 1978; 15:401
9 Chevalier RL, Finn WF. Nephron 1980; 25:77

689