

ALTERED BETA-RECEPTOR RESPONSIVENESS IN URAEMIC RATS

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Summary

Beta-receptor responsiveness was evaluated in 24-hour nephrectomised rats. Heart rate responses following intravenous isoproterenol injections into conscious uraemic (n=9) and sham operated controls (n=7) were measured.

These preliminary results indicate that heart rate at rest and after blockade of the autonomic nervous system was slower in uraemic rats. Blood pressure before and after autonomic blockade was not different between groups, Maximal heart rate increase following intravenous isoproterenol was significantly less pronounced in uraemic than in control animals (130 vs 170 beats/min, $p < 0.05$). The blood pressure decreasing effect of intravenous isoproterenol was enhanced in the nephrectomised group ($p < 0.01$).

Introduction

Cardiovascular instability is a major debilitating factor for patients on chronic intermittent haemodialysis. In subgroups of these patients, an inappropriate heart rate response to hypotensive episodes has been reported [1,2]. This observation has been attributed to haemodialysis-associated autonomic insufficiency [1]. However, autonomic dysfunction alone probably does not explain this phenomenon [2].

The present study investigates beta-receptor responsiveness in acute uraemia. Specifically, we tested the heart rate response to isoproterenol in rats 24 hours following bilateral nephrectomy.

Material and methods

Male Sprague Dawley rats (180–250g b.w.) were housed in single cages in temperature, light, and humidity controlled rooms. Animals were bilaterally nephrectomised or sham nephrectomised; 24 to 26 hours later permanent

catheters were implanted into the femoral artery and vein under ether anaesthesia. Intra-arterial mean pressure (MAP) and heart rate were continuously recorded. After stabilisation of MAP, animals were atropinised and ganglion blocked with pentolinium tartrate. When blood pressure had reached a plateau, isoproterenol was intravenously injected in cumulative doses (4–4000ng/kg/min). Results are given as mean \pm SEM.

Results

Resting heart rate was reduced in uraemic rats before (398 ± 16 vs 481 ± 22 beats/min, $p < 0.05$), and after blockade of the autonomic nervous system (292 ± 13 vs 399 ± 16 beats/min, $p < 0.01$). When isoproterenol was injected intravenously, a maximum effect was observed between 400 and 1000ng/kg (bolus injection). The highest dose given in each animal was 4000ng/kg. The maximal increase in heart rate was reduced in uraemic rats (131 ± 10 vs 170 ± 15 beats/min, $p < 0.05$).

Discussion

Our preliminary results suggest that cardiac beta-receptor responsiveness is blunted in acute uraemia in the rat. In a previous study we reported that alpha-receptor responsiveness is increased in acute uraemia (but decreased in chronic uraemia) [4]. At present, we can only speculate as to the mechanism of this abnormality. High circulating concentrations of noradrenaline have been demonstrated in acute uraemia [3]. This may lead to 'down'-regulation of the beta-receptors. However, ligand-induced changes of adrenergic receptors often take more than 24 hours to occur.

Resting heart rate was lower in uraemic rats and this was also true after blockade of the autonomic nervous system. This may be an indication that the altered responsiveness to isoproterenol may not or not only be due to change of the beta-receptor. Post-receptor events (cAMP production etc) may also explain the observed reduced tachycardia in response to isoproterenol. On the basis of the present experiments we cannot state which of the many uraemia-associated changes may explain our findings. The role, if any, of acidosis, hypokalaemia, PTH excess [5] in the genesis of this abnormality will have to be elucidated in further experiments. The potential clinical implications of this experimental study, however, are obvious.

References

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