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DIABETES-INDUCED DECREASE IN RENAL OXYGEN TENSION: EFFECTS OF AN ALTERED METABOLISM

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1. INTRODUCTION

The metabolism within different parts of the kidney is highly heterogeneous and is likely to reflect the local energy demand and milieu in that specific region. The metabolism in the renal cortex has been found to be highly dependent on the availability of oxygen, i.e. aerobic metabolism. Glucose oxidation in the renal cortex is relatively low compared to that of the renal medulla. The metabolism within the renal medulla is also heterogeneous, with high glucose oxidation and high oxygen consumption in the outer part of the medulla, while the deeper situated inner medulla is highly dependent on anaerobic metabolism, i.e. low oxygen consumption and high glycolytic rate[1, 2].

The blood flow to the renal medulla is derived through the *vasa recta*, acting as a counter current system in order to maintain the high osmolar gradient necessary for the formation of concentrated urine. While electrolytes are re-circulated from the ascending to the closely located descending *vasa recta*, oxygen is shunted in the opposite direction, resulting in a low delivery of oxygen to the medullary region[3, 4]. Conditions which alter the shunting of oxygen, with concomitant alteration in medullary oxygen delivery, have the potential to influence the medullary oxygen tension (pO_2)[5].

Long-term hyperglycemia, e.g. diabetes mellitus, is known to significantly increase the risk of developing progressive renal dysfunction[6]. The exact mechanism accounting for the increased risk is not known, but it has been suggested that aggravated low pO_2 in the renal medulla may cause progression of nephropathy during certain pathological conditions[7, 8].

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2. DIABETES-INDUCED ALTERATION IN THE RENAL METABOLISM AND INTERSTITIAL pH

Diabetes-induced activation of the polyol pathway has been demonstrated in numerous tissues[9-12], including the renal medulla[13]. Increased activity through the polyol pathway alters the cellular redox-state, mainly due to increased NADH/NAD^+ ratio[14]. This will concomitantly shift the equilibrium between pyruvate and lactate, resulting in an increased lactate/pyruvate ratio, predominately as a result of increased lactate concentration[15]. Long-term diabetes has been shown to increase the lactate/pyruvate ratio in both the renal cortex and in the medulla, but inhibition of the polyol pathway only prevents the increase in the medullary region (Fig. 1)[13]. This finding is consistent with the almost exclusive presence of the enzyme aldose reductase in the medullary region[16].

It is important to note that the increased formation of lactate in our previous study[13] was not a result of hypoxia, since the levels of purine-base metabolites (adenosine, inosine and hypoxanthine) did not increase after the onset of hyperglycemia. Increased lactate/pyruvate ratio is known to occur during sustained hyperglycemia even though the oxygen supply is sufficient for full mitochondrial respiration. This state is commonly referred to as "pseudohypoxia" and is a result of the altered intracellular redox status[15].

The increased formation of lactate found in the renal medulla of diabetic animals resulted in a significantly lower interstitial pH in this region (Fig. 2)[13]. The increased lactate concentration will decrease the pH and the protons will re-circulate, in the same manner as electrolytes, in the medullary structures due to the counter-current mechanism in the *vasa recta*.

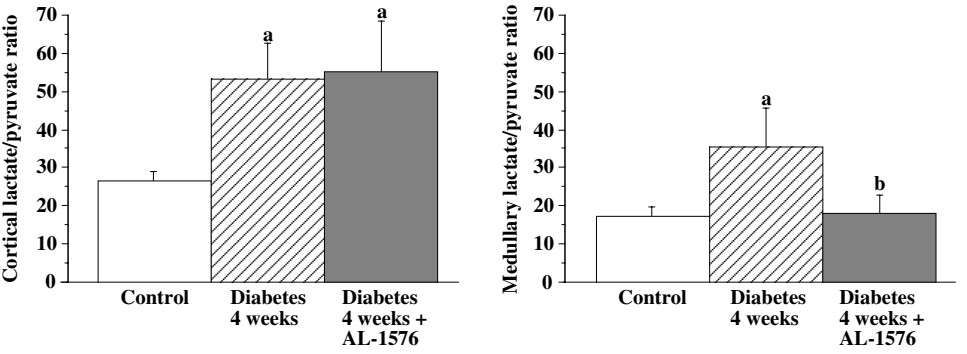

Figure 1. Lactate/pyruvate ratios in the renal cortex and the medulla in control and diabetic animals with and without treatment with the specific aldose reductase inhibitor AL-1576. a denotes $p<0.05$ versus non-diabetic control animals, whereas b denotes $p<0.05$ versus diabetic animals. Values are presented as mean ± SEM. Modified from data originally published by Palm *et al.*[13].