Action of the Competitive Angiotensin II Antagonist Saralasin during the Initial Phase of Glycerol-Induced Acute Renal Failure of the Rat

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Summary. The effects of the competitive angiotensin II antagonist saralasin (1-sarcosine-8-alanine-5-isoleucine-angiotensin II) on renal function in healthy rats and in rats with myohemoglobinuric acute renal failure were studied. Acute renal failure was induced by an intramuscular injection of 50% glycerol (10 ml \cdot kg^{-1}). Functional impairment of the glycerol treated animals consisted in a decrease of renal blood flow (electromagnetic flowmeter) and GFR and in an increase of urine volume and arterial blood pressure.

In healthy rats saralasin (6 \mu g \cdot kg^{-1} \cdot min^{-1} \cdot i.v.) had no renal effects by itself but antagonized the angiotensin II (200 ng \cdot kg^{-1} \cdot min \cdot i.v.) induced fall of renal blood flow and GFR and the increase of arterial blood pressure. Given to glycerol treated animals saralasin did not induce any change of arterial blood pressure, renal blood flow, GFR or the urinary excretion of fluid and sodium.

Key words: Renal function -- Renal blood flow -- Glomerular filtration rate -- Urine volume -- Urinary sodium excretion.

INTRODUCTION

Several lines of evidence suggest that the renin-angiotensin system may play a role in the pathogenesis of acute renal failure. Thus, it has been shown that renin levels in peripheral blood are elevated in acute renal failure in man and experimental animals (Tu, 1965; Brown et al., 1970; Hofbauer et al., 1976). In contrast, a decrease in peripheral renin activity during the early phase of acute renal failure has been described in dehydrated animals (Baranowski et al., 1975; Matthews et al., 1974). High salt intake, which is known to decrease peripheral blood and intrarenal renin content, prevents acute renal failure in the rat (McDonald et al., 1969; Thiel et al., 1970). Angiotensin II infusion into rabbits induces acute renal failure with tubular necrosis resembling acute renal failure in man in some of its aspects (Gavras et al., 1971). Antibodies to renin or angiotensin II, however, did not prevent acute renal failure (Flamenbaum et al., 1973; Oken et al., 1975).

In the present study a possible role of angiotensin II in acute renal failure was evaluated by use of the competitive angiotensin II antagonist saralasin (1-sarcosine-8-alanine-5-isoleucine-angiotensin II). Since the molecular weight of saralasin is similar to that of angiotensin II the antagonist might gain access to the intrarenal angiotensin II receptors more easily than antibodies of large molecular size. As an experimental model of acute renal failure we chose the myohemoglobinuric acute renal failure of the rat. Conventional clearance methods were utilized in assessing renal function. Renal blood flow, which we considered as crucial in evaluating any angiotensin II—antagonistic effect, was measured with a noncannulating electromagnetic flow transducer. By this method we hoped to obtain more precise information on changes in renal blood flow than by indirect methods used for renal blood flow measurements in the rat.

METHODS

The experiments were performed on male Sprague Dawley rats. The animals were deprived of food (Altromin-standard-diet. Producer: Altromin GmbH, Lage/Lippe, Federal Republic of Germany) overnight with water ad libitum. During the experiments the animals were placed on a heated table and rectal temperature was maintained at 37°C. The animals were anaesthetized by intraperitoneal injection of sodium thiobutabarbitral (Inactin®, 100 mg \cdot kg^{-1}) and subsequently tracheotomized. The jugular vein was
cannulated for infusion and the right carotid artery for blood sampling and measurement of blood pressure using a Statham pressure transducer. The urinary bladder and the left kidney were exposed by an abdominal incision. The urinary bladder and the left ureter were cannulated. The kidney was fixed in a perspex holder and bathed in paraffin oil at 37°C. Blood flow through the left renal artery was measured by a 1.0 mm flow transducer connected to an electromagnetic flowmeter and a Schwartz-dynograph. To achieve zero flow the renal artery was completely occluded with a forceps for a few seconds distal to the flow probe. The flowmeter system was calibrated by placing the flow transducer around the left carotid artery of anaesthetized rats and by timing the outflow of the blood. After surgery the animals received 2 ml of isotonic saline i.v. Total kidney GFR was determined as inulin clearance. After a priming dose of 0.5 ml of 5% inulin solution in isotonic saline i.v. Total kidney GFR was determined as inulin clearance. After a priming dose of 0.5 ml of 5% inulin solution in isotonic saline a sustaining infusion (0.1 ml min⁻¹) of 1.5% inulin was given i.v. The drugs used were dissolved in this solution. The volume infused was identical in all experiments. The experiments were started 1 h after beginning the infusion. In the middle of each clearance period a 100 µl sample of blood was taken from the carotid artery for chemical analysis and replaced by injecting an equal volume of isotonic saline. In 6 rats with an average body weight of 311 g (range from 226 - 360 g) val 5-angiotensin II was infused for 50 min after two control clearance periods. Clearance determinations were performed every 10 min during the angiotensin II infusion. In 6 rats (mean body weight 306 g, range from 274 - 350 g) the same protocol was followed, but saralasin was then infused for 30 min and clearances were measured every 10 min. In 8 rats (mean body weight 322 g, range from 281 - 356 g) the same protocol was followed with the exception that no saralasin was infused.

In all rats the clearance determinations for each experimental period were averaged and the mean values were utilized in the statistical analysis (Student's t-test for paired groups).

The inulin concentration in plasma and urine was determined by the method of Führ et al. (1955). Sodium and potassium concentrations in plasma and urine were measured with an Eppendorf flame photometer.

RESULTS

Figure 1 demonstrates the effects of angiotensin II on kidney function and the blockade achieved with saralasin. Angiotensin II increased blood pressure and

![Figure 1](image_url)

**Fig. 1.** Blockade of the renal effects of angiotensin II by saralasin in healthy anaesthetized rats. Angiotensin II (200 ng kg⁻¹ min⁻¹) was infused intravenously for 50 min into 2 groups of rats (group A: open circles, broken lines, n = 6; group B: closed circles, continuous lines, n = 5). In group B saralasin (6 µg kg⁻¹ min⁻¹) was infused together with angiotensin II 20 min after the start of the angiotensin II infusion. Values are means ± S.E.M. of each experimental period. **AP** arterial blood pressure; **RBF** renal blood flow; **GFR** glomerular filtration rate; **V** urine flow; **E_Na** urinary sodium excretion; **T_%Na** fractional tubular sodium reabsorption. The dimension g stands for g weight of the left kidney.