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Hepatic blood flow and drug metabolism in glycerol-rechallenged rats

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Summary. To analyze the hepatic blood flow and drug metabolism during glycerol-induced acute renal failure, 24 male Wistar rats were randomly divided into three groups: Group I received an intra-muscular injection of 1 ml/100 g body weight 50% glycerol, group II a second injection on day 14 and group III a second injection on day 42 after the first injection respectively. The inulin clearance, the aminopyrine N-demethylase activity, the NADPH-cytochrome P-450 activity and the cardiac output and blood flow to the organs were measured before and after glycerol injection. The total hepatic and renal blood flow decreased less significantly in group II compared to group I and III. Various P 450 activities were kept on a high level only in group II. This observation indicates that the maintenance not only of renal but also of hepatic blood flow plays an important role in preventing the development of glycerol-induced acute renal failure. The mechanism may be the induction of various P 450 activities resulting in an increased hepatic clearance of nephrotoxic substances.

Key words: Acute renal failure – Hepatic blood flow – P 450 activity

Introduction

We reported that both renal blood flow and total hepatic blood flow play an important role in preventing the development of glycerol induced acute renal failure (ARF) in long-term experiments in saline loaded rats [3]. The development of ARF was suppressed when rats which had recovered from glycerol-induced ARF were rechallenged with glycerol (1). In order to study this process, renal function, cardiac output, hepatic blood flow and hepatic microsomal P-450 (aminopyrine N-demethylase activity, NADPH-cytochrome P-450 reductase activity and cytochrome B_5 contents) were measured in glycerol-rechallenged rats.

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Materials and methods

Experiments were performed on male Wistar rats maintained on a standard diet and tap water, weighing 250–300 g. The rats were divided into three groups: Group I received an intra-muscular injection of 1 ml/100 g, of body weight 50% glycerol. Group II received a second injection of glycerol on 14th day after the first injection. Group III received a second injection on 42nd day after the first injection. The rats were anesthetized with pentobarbital sodium (40 mg/kg, i.p.) and polyethylene cannulas (PE-50) were inserted into the femoral artery and the left ventricle via the right carotid artery (Fig. 1). The rats were allowed to recover for 24 h after anesthesia and surgery. The cardiac output and blood flow to the organs were measured using a microsphere technique [7, 8]. Measurements were made before and at 4, 10 h after glycerol injection. Inulin clearance was measured using ^{3}H-Inulin before ant at 24 h after the glycerol injection (Fig. 2, Table 1).

Aminopyrine N-demethylse activity, NADPH-cytochrome P-450 reductase activity and cytochrome B5 contents were measured before, and at 24 and 48 h after the glycerol injection [4, 5, 6].

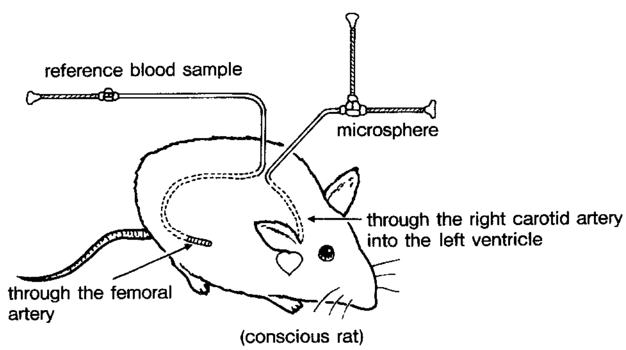

Fig. 1. Preparation of microsphere method

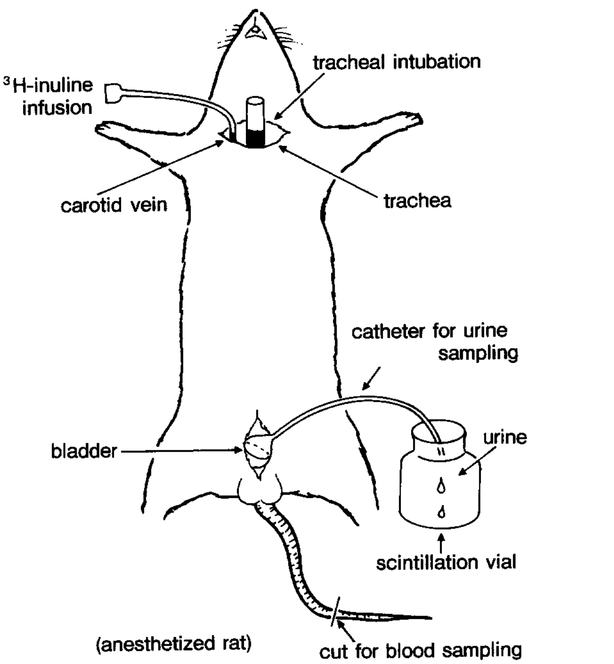

Fig. 2. Preparation of the measurement method of inuline clearance

Results and discussion

ARF did not occurr in Group II (Fig. 3). Cardiac output after glycerol injection decreased in three groups (Fig. 4). Total hepatic blood flow before the glycerol injection was significantly higher only in Group II (Fig. 5). Total hepatic blood flow and renal blood flow after the glycerol injection decreased less significantly in Group II as compared to Groups I and III. Inulin clearance before the glycerol injection was at the same level in the three groups but after the glycerol injection decreased less significantly in Group II (Fig. 6). Various hepatic P-450 activities were induced after the first injection of glycerol and remained at a high level in Group II (Fig. 7–9). These results suggest that the maintenance of both renal blood flow and hepatic blood flow play an important role in preventing the development of glycerol-induced acute renal failure and that the maintenance of total hepatic blood flow with induction of various P-450 will increase the

Table 1. Calculation formula of inuline clearance

Inulin clearance (μl/min · 100 g B.W.)

$$= \frac{\text{Radioactivity in urine per sampling time (20 min)}}{\text{Radioaetirity in serum per volume (40 μl)}} \times \frac{100}{\text{Body weight (g)}}$$

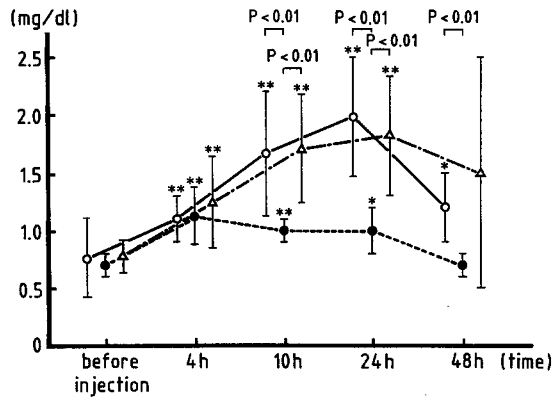

Fig. 3. Change in serum creatinine. ○—○ Group I; ●- - -● Group II; △—·—△ Group III; (mean ± SD); $^*P<0.05$; $^{**}P<0.01$ (significant difference from the value before injection)

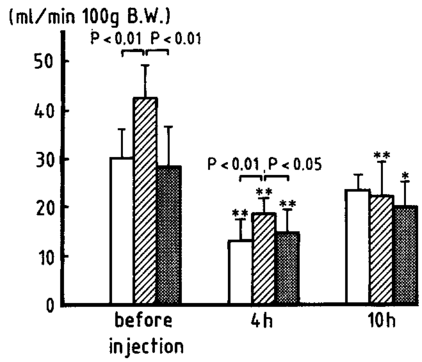

Fig. 4. Change in cardiac output before and after glycerol injection. □ Group I; ▨ Group II; ▩ Group III (mean ± SD); $^*P<0.05$; $^{**}P<0.01$ (significant difference from the value before injection)

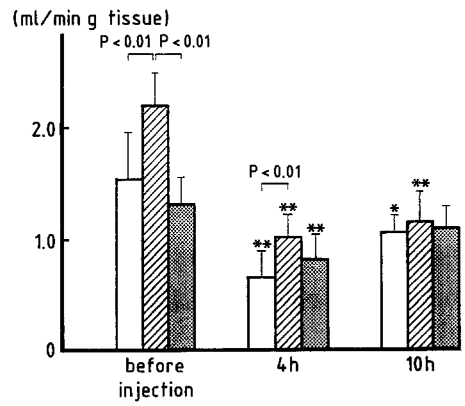

Fig. 5. Change in total hepatic blood flow. □ Group I; ▨ Group II; ▩ Group III (mean ± SD); $^*P<0.05$; $^{**}P<0.01$ significant difference from the value before injection)

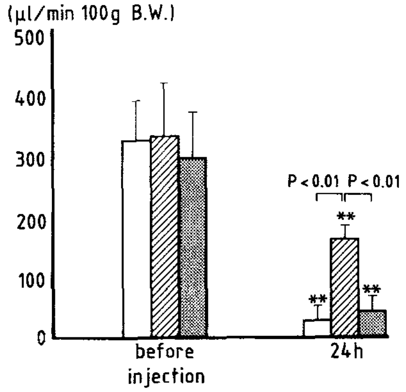

Fig. 6. Change in inulin clearance. □ Group I; ▨ Group II; ▩ Group III (mean ± SD); $^{**}P<0.01$ (significant difference from the value before injection)

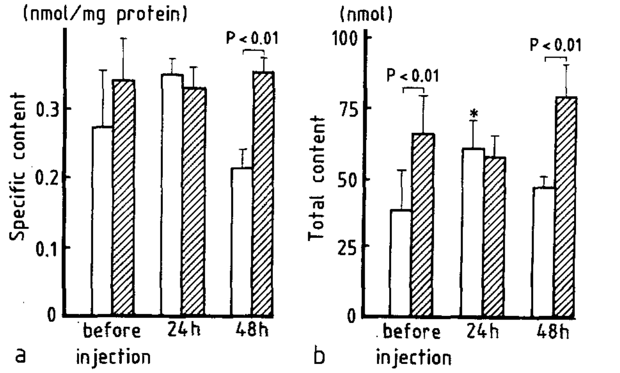

Fig. 9a and b. Change in the specific (a) and total (b) contents of cytochrome b_5 in rat liver microsomes. □ Group I; ▨ Group II (mean ± SD); $^{*}P<0.05$; $^{**}P<0.01$ (significant difference from the value before injection)

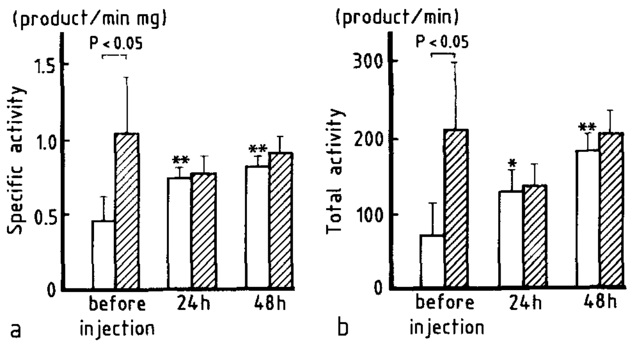

Fig. 7a and b. Change in the specific (a) and total (b) activity of aminopyrine N-demethylase in rat liver microsomes. □ Group I; ▨ Group II (mean ± SD); $^{*}P<0.05$; $^{**}P<0.01$ (significant difference from the value before injection)

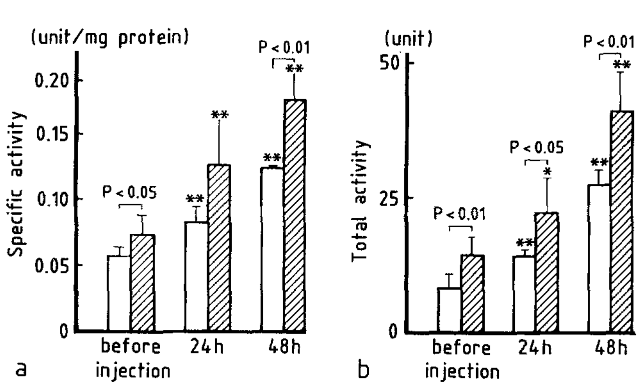

Fig. 8a and b. Change in the specific (a) and total (b) activity of NADPH-cytochrome P-450 reductase in rat liver microsomes. □ Group I; ▨ Group II (mean ± SD); $^{*}P<0.05$; $^{**}P<0.01$ (significant difference from the value before injection)

hepatic clearance of nephrotoxic substances induced by glycerol injection. Hiley et al. [2] also reported that total hepatic blood flow was significantly higher in recovery groups than in non-recovery groups after the glycerol injection. In conclusion, the maintenance of renal blood flow and total hepatic blood flow as well as various hepatic P-450 activities play an important role in the prevention of glycerol-induced acute renal failure.

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