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Effect of Propranolol on Glycerol Induced Acute Renal Failure in Rats

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The effect produced by propranolol, administered for a prolonged period of time and in large doses, on renal function in rats has been studied, as well as the modifications induced by this treatment in an experimental model of acute renal failure, and the effects of a single dose of propranolol given 1 hour before provoking failure.

Propranolol, administered chronically, causes sodium and water retention and increases creatinine clearance.

Acute renal failure induced by glycerol in rats treated for 7 days with propranolol is less severe than the one produced in untreated animals.

In this ARF model, a single dose of propranolol does not seem to have a protective effect.

According to the most widely accepted opinion, glycerol-induced ARF is due essentially to hemodynamic alterations caused by the decrease in the effective circulating plasma volume, consequence of a redistribution of fluid into the compartments of the body. The decrease in effective circulating volume provokes a diminution of renal plasma flow which induces the reduction in glomerular filtration responsable for the failure (12, 23, 24). In the onset and/or perpetuation of ARF, the role of renin might be significant, particularly of the renal renin. It is speculated that coincident with diminution of the glomerular filtrate (GF) an elevation in renin activity is produced (5, 8) especially at the intrarenal level. Locally, large concentrations of angiotensin II are generated which produce vasoconstriction of the afferent arterioles and perpetuate the decrease in renal plasma flow, and as a result, of GF.

Since propranolol lowers the secretion of renin by the juxtaglomerular apparatus (6), we have employed this drug prior to inducing ARF in an attempt to modify the physiopathology of the failure and valuate

the role of renin in ARF. At the same time, the effect of propranolol, administered for 7 days and in large doses, have been studied in normal rats.

Materials and Methods

50 female Wistar rats, divided into 5 equal groups were used. The average weight of the rats was 244 (±8.5 g SEM). These groups were treated as shown in the table I.

During 4 days after glucose or glycerol injection urine was collected at 24 hour intervals from all of the groups for determination of sodium, potassium, urea and creatinine. Urine was collected in vials containing 1 ml of mineral oil equilibrated with water to avoid evaporation and decomposition. Urine contaminated with food or excrements was discarded. After blood was extracted by aortic puncture upon anesthesia with ether to determine haematocrit, Na, K, urea and creatinine, kidneys were removed and weighed.

All the animals, for the entire duration of the experiment had free access to standard rat chow and tap water. In groups III and IV treated parenterally with propranolol tap water substituted by propranolol 9 mg/kg b.w./20 ml water.

Plasma and urine determinations were made as follows: Na and K using a flame spectrophotometer, model I.L. 140 (Instrumentation Lab. Lexington, Mass.). Urea with a SMA 12/60 autoanalyzer (Technicon Instrument Corp.). Creatinine with the alkaline picrate colorimetric method (9) and haematocrit using the microhematocrit technique.

All results are expressed as averages ± standard error of the mean. The student «t» test was applied in statistical analysis of the data.

Results

Figure 1 shows diuresis and elimination of Na and K during the 4 days of the experiment. ARF induced by glycerol (Group II) is a polyuric failure accompanied by decrease in sodium and potassium excretion. In the animals treated with propranolol (Group III), there is a reduction in diuresis and sodium excretion with respect to group I (control). Group IV (rats given propranolol and induced to kidney failure), presents marked polyuria

Table I. *Pattern of treatment of the five group of rats.*
Glucose, glycerol and propranolol are administered as i.m. injections.

Group	Pretreatment twice a day for 7 days	ARF or SHAM induction once at the 8th day (Doses: 10 ml/kg b.w.)	Post treatment twice a day for 5 days	Drinking fluid all the experience
I	0.25 ml Isotonic glucose	Isotonic glucose	0.25 ml Isotonic glucose	Tap water
II	0.25 ml Isotonic glucose	Glycerol 50 %	0.25 ml Isotonic glucose	Tap water
III	18 mg/kg b.w. Propranolol	Isotonic glucose	18 mk/kg b.w. Propranolol	9 mg/kg b.w. Propranolol
IV	18 mg/kg b.w. Propranolol	Glycerol 50 %	18 mk/kg b.w. Propranolol	9 mg/kg b.w. Propranolol
V		Propranolol (18 mg/kg b.w.) 1 h after Glycerol 50 %	18 mg/ kg b.w. Propranolol	Tap water

during the first two days with respect to groups I and II; last days diuresis is similar to the control group. It is observed that Na excretion for the first 24 hours is reduced in both types of failure, with reference to the control group, although in the propranolol treated animals excretion is greater during the first days.

In figure 2, the total urea and creatinine elimination during the four days is de-

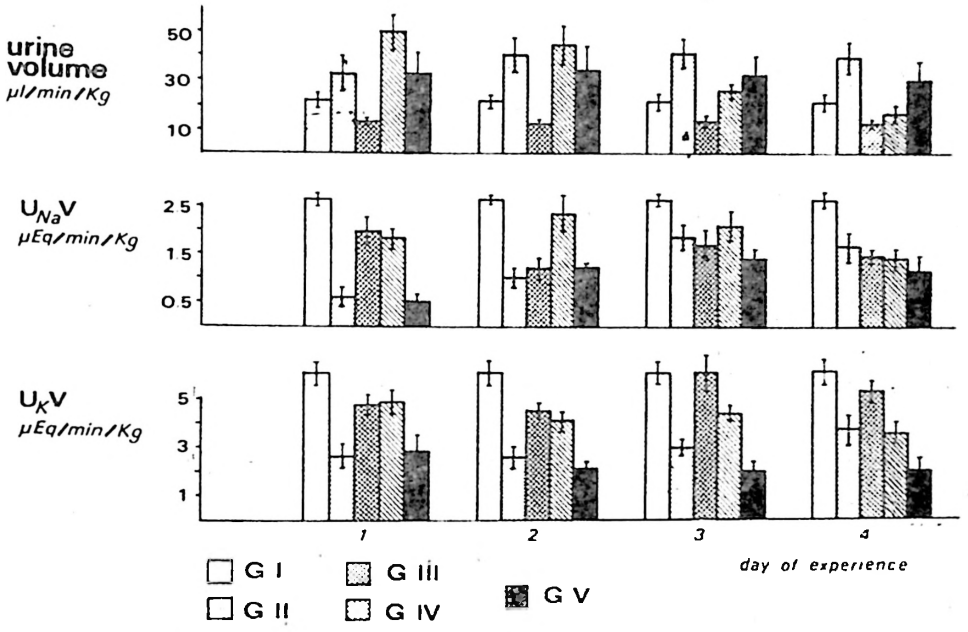

Fig. 1. *Diuresis and urinary excretion of Na and K during the 4 days of the experiment.* See table I for the characteristics of each group.

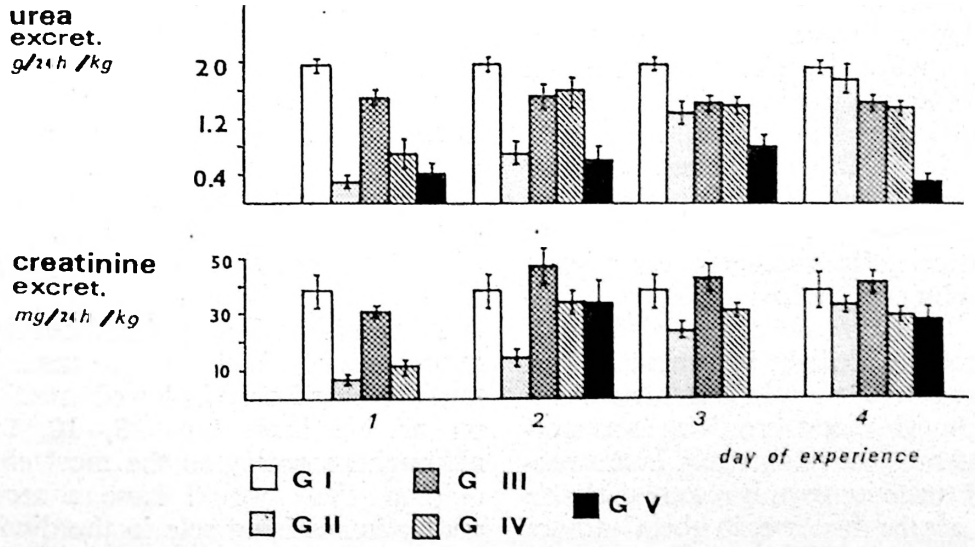

Fig. 2. *Urea and creatinine elimination in urine during the 4 days of the experiment.* See table I for the characteristics of each group.

Table II. *Blood data (Mean values ± S.E.M.) obtained on the 4th day of the experiment.* C_{cr} = endogenous creatinine clearance. Kw = (Kidney weight/Total body weight) × 100. See table I for the characteristics of each group.

Group	Hct %	Na mEq/l	K mEq/l	Urea g/l	Creat mg/100 ml	Ccr ml/min/kg	Kw %
I	41.9 ± 1.4	130.5 ± 1.1	3.87 ± 0.17	0.38 ± 0.15	0.68 ± 0.03	4.08 ± 0.22	0.64 ± 0.01
II	37.7 ± 2.2	129.4 ± 2.7	4.27 ± 0.39	2.01 ± 0.76	2.9 ± 0.98	1.65 ± 0.26	1.05 ± 0.07
p*	< 0.05	> 0.35	> 0.20	< 0.05	< 0.05	< 0.0005	< 0.0005
p**	> 0.4	< 0.0005	< 0.05	< 0.05	< 0.05	< 0.005	< 0.0125
III	40 ± 0.8	142.4 ± 1.8	3.93 ± 0.18	0.34 ± 0.02	0.6 ± 0.02	5.97 ± 0.56	0.65 ± 0.02
p*	> 0.1	< 0.0005	> 0.35	> 0.35	> 0.45	< 0.0005	> 0.49
p**	< 0.01	> 0.1	< 0.01	< 0.025	< 0.05	< 0.0005	< 0.0125
IV	37.1 ± 1	144.6 ± 1	3.4 ± 0.07	0.56 ± 0.1	0.67 ± 0.04	3.18 ± 0.39	0.80 ± 0.06
V	41.2 ± 1.1	147.0 ± 2.2	3.9 ± 0.6	3.4 ± 0.9	5.5 ± 1.4	1.8 ± 0.9	0.98 ± 0.08
p***	> 0.1	< 0.0005	> 0.3	> 0.1	< 0.05	> 0.4	> 0.25
p**	> 0.01	> 0.15	> 0.15	< 0.0025	< 0.0025	< 0.05	< 0.05

p* = with respect to group I; p** = with respect to group IV; p*** = with respect to group II.

tailed. In group II in which failure was induced with glycerol, urea and creatinine elimination during the first days was smaller than the one of the control groups. The fourth day, these animals were able to eliminate these substances in amounts similar to those of normal rats. A similar phenomenon occurred with group IV although to a lesser degree. In the group IV, the first day of failure the rats excreted little amounts of urea and creatinine, although significantly more than group II (not pretreated with propranolol).

Table II shows the values obtained in the five groups from the blood extracted on the fourth day of the experiment. In group II an increase in creatinine and urea concentration with respect to group I can be observed, accompanied by reduction in creatinine clearance. Group IV only evidences a slight increment in urea wih a small reduction in creatinine clearance although blood creatinine was normal. The increase in natremia in the propranolol treated groups is also remarkable as well as the increase in the clearance of group II with respect to I. The increase in kidney weight for group II is marked while the increase for group IV is less evident.

Group V is almost identical to group II, there are no significant differences in the parameters of excretion of water, Na, K, Cl and creatinine or in plasma concentrations of Na, K, Cl and creatinine. Kidney weight and creatinine clearance are similar in both groups.

Discussion

ARF induced with glycerol, according to most authors, is caused by hemodynamic disturbances which decrease the efficient plasma volume. This condition produces a decrease in renal blood flow (2) which leads to reduction of the glomerular filtrate (12, 23, 24).

Other authors have pointed out different hypotheses of which the two most important are based on tubular obstruction and on passive back flow (3, 10, 27, 28) although according to the most extended opinion, these would have a secondary and/or intensifying role in the diminution of the glomerular filtration (5, 12, 15).

There is evidence that the reduction in

glomerular filtration coincides with an increase in plasma renin activity (PRA) in man (4, 14, 19, 22, 30) and in animals (5, 8). Some authors have advanced the theory that the large concentrations of intrarenal angiotensin generated by liberation of renin *in situ*, might maintain or increase vasoconstriction of the afferent glomerular arteriole.

The perpetuation of this mechanism of response of the glomerulus primarily induced by the decrease in active plasma volume, might maintain the reduction of the glomerular filtrate (12).

Several experiments have been made attempting to modify the different components of the renin angiotensin system. McDONALD *et al.* (17) employing sodium overloads in the diet of rats were able to protect them from glycerol induced ARF. This protection was atributed to the depletion of intrarenal renin associated with the prolonged ingestion of excessive sodium (29). On the other hand the use of potassium chloride, a procedure which inhibits intrarenal synthesis and liberation of renin, does not protect the rats from renal failure induced by mercury chloride (11). The explanation could be that ClK reduced PRA as much as chronic excess of salt but does not deplete the juxtaglomerular apparatus of renin as effectively. This suggests a more important role of intrarenal renin than plasma renin in the experimental ARF.

Passive inmunization against angiotensin II, when the antibodies are administered simultaneously with or very shortly after injection of glycerol seems to prevent uremia (25, 26). However, other authors were unable to protect the animals against experimental ARF using either active or passive inmunization (20). These differences might be explained by the dissimilarities in the affinity and quantity of antibodies used (26).

In the present experiments, propranolol has been used, as a drug which seems to decrease renin secretion (6) in human (18, 31) and animals (1). Administration of large doses of propranolol for a prolonged period of time reduces diuresis in the rat, as well as Na and urea excretion in urine (7, 16, 21) a phenomenon recently observed in humans with the use of other beta blockers (32). An increase in creatinine clearance was found. Animals treated chronically with large doses of propranolol, when injected with glycerol showed a less intense polyuric ARF than those animals not pretreated. On the first day urea and creatinine excretion were low, they reached normal levels more quickly than untreated rats. Urea and creatinine concentrations in plasma were elevated, although significantly less in treated animals, corresponding to greater creatinine clearance and lower kidney weight. A similar effect has been found in another ARF model (13).

A single intramuscular dose of propranolol one hour before inducing ARF was not effective in preventing failure.

The partial protection observed, which seems to be exercised by propranolol administered in large dose during 7 days, could be due to two reasons: first, to the direct inhibitory activity of renin liberation in the juxtaglomerular apparatus; and second to the increase of volume of extracelular space.

Propranolol seems to provoke this expansion of extracelular volume through water and sodium retention and it is possible that the hydrosaline expansion referred diminishes renin secretion with the result that propranolol may act through this mechanism rather than exercising a direct anti-renin effect.

Although these results do not allow to deduce the role of the renin angiotensin system in ARF, the protective function performed by propranolol in ARF is another indirect argument favoring the physiopathological importance of elevated intrarenal concentrations of renin.

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Resumen

Se ha estudiado el efecto producido por la administración de propranolol a altas dosis y durante una semana sobre algunos aspectos de la función renal de ratas normales y con fracaso renal agudo (FRA). Asimismo se ha estudiado el efecto del propranolol administrado en una sola dosis, 1 hora antes de provocar el FRA.

La administración crónica de propranolol produce retención de agua y sal y aumento de aclaramiento de creatinina. El FRA inducido por administración intramuscular de glicerina en estos animales pretratados con propranolol es significativamente más leve que el que se produce en los animales no pretratados. La administración de una sola dosis de propranolol no ejerce ninguna protección.

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