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Effect of 8-phenyltheophylline, enprofylline and hydrochlorothiazide on glycerol-induced acute renal failure in the rat

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The adenosine antagonist 8-phenyltheophylline (8-PT) is a diuretic in normal rats and can ameliorate glycerol-induced acute renal failure (ARF) in this species. To define which action of 8-PT is important in its salutary effect in ARF, we have compared its effects with those of enprofylline (a xanthine with little affinity for adenosine receptors) and with those of the tubular diuretic hydrochlorothiazide. In one series of experiments, groups of rats with ARF of 24 h duration were given a single dose of drug or vehicle. Only 8-PT enhanced urine volume when compared with the vehicle-treated group. In a second set of experiments, groups of glycerol-injected rats received drug or vehicle treatment (i.p.) twice daily for 2 days. Rats which received a course of 8-PT treatment had significantly lower plasma urea and creatinine concentrations, a higher glomerular filtration rate, a lower kidney weight and improved kidney morphology when compared with vehicle-treated rats. The only beneficial effect noted after enprofylline treatment was an improved kidney morphology. Hydrochlorothiazide treatment compared with vehicle treatment did not ameliorate any index of renal function but resulted in significant elevations in plasma urea and creatinine levels. The inability of enprofylline or hydrochlorothiazide to mimic the effects of 8-PT in ARF indicate that the effects of 8-PT are probably associated with adenosine receptor blockade and not with a tubular diuretic action.

Recently we reported that early administration of 8-phenyltheophylline (8-PT) can ameliorate some of the biochemical, functional and morphological correlates of glycerol-induced acute renal failure (ARF) in the rat (Bowmer et al 1986). Treatment with 8-PT improved glomerular filtration rate (GFR), decreased plasma urea and creatinine levels and improved kidney morphology. We attributed this effect of 8-PT to its potent antagonist action at adenosine receptors, particularly those which mediate vasoconstriction of the afferent renal arterioles (Churchill & Bidani 1982).

There are, however, other possible explanations for the protective effect of 8-PT in glycerol-induced ARF. For instance, 8-PT has been shown to exert a diuretic action (Collis et al 1986) in the normal rat which is not associated with a change in glomerular filtration rate (GFR) (Bowmer et al 1986). This suggests that the adenosine antagonist may have an action on the renal tubule to promote diuresis, which could be of benefit in ARF. In the present paper we have examined this possibility by comparing the effects of 8-PT with those of the tubular diuretic, hydrochlorothiazide, in rats with acute renal failure. An alternative possibility is that the protective action of 8-PT may be due to a pharmacological action of the xanthine which is unrelated to adenosine receptor blockade. We have investigated this possibility by determining the effects of enprofylline in ARF. This xanthine has a very low affinity for adenosine receptors (Collis et al 1986).

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MATERIALS AND METHODS

Materials

8-PT was obtained from Calbiochem Ltd, enprofylline was a gift from Draco, Lund, Sweden and hydrochlorothiazide and inulin were obtained from Sigma Chemical Co. [^{3}H(G)]Inulin (180 mCi g^{-1}) of stated radioactive purity 98% was obtained from New England Nuclear Ltd, and was used without further purification. Reagents for the assay of creatinine and urea were purchased from Pierce and Warriner and BDH Ltd, respectively.

Induction of acute renal failure

The method for production of ARF has been previously described in detail (Bowmer et al 1982). Male Wistar Albino rats (250–300 g) were deprived of water for 24 h and ARF was produced by i.m. injection of 50% v/v glycerol in sterile saline (0·9% w/v NaCl), 10 mL kg^{-1}.

Evaluation of diuretic activity

The method employed to assess diuretic activity was similar to that described by Kau et al (1984). Rats that had been starved overnight, but with free access to water, were orally dosed with saline (25 mL kg^{-1}) and placed in metabolism cages. Urine was collected for 6 h and its volume recorded. The rats were denied access to food and water whilst in the metabolism cages. Six days later these animals were injected with glycerol as described above and 24 h later were given i.p. either 8-PT (10 mg kg^{-1}), hydrochlorothiazide (1·0 or 3·0 mg kg^{-1}), enprofylline (7·6 mg kg^{-1}) or vehicle (1·0 mL kg^{-1} of 50% v/v polyethylene glycol 400 in 0·1 M NaOH) which was used to dissolve the drugs. Rats were then given saline orally (25 mL kg^{-1}), placed in metabolism cages and the urine collected. After the 6 h collection of urine the rats were anaesthetized with ether and a blood sample taken by cardiac puncture for subsequent analysis of plasma urea and creatinine.

Evaluation of the effect of drug treatment on the development of ARF

Immediately after the injection of glycerol, rats were treated i.p. with either 8-PT (10 mg kg^{-1}), enprofylline (7·6 mg kg^{-1}), hydrochlorothiazide (1 mg kg^{-1}) or vehicle (1·0 mL kg^{-1}). Three further injections were made at 12, 24 and 36 h after the initial dose of drug or vehicle. Some glycerol-injected rats were allowed to develop ARF without any intervention. The dose of enprofylline was equal to that of 8-PT on a mole basis.

Blood samples (about 0·7 mL) were taken from the tail vein before (0 h) and 24 h after glycerol administration. Forty-eight hours after glycerol injection rats were anaesthetized with sodium pentobarbitone (60 mg kg^{-1}) and cannulae placed in the left jugular vein and right carotid artery. The single-injection method of Hall et al (1977) was then used to measure the clearance of [^{3}H]inulin (100 mg kg^{-1}; 20 μCi kg^{-1} i.v.) from plasma (C_{IN}). At the end of the experiment a blood sample was taken from the carotid artery and the kidneys removed, bisected longitudinally and placed in formal-saline (BDH Ltd).

Plasma creatinine and urea

Standard spectrophotometric assays were used: creatinine by reaction with alkaline picrate solution and urea by reaction with diacetylmonoxime (Henry et al 1974).

Kidney histology

A longitudinal section was cut from one kidney of each rat and stained with haemotoxylin and eosin. The sections were examined by a pathologist who was unaware of the treatment the donor animal had received. The degree of renal damage was assessed accordingly to a scoring system previously reported (Bowmer et al 1986). The degree of necrosis and presence of casts were each scored out of 5. The two scores for each kidney were added to give the total damage score (maximum 10).

Analysis of results

Results are expressed as mean ± s.e. mean. Statistical comparisons of data from the evaluations of diuretic activity and drug treatment were made by either a non-paired Student's *t*-test or one-way analysis of variance (ANOVA) after which the means were compared by the Method of Least Significant Difference (Snedecor & Cochran 1967). There was no significant correlation between kidney weight and body weight, so kidney weight was not expressed as a function of body weight. Statistical analysis of the histological damage score was made by a one-sided Mann Whitney test.

RESULTS

Evaluation of diuretic activity in rats that had developed ARF

Urine volumes recorded in control 6 h collection periods from the six different groups of rats showed no significant differences ($P > 0·05$; ANOVA: Table 1). The degree of renal failure that developed in the six groups of rats 30 h after glycerol injection as assessed by plasma urea and creatinine, also showed no statistically different intergroup variation ($P > 0·05$ ANOVA; Table 1) despite the various treatments at 24 h.

First, a comparison was made of differences in urine volume within each group of rats (Student's *t*-test). In the group that received no treatment (Group 1), ARF resulted in a significant 63% reduction in urine volume whilst vehicle (Group 2)-, enprofylline (Group 4)- and hydrochlorothiazide 1 mg kg^{-1} (Group 5)-injected rats with ARF showed no significant differences in urine volume when compared with control volumes. By contrast, rats with ARF and injected with 8-PT (Group 3) produced a significant 74% increase in urine volume. In the group of rats with ARF that received 3 mg kg^{-1} hydrochlorothiazide (Group 6) there was a dramatic reduction in urine volume with 5 rats anuric and a

Table 1. Effect of 8-phenyltheophylline (8-PT), enprofylline, hydrochlorothiazide (HCZ) and their vehicle on urine volume in rats 24 h after induction of glycerol-induced ARF.

	Urine volume (mL/100 g/6 h)	Creatinine (mg/100 mL)	Urea (mg/100 mL)
Group 1			
Control	1·67 ± 0·20		
ARF + no treatment	0·62 + 0·14***	4·18 ± 0·31	267 ± 16
Group 2			
Control	2·02 ± 0·19		
ARF + vehicle (1·0 mL kg^{-1} i.p.)	1·89 ± 0·29	3·97 ± 0·43	229 ± 28
Group 3			
Control	1·82 ± 0·20		
ARF + 8-PT (10 mg kg^{-1} i.p.)	3·16 ± 0·46*	3·81 ± 0·50	219 ± 18
Group 4			
Control	1·79 ± 0·20		
ARF + enprofylline (7·6 mg kg^{-1} i.p.)	1·69 ± 0·36	3·83 ± 0·21	244 ± 15
Group 5			
Control	1·94 ± 0·32		
ARF + HCZ (1 mg kg^{-1} i.p.)	1·38 ± 0·37	4·62 ± 0·40	227 ± 13
Group 6			
Control	2·02 ± 0·14		
ARF + HCZ (3 mg kg^{-1} i.p.)	†1·14 ± 0·09**	4·49 ± 0·16	277 ± 21

Results are given as mean ± s.e. mean and n = 8 for each group except † where n = 3 since 5 rats were anuric.
Urine was collected over 6 h after oral administration of saline (25 mL kg^{-1}). The control values were obtained in rats with normal renal function and 7 days later the animals were studied with acute renal failure.
*$P < 0·05$; **$P < 0·01$; ***$P < 0·001$ relative to control data in each group. Statistical analysis was performed using a Student's t-test.

significant 44% decrease ($P < 0·01$) in urine volume in the remaining 3 animals.

Second, a comparison (ANOVA) between Groups 1–5 was then made of urine volumes excreted from rats when they had developed ARF. The volume of urine excreted in vehicle-, 8-PT- and enprofylline-injected rats was significantly greater ($P < 0·05$) than in rats receiving no treatment. Rats with ARF that were treated with 1 mg kg^{-1} of hydrochlorothiazide excreted a volume of urine, which although greater, was not significantly different ($P > 0·05$) from that produced by untreated rats with ARF. The volume of urine produced in the 8-PT-treated rats was significantly greater ($P < 0·05$) than that in rats receiving vehicle. However, rats treated with enprofylline and hydrochlorothiazide (1 mg kg^{-1}) had mean urine volumes which were not significantly different ($P > 0·05$) from the vehicle-treated group.

Evaluation of drug treatment initiated at the time of glycerol injection

Following the injection of glycerol, mean plasma creatinine and urea concentrations of untreated rats increased by about seven fold at 48 h (Table 2). In vehicle-treated rats the levels of urea and creatinine were lower than in untreated animals at both 24 and 48 h, but this difference was not statistically significant ($P > 0·05$). However, 8-PT treatment resulted in levels of urea and creatinine that were significantly lower at 24 and 48 h than in either untreated or vehicle-treated rats. The effect of enprofylline was similar to that of vehicle treatment in that the levels of urea and creatinine were lower than those in rats that received no treatment, but this reduction was not statistically significant. In marked contrast to the effects of 8-PT treatment, hydrochlorothiazide (1 mg kg^{-1}) administration produced significantly elevated concentrations of urea and creatinine at both times when compared with vehicle treatment. In addition, the levels of urea and creatinine at 48 h after hydrochlorothiazide treatment were significantly higher in comparison with untreated rats (Table 2).

Table 2. Plasma urea and creatinine in glycerol-injected rats treated by i.p. injection with either 8-phenyltheophylline (8-PT, 10 mg kg^{-1}), enprofylline (7·6 mg kg^{-1}), hydrochlorothiazide (1 mg kg^{-1}) or vehicle (1·0 mL kg^{-1}) twice daily for 2 days.

	No treatment	Vehicle	8-PT	Enprofylline	Hydrochlorothiazide
Plasma urea (mg dL^{-1})					
0 h	48 ± 2	49 ± 2	48 ± 3	43 ± 3	47 ± 3
24 h	246 ± 18	201 ± 22	122 ± 10***†	223 ± 23	298 ± 17‡
48 h	323 ± 36	245 ± 41	122 ± 10***†	292 ± 43	476 ± 32***§
Plasma creatinine (mg dL^{-1})					
0 h	0·61 ± 0·03	0·60 ± 0·03	0·68 ± 0·04	0·65 ± 0·03	0·46 ± 0·03**†
24 h	3·68 ± 0·33	2·94 ± 0·33	1·91 ± 0·08***†	3·40 ± 0·39	4·15 ± 0·22†
48 h	4·57 ± 0·58	3·26 ± 0·67	1·47 ± 0·09***†	4·08 ± 0·66	6·30 ± 0·33*§

Results are given as mean ± s.e. mean and n = 12 for each group.
*$P < 0·05$, **$P < 0·01$, ***$P < 0·001$ relative to untreated rats.
†$P < 0·05$, ‡$P < 0·01$, §$P < 0·001$ relative to vehicle-treated rats.
Statistical analysis was performed using ANOVA.

We, and others, have previously reported that the mean C_{IN} in a group of normal rats is about 1 mL min^{-1} 100 g b wt^{-1} (Harvey & Malvin 1965; Bowmer et al 1986). Forty-eight hours after glycerol injection the mean C_{IN} of untreated rats was 14% of this value (Fig. 1). Treatment with either vehicle, 8-PT or enprofylline resulted in a significantly greater C_{IN} when compared with untreated animals; but the improvement in C_{IN} was greatest with 8-PT treatment. The C_{IN} in this group of rats was significantly higher than after vehicle treatment. C_{IN} in rats after hydrochlorothiazide treatment (1 mg kg^{-1}) or enprofylline treatment was not significantly different from the value obtained for vehicle-treated animals, however C_{IN} was 20% lower in the hydrochlorothiazide-treated group than in vehicle-treated rats.

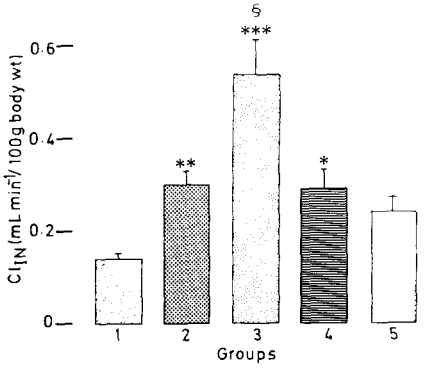

FIG. 1. The clearance of [^{3}H]inulin (C_{IN}) in glycerol-injected rats 48 h after treatment with either vehicle (1·0 mL kg^{-1}), 8-phenyltheophylline (10 mg kg^{-1}), enprofylline (7·6 mg kg^{-1}) or hydrochlorothiazide (1 mg kg^{-1}) twice daily i.p. Key to groups; (1) no treatment; (2) vehicle; (3) 8-phenyltheophylline; (4) enprofylline; (5) hydrochlorothiazide. Columns represent mean values with vertical bars showing s.e. means and n = 12 for each group. $^*P < 0{\cdot}05$, $^{**}P < 0{\cdot}01$, $^{***}P < 0{\cdot}001$ relative to group 1. §$P < 0{\cdot}001$ relative to group 2. Statistical analysis was performed using ANOVA.

The total kidney weight in normal rats of the weight range used here is about 2 g (Bowmer et al 1986), but 48 h after induction of ARF in untreated rats the mean kidney weight was 3 g (Fig. 2). Treatment with 8-PT or enprofylline resulted in a significantly lower kidney weight when compared with untreated animals (Fig. 2). Furthermore, kidney weight in 8-PT-treated animals, but not in those treated with enprofylline, was also significantly lower than the weight recorded in vehicle-treated rats. The kidney weights of rats treated with

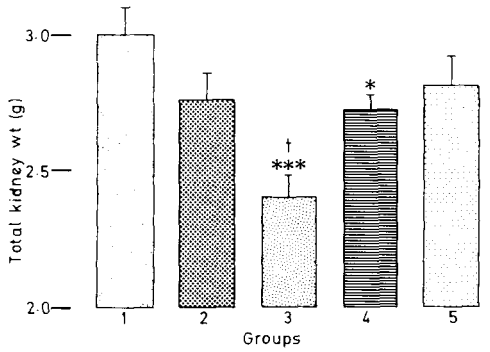

FIG. 2. Total kidney weight of glycerol-injected rats 48 h after treatment with vehicle (1·0 mL kg^{-1}), 8-phenyltheophylline (10 mg kg^{-1}), enprofylline (7·6 mg kg^{-1}) or hydrochlorothiazide (1 mg kg^{-1}) twice daily i.p. Key to groups: (1) no treatment; (2) vehicle; (3) 8-phenyltheophylline; (4) enprofylline; (5) hydrochlorothiazde. Columns represent mean values with vertical bars showing s.e. means and n = 12 for each group. $^*P < 0{\cdot}05$; $^{***}P < 0{\cdot}001$ relative to group 1. †$P < 0{\cdot}05$ relative to group 2. Statistical analysis was performed using ANOVA.

hydrochlorothiazide were not significantly different from untreated animals.

Data from histological examination of kidneys taken from rats after various treatments are shown in Table 3. The degree of kidney damage in each of the treated groups was not significantly different from the damage noted in the kidneys taken from untreated animals. However, comparison of the damage scores in drug-treated rats with the score in the vehicle group showed that the damage in the hydrochlorothiazide-treated rats was not significantly different whilst damage in the 8-PT and enprofylline groups was significantly less.

Table 3. Effect of 8-phenyltheophylline (8-PT, 10 mg kg^{-1}), enprofylline (7·6 mg kg^{-1}) and hydrochlorothiazide (HCZ, 1 mg kg^{-1}) given i.p. twice daily for 2 days on the renal damage associated with glycerol-induced acute renal failure.

Group	Damage score
No treatment	7·3 ± 0·5
Vehicle treatment	8·6 ± 0·4
8-PT treatment	6·8 ± 0·4***
Enprofylline treatment	6·7 ± 0·5**
HCZ treatment	8·0 ± 0·2

$^{**}P < 0{\cdot}01$; $^{***}P < 0{\cdot}001$ relative to vehicle treatment and n = 12 for each group. Statistical analysis was performed using a one-sided Mann Whitney test.

Kidneys were fixed and sectioned 48 h after injection of glycerol.

Maximum possible damage score = 10.

DISCUSSION

The results of this study confirm our previous report that 8-PT can ameliorate glycerol-induced ARF in the rat (Bowmer et al 1986) and they also demonstrate a marked diuretic effect of the compound in that species. By contrast, neither the xanthine enprofylline nor the diuretic hydrochlorothiazide were consistently beneficial in this form of ARF.

The dose of 8-PT used in this study has been shown to antagonize adenosine-induced bradycardia in the rat (Bowmer et al 1986; Collis et al 1986). Enprofylline, however, is devoid of adenosine antagonism at a dose of 10 mg kg^{-1} (Collis et al 1986) which is greater than the one used in the present study (7·6 mg kg^{-1}). Since the salutary effects of 8-PT on plasma urea and creatinine levels, GFR, kidney weight and urine flow in rats with ARF were not exhibited by enprofylline, it is reasonable to assume that they are associated with adenosine receptor blockade. Both xanthines reduced the severity of morphological damage associated with ARF, but this effect was only significant when compared with vehicle-treated animals with ARF and not when compared with rats treated with glycerol alone. Consequently, adenosine receptor blockade may not be responsible for the reduction in renal damage exerted by the two xanthines. A number of xanthines, including enprofylline, raise urinary levels of PGE_2 and $PGF_{2\alpha}$ in the rat (Baer et al 1983). One possibility is that this effect, which is thought to be due to increased renal eicosanoid synthesis, may have a renal protective action. Prostaglandins of the E series have been reported to reduce tubular lesions in some, but not all, forms of ARF (Werb et al 1978; Mandal & Miller 1982; Neumayer et al 1985).

Most of the beneficial effects of 8-PT in ARF could be due to its diuretic action (Collis et al 1986). The diuretic effect of 8-PT in the normal rat may be via a tubular action. In fact, the adenosine antagonist theophylline, in the form of aminophylline, has been shown to inhibit tubular reabsorption of sodium in man (Brater et al 1983). However, results of the present study indicate that a tubular site of action for 8-PT is unlikely to account for its diuretic or its other salutary effects in ARF. This conclusion is reached because hydrochlorothiazide, a diuretic with a tubular site of action, did not cause diuresis and was not beneficial in ARF. By contrast to hydrochlorothiazide treatment, 8-PT administration resulted in a significant increase in GFR when compared with vehicle treatment. It is therefore likely that this effect is responsible for the diuretic action of 8-PT in ARF.

The initial dose of hydrochlorothiazide (1 mg kg^{-1}) was chosen because it was equi-effective as a diuretic with 10 mg kg^{-1} of 8-PT in the normal rat (Kau et al 1984; Collis et al 1986). Because 1 mg kg^{-1} of hydrochlorothiazide was ineffective as a diuretic in rats with ARF, we also examined the effects of a higher dose (3 mg kg^{-1}). This higher dose of hydrochlorothiazide actually decreased urine volume in rats with ARF which suggests that the lack of effect of the 1 mg kg^{-1} dose of hydrochlorothiazide was due to the occurrence of ARF and not to the dose level being inadequate. The absence of a diuretic effect of the thiazide in this model of ARF may be due to the fact than an impairment of tubular sodium reabsorption is already present (Bardgette et al 1978).

When treatment with hydrochlorothiazide was initiated at the same time as the glycerol injection, and was then continued for 2 days, an exacerbation of the plasma levels of urea and creatinine was observed. A possible explanation for this phenomenon is provided by a report that hydrochlorothiazide decreased renal blood blow in ischaemic ARF (Patak et al 1979). Such an effect would be expected to decrease GFR and to increase plasma urea and creatinine levels further. In support of this, inulin clearance was about 20% less in thiazide-treated rats with ARF than in those treated with vehicle alone (Fig. 1). This difference in GFR (which was already markedly depressed) did not, however, reach statistical significance. An alternative explanation of the results is that administration of hydrochlorothiazide simultaneously with glycerol, evokes an early diuresis which then makes worse the subsequent development of renal failure. Dehydration is known to increase the severity of this type of renal failure (Thiel et al 1967), and this would be enhanced by the deprivation of water for 24 h before glycerol administration. Once renal failure has developed, treatment with the thiazide causes neither diuresis nor an increase in plasma urea and creatinine (Table 1).

The vehicle for 8-PT also had beneficial effects on plasma urea and creatinine levels, on kidney weight and on GFR in glycerol-induced ARF, as we have previously reported (Bowmer et al 1986). It is likely that this effect is due to the polyethylene glycol component, which, by virtue of its hyperoncotic and impermeant nature may reduce cell swelling and oedema in damaged kidneys (Frega et al 1979; Leaf et al 1983). The moderate diuretic effect of the vehicle was unexpected since it is known to have a slight antidiuretic effect in normal rats (Collis et al 1986). Presumably, the beneficial effect of the

vehicle on kidney oedema and GFR in ARF can override the underlying tendency for the hyperoncotic polyethylene glycol to cause fluid retention (Bennett & Gardiner 1984).

The timing and/or the duration of the administration of 8-PT also appears to be important in determining its effect in ARF. A single dose of 8-PT did not alter plasma urea or creatinine levels in rats with ARF when it was given 24 h after glycerol injection (Table 2). A similar dependency on early administration in the treatment of glycerol-induced ARF has been reported for the adenosine antagonist aminophylline (Bidani & Churchill 1983).

In conclusion the results of this study demonstrate that neither enprofylline nor hydrochlorothiazide can mimic the range of beneficial effects produced by 8-PT in this form of ARF. The amelioration of ARF is therefore unlikely to be due to diuretic action at the tubular level but is probably associated with adenosine receptor blockade.

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