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Alteration of monocrotaline pyrrole-induced cardiopulmonary effects in rats by hydrallazine, dexamethasone or sulphinpyrazone

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1 The effects of intraperitoneal hydrallazine, dexamethasone, or sulphinpyrazone on the toxicity of monocrotaline pyrrole (MCTP) were examined in rats 14 days after injection of MCTP (5 mg kg^{-1}, i.v.).

2 MCTP alone caused increases in lung weight, and of both lactate dehydrogenase activity and protein concentration in bronchopulmonary lavage fluid. Right ventricular hypertrophy also occurred.

3 Hydrallazine (3 mg kg^{-1}, daily), a vasodilator and platelet prostaglandin synthesis inhibitor, reduced the degree of right ventricular hypertrophy and the elevation in the concentration of protein in lavage fluid.

4 Dexamethasone (27 $\mu g\ kg^{-1}$, daily), an anti-inflammatory agent and inhibitor of phospholipase, also reduced the right ventricular hypertrophy and the increased protein concentration in lavage fluid caused by MCTP.

5 Sulphinpyrazone (100 mg kg^{-1}, twice daily), an inhibitor of platelet prostaglandin biosynthesis, prevented right ventricular hypertrophy in the MCTP treated rats without affecting any of the indices of lung injury.

6 These results provide further support for the hypothesis that platelets and vasoconstrictor agents play a role in the development of MCTP-induced pulmonary hypertension.

Introduction

Administration of monocrotaline (MCT) or its toxic metabolite dehydromonocrotaline (monocrotaline pyrrole; MCTP) to rats results in a syndrome which has many characteristics in common with primary pulmonary hypertension in man (Wagenvoordt & Wagenvoordt, 1970). Rats treated with MCT or MCTP develop increased pulmonary arterial pressure, right ventricular hypertrophy, pulmonary vascular lesions and platelet-containing thrombi in the vasculature (Merkow & Kleinerman, 1966; Meyrick *et al.*, 1980; Bruner *et al.*, 1983). The vascular lesions are accompanied by an inflammatory response that includes perivascular cuffing and leukocyte infiltration (Lalich & Ehrhart, 1962). Associated with these lesions are increased lung weight and elevated lactate dehydrogenase activity and protein concentration in cell-free bronchopulmonary lavage fluid (Bruner *et al.*, 1983). The mechanisms by which MCT or MCTP produce these changes are unknown. A role for the platelet in the pathogenesis of MCTP-induced damage was implied by the observation that a lowering of the platelet count at critical periods during the course of MCTP toxicity reduced the development of right ventricular hypertrophy (Roth *et al.*, 1983).

The present experiments were designed to provide further information about the mechanisms by which MCTP acts by examining the effects of pharmacological intervention on the responses to MCTP. Three drugs were chosen for their vasodilator, glucocorticoid or platelet function inhibitory properties. Hydrallazine hydrochloride (HD) is a vasodilator used with modest success in cases of human primary pulmonary hypertension (Fein & Frishman, 1980). Besides acting as a vasodilator, hydrallazine also inhibits platelet aggregation and thromboxane biosynthesis *in vitro* (Greenwald *et al.*, 1978). Glucocorticoids have a wide spectrum of pharmacological actions (Haynes & Larner, 1975). They are frequently used for their anti-inflammatory and immunosuppressant effects. Since inflammatory changes are seen in con-

junction with MCT or MCTP treatment, we examined the effects of dexamethasone (DX) on MCTP toxicity. Dexamethasone also inhibits release of arachidonic acid from phospholipids through interference with phospholipase A_2 (Flower, 1978) and may thereby decrease the production of vasoconstrictor prostaglandins. The third drug used was sulphinpyrazone (SP), a reversible inhibitor of cyclooxygenase in the prostaglandin synthesis pathway (Fuster & Chesebro, 1981). Platelet prostaglandin synthesis in rats is decreased by sulphinpyrazone without a concomitant decrease in vascular prostacyclin synthesis (Livio *et al.*, 1980). Sulphinpyrazone also increases platelet survival time in rats (Wilkinson *et al.*, 1979). MCTP-induced lung injury and right ventricular hypertrophy were examined in rats after treatment with one of these three drugs.

Methods

Dehydromonocrotaline (MCTP) was synthesized from MCT (Trans World Chemicals, Washington, DC) via an N-oxide intermediate as described by Mattocks (1969). The structure of the product was confirmed by mass spectrometry. MCTP was stored under dry N_2 at $-20°C$ and protected from light and, immediately before use, it was dissolved in N,N-dimethylformamide (DMF) to make a solution containing $10\,mg\,ml^{-1}$. Rats were given either MCTP ($5\,mg\,kg^{-1}$) or DMF ($0.5\,ml\,kg^{-1}$) via the tail vein. All experiments were done using a 2-way factorial design so that each animal was treated with both a drug or its vehicle and MCTP or its vehicle.

Hydrallazine hydrochloride (Apresoline, CIBA Pharmaceutical Company, Summit, NJ) was administered ($3\,mg\,kg^{-1}$, i.p.) daily, a dose shown to normalize the hyperactive platelets of retired breeder rats (Burns & Saunders, 1979). Controls received saline (0.9% w/v NaCl solution) $1.5\,ml\,kg^{-1}$. Rats were treated on 3 consecutive days before MCTP administration and for the remainder of the 14 day experimental period.

Dexamethasone (Azium, Schering Corporation, Kenilworth, NJ) was administered ($0.027\,mg\,kg^{-1}$, i.p.) daily. This dose was anti-inflammatory and had minimal effects on adrenal, thymus and body weight in rats treated for 4 days (Dr Elliot Collins, Schering Corporation, personal communication). Controls received saline, $0.5\,ml\,kg^{-1}$. Rats were treated as above for 3 days before MCTP administration and throughout the 14 day experimental period.

A suspension of sulphinpyrazone (SP) ($100\,mg\,ml^{-1}$) was prepared by homogenizing the contents of a 200 mg Anturane capsule (CIBA Pharmaceutical Company, Summit, NJ) in 2 ml propylene glycol. Rats were treated with sulphinpyrazone ($100\,mg\,kg^{-1}$, i.p.) every 12 h. This dose reduced platelet aggregation in response to arachidonic acid *in vitro* by approximately 50%. Controls received propylene glycol $1\,ml\,kg^{-1}$. Rats were treated for 2 days before MCTP administration and throughout the 14 day experimental period.

Lactate dehydrogenase activity and protein release into the airways were measured in cell-free bronchopulmonary lavage fluid 14 days after MCTP treatment. Rats were anaesthetized with sodium pentobarbitone ($50\,mg\,kg^{-1}$, i.p.), and the trachea was cannulated with an 18 g needle covered with PE-260 tubing. Heparin, 500 u, was injected into the abdominal vena cava, and 3–5 ml of blood was withdrawn after allowing 1 min for the heparin to distribute. The thoracic cavity was then opened and the lungs were carefully dissected free. Using a glass syringe, saline at room temperature was introduced into the airways via the tracheal cannula and immediately withdrawn. This procedure was repeated with fresh saline and the two washes were combined. The total volume of saline used was the same for all animals killed on a given day. This volume was determined by multiplying the mean body weight (in kg) of all of the animals for that day by $23\,ml\,kg^{-1}$ (Mauderly, 1977). The pooled lavage sample was centrifuged at 600 *g* for 15 min. Blood samples were spun at 10,000 *g* for 10 min. Lactate dehydrogenase (LDH) activity in the cell-free supernatant of the lavage fluid and in the plasma was assayed by the spectrophotometric method of Bergmeyer & Bernt (1974). This method measures LDH activity by quantifying the disappearance of the cofactor NADH using pyruvate as substrate. Protein concentrations in the cell-free lavage fluids were measured (Lowry *et al.*, 1951) using bovine serum albumin as a standard.

Right ventricular hypertrophy was used as an index of pulmonary hypertension. Hearts were kept briefly in cold saline after removal from the rat. The atria were trimmed from the ventricles and discarded. The right ventricle (RV) was then cut away, leaving the left ventricle plus septum (LV + S) intact. Each piece was weighed to the nearest mg. Increases in the ratio RV/(LV + S) when the (LV + S) weight is unchanged indicate right ventricular hypertrophy (Fulton *et al.*, 1952).

Results are expressed as mean ± s.e.mean or median and range, as appropriate. Two-way factorial analysis of variance was used to analyse the changes. Homogeneity of variance among the groups was tested by the F_{max} procedure. When the variances were homogeneous, the least significant difference (l.s.d.) test was used for individual comparisons. When the variances were non-homogeneous, the planned individual comparisons were made using the non-parametric rank sum test. The criterion for a statistically significant difference was $P < 0.05$ in all cases.

Table 1 Effects of hydrallazine on monocrotaline pyrrole (MCTP) toxicity

	Treatment[a]			
	Sal/DMF	*HD/DMF*	*Sal/MCTP*	*HD/MCTP*
Body weight gain (g)	103±8	94±6	73±16	84±4
Wet lung weight (g)	1.12(1.02–1.36)	1.21(1.13–1.25)	1.75(1.19–2.19)[b]	1.52(1.12–1.98)
Wet lung/BW (×1,000)	3.41(2.97–4.11)	3.67(3.38–4.00)	6.14(4.32–8.14)[b]	4.39(3.38–6.21)
Lavage fluid LDH activity (u 100 ml^{-1})	1.6(1.5–1.9)	1.5(0.1–1.9)	5.6(2.3–47.1)[b]	4.6(2.2–8.4)[c]
Lavage fluid protein (mg ml^{-1})	0.08(0.07–0.12)	0.07(0.05–0.08)	0.73(0.20–1.20)[b]	0.22(0.07–0.75)[c,d]
RV/BW (×1,000)	0.708±0.024	0.760±0.017	0.959±0.058[e]	0.817±0.030[f]
RV/(LV+S)	0.308(0.295–0.366)	0.327(0.292–0.337)	0.405(0.332–0.534)[b]	0.349(0.340–0.364)[c,d]

[a]Rats were treated daily with hydrallazine (HD), 3 mg kg^{-1}, or an equivalent volume of saline (Sal). After 3 days of pretreatment, rats received N,N-dimethylformamide (DMF) 0.5 ml kg^{-1} or MCTP 5 mg kg^{-1} in DMF via the tail vein. The rats were killed 14 days after the injection of MCTP. Body weight (BW) gain is the difference between body weight at 14 days and on the day of MCTP treatment. Values are median (range) except for body weight gain and RV/BW which are mean ± s.e.mean, $n = 6–8$.
[b]Significantly different from saline/DMF group (Rank sum test, $P < 0.05$).
[c]Significantly different from hydrallazine/DMF group (Rank sum test, $P < 0.05$).
[d]Significantly different from saline/MCTP group (Rank sum test, $P < 0.05$).
[e]Significantly different from saline/DMF group (2-way factorial ANOVA, l.s.d. test, $P < 0.05$).
[f]Significantly different from saline/MCTP group (2-way factorial ANOVA, l.s.d. test, $P < 0.05$).

Results

Consistent with previous results (Bruner *et al.*, 1983), MCTP caused an increase in lung weight, lavage fluid LDH activity, lavage fluid protein concentration and the ratio of RV/(LV + S) compared with values in rats give DMf (see Tables 1, 2 and 3). Hydrallazine treatment reduced the right ventricular hypertrophy and elevation in lavage fluid protein conenctration induced by MCTP but had no effect on

Table 2 Effects of dexamethasone on monocrotaline pyrrole (MCTP) toxicity

	Treatment[a]			
	Sal/DMF	*DX/DMF*	*Sal/MCTP*	*DX/MCTP*
Body weight gain (g)	116(98–138)	67(30–76)[b]	37(−56–117)[b]	47(37–77)
Wet lung wt (g)	1.27(1.15–1.41)	1.05(0.96–1.14)[b]	2.48(1.38–4.34)[b]	1.38(1.14–1.96)[c,d]
Wet lung/body weight (×1,000)	3.6(3.5–4.3)	3.5(3.2–4.1)	7.7(4.3–18.5)[b]	4.5(4.0–6.8)[c,d]
Lavage fluid LDH activity (u 100 ml^{-1})	1.7(1.2–2.3)	2.0(1.6–2.2)	13.6(3.5–25.7)[b]	15.1(6.7–24.6)[c]
Lavage fluid protein (mg ml^{-1})	0.04±0.01	0.06±0.01	2.19±0.87[e]	0.29±0.05[f,g]
RV/BW (×1,000)	0.696±0.038	0.716±0.020	0.960±0.078[e]	0.778±0.035[g]
RV/(LV+S)	0.330(0.290–0.345)	0.291(0.240–0.324)[b]	0.378(0.309–0.486)[b]	0.315(0.274–0.337)[d]

[a]Rats were treated daily with dexamethasone (DX), 27 μg kg^{-1}, or saline (Sal) 0.5 ml kg^{-1}. After 3 days of pretreatment, rats received DMF 0.5 ml kg^{-1} or MCTP 5 mg kg^{-1} in DMF via the tail vein. The rats were killed 14 days after injection of MCTP. Body weight gain is the difference between body weight at 14 days and that on the day of MCTP treatment. Wet lung/body weight ratios were calculated using the body weight (BW) at 14 days. Values are median (range) except for lavage fluid protein and RV/BW which are mean ± s.e.mean, $n = 7–8$.
[b]Significantly different from saline/DMF group (Rank sum test, $P < 0.05$).
[c]Significantly different from DX/DMF group (Rank sum test, $P < 0.05$).
[d]Significantly different from saline/MCTP group (Rank sum test, $P < 0.05$).
[e]Significantly different from saline/DMF group (2-way factorial ANOVA, l.s.d. test, $P < 0.05$).
[f]Significantly different from DX/DMF group (2-way factorial ANOVA, l.s.d. test, $P < 0.05$).
[g]Significantly different from saline/MCTP group (2-way factorial ANOVA, l.s.d. test, $P < 0.05$).

Table 3 Effects of sulphinpyrazone on monocrotaline pyrrole (MCTP) toxicity

	Treatment[a]			
	Veh/DMF	*SP/DMF*	*Veh/MCTP*	*SP/MCTP*
Body weight gain (g)	88(63–104)	20(1–67)[b]	68(−24–102)	47(24–60)
Wet lung weight (g)	1.09±0.06	0.99±0.06	1.74±0.26[c]	1.48±0.16[d]
Wet lung/BW (×1,000)	3.67(3.29–4.03)	4.16(3.69–4.58)	6.88(3.58–13.41)[b]	5.46(4.06–6.66)
Lavage fluid LDH activity (u 100 ml)	1.7(1.4–2.1)	1.5(1.1–2.2)	7.1(2.2–20.9)[b]	14.0(1.5–31.2)
Lavage fluid protein ($mg\,ml^{-1}$)	0.08±0.01	0.06±0.01	1.16±0.56[c]	0.26±0.08[d]
RV/BW (×1,000)	0.657±0.012	0.628±0.022	0.779±0.037[c]	0.656±0.026[e]
RV/(LV+S)	0.302±0.011	0.308±0.008	0.367±0.011[c]	0.323±0.014[e]

[a]Rats were treated two times daily with sulphinpyrazone (SP), 100 $mg\,kg^{-1}$, or propylene glycol (Veh) 1 $ml\,kg^{-1}$, i.p. After 2 days of pretreatment, rats received DMF 0.5 $ml\,kg^{-1}$ or MCTP 5 $mg\,kg^{-1}$ in DMF via the tail vein. The rats were killed 14 days after injection of MCTP. Body weight (BW) gain is the difference between body weight at 14 days and that on the day of MCTP treatment. Values are mean ± s.e.mean except for body weight gain and lavage fluid LDH activity which are presented as median (range); $n = 5–6$.
[b]Significantly different from Veh/DMF group (Rank sum test, $P < 0.05$).
[c]Significantly different from Veh/DMF group (2-way factorial ANOVA, l.s.d. test, $P < 0.05$).
[d]Significantly different from SP/DMF group (2-way factorial ANOVA, l.s.d. test, $P < 0.05$).
[e]Significantly different from Veh/MCTP group (2-way factorial ANOVA, l.s.d. test, $P < 0.05$).

lavage LDH activity. In rats not given MCTP, hydrallazine had no effect on any of these parameters (Table 1).

The effects of dexamethasone (DX) treatment are summarized in Table 2. Dexamethasone treatment in rats not given MCTP led to a smaller gain in body weight than the saline-treated controls. In rats treated with MCTP, dexamethasone greatly reduced the evoked increase in lung weight and accumulation of protein in lavage fluid. Dexamethasone itself caused a decrease in the RV/(LV + S) ratio and reduced the hypertrophy due to MCTP treatment. This may be related to the effect of dexamethasone on body weight since if right ventricular hypertrophy was expressed as the ratio RV / body weight there was no apparent effect of dexamethasone itself on this parameter. However, calculations using this latter ratio showed a statistically significant difference between the dexamethasone-treated group that was given MCTP and their control group given saline and MCTP.

Sulphinpyrazone treatment prevented the right ventricular hypertrophy in the MCTP treated rats but did not affect any of the indices of lung injury (Table 3). Sulphinpyrazone itself reduced considerably the gain in body weight measured in vehicle-treated control rats.

Discussion

All three of the drugs tested afforded some degree of protection from MCTP-induced right ventricular hypertrophy. Although each drug has more than one action, one effect was common to all three, namely the ability to inhibit prostaglandin synthesis. Hydrallazine and sulphinpyrazone tend to inhibit platelet thromboxane synthesis more than vascular PGI_2 production (Greenwald *et al.*, 1978; Livio *et al.*, 1980; Srivastava & Awasthi, 1982), while dexamethasone reduces the synthesis of all eicosanoids by decreasing the availability of arachidonic acid substrate (Flower, 1978). This common mechanism suggests that platelet thromboxane synthesis could be important in the development of MCT-induced pulmonary hypertension.

However, other actions of these drugs could also have contributed to the protection. Hydrallazine, as a potent vasodilator, may have reduced the pulmonary vascular resistance, thereby reducing the stimulus for right heart hypertrophy. Kay *et al.* (1976) found that cinnarizine given chronically to rats did not protect them from MCT toxicity. Since cinnarizine inhibits calcium fluxes into depolarized smooth muscle cells, thereby reducing smooth muscle contraction to a wide variety of stimuli (Godfraind & Kaba, 1969), a lessening of vasoconstriction may, by itself, be insufficient to protect from right ventricular hypertrophy. However, there was no indication in that study that the dose of cinnarizine used actually decreased vasoconstriction *in vivo*, so the vasodilator action of hydrallazine cannot be ruled out as a possible contribution to its protective effect.

Dexamethasone has other actions in addition to its effects on eicosanoids. For example, as an anti-inflammatory and immunosuppressive agent it could

have reduced the inflammatory response in the lung and thus reduced the injury. The possibility also exists that dexamethasone's protective effect may be unrelated to its specific pharmacological actions. In rats given dexamethasone the gain in body weight was smaller than in the saline-treated controls. Animals in which weight gain was prevented by diet restriction were protected from the lung injury and right ventricular hypertrophy caused by MCT (Hayashi *et al.*, 1979) or MCTP (Ganey & Roth, 1983). Accordingly, protection from MCTP by dexamethasone may have been the result of its effects on growth rather than a specific pharmacological effect.

Sulphinpyrazone is known to have an uricosuric action in the kidney, although it seems unlikely that such an effect could explain the protective effects of sulphinpyrazone in MCTP-induced pulmonary hypertension. Like dexamethasone, however, sulphinpyrazone may have acted somewhat nonspecifically by inhibiting growth, as evidenced by the decrease in body weight gain in sulphinpyrazone-treated rats relative to rats not treated with sulphinpyrazone (Table 3).

These experiments provide further support for the hypothesis that platelets and vasoconstrictors play a role in the development of MCTP-induced pulmonary hypertension. Understanding the mechanisms responsible for MCTP-induced injury in rats may be useful in developing therapeutic approaches to primary pulmonary hypertension in humans.

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