Free Rad. Res. Comms., Vol. 2, No. 2, pp. 125–127
8755-0199/86/0202-0125 $25-00/0

Printed in Great Britain

INFLUENCE OF THE IRON CHELATING AGENT DESFERRIOXAMINE ON TWO RAT INFLAMMATORY MODELS

R. HIRSCHELMANN and H. BEKEMEIER

Department of Pharmacology, Section of Pharmacy, Martin Luther University Halle-Wittenberg, DDR-4050 Halle (S.), Weinbergweg 15

(Received in revised form March 14, 1986)

The carrageenin rat paw edema was dose-dependently inhibited by i.v. and i.m. administration of desferrioxamine, a specific iron chelating agent. Therefore, iron-catalyzed formation of free radicals might be involved in this acute inflammatory reaction. In contrast, no antiinflammatory activity of desferrioxamine could be seen in rat adjuvant arthritis, a model of subacute and chronic inflammation.

INTRODUCTION

Oxygen free radicals are claimed to play an important role in tissue damage and inflammation[1,2,3,4]. Most convincing data supporting this hypothesis have been found *in vitro*. Obviously, these findings are difficult to verify *in vivo* and, therefore, not all results from animal experiments are completely in line with the free radical theory of oxygen toxicity[3,5]. Iron catalyses the formation of hydroxyl radicals from hydrogen peroxide and superoxide radicals which are released during phagocytosis, and of lipid peroxidation. Therefore, the specific iron chelating agent desferrioxamine was proposed to inhibit inflammation and it was already successfully used in animal inflammatory models[6]. These *in vivo* findings need confirmation and extension. In the present study we report the effects of desferrioxamine in an acute inflammation, the carrageenin rat paw edema as well as in rat adjuvant arthritis, a subacute and chronic inflammatory process.

MATERIALS AND METHODS

Rats of a Wistar outbred strain (Falcke, Barby) were used. Carrageenin edema was induced in female animals, body weight 100 to 150 g, by injecting 0.1 ml of a 1% aqueous solution of carrageenin (FMC Corp., Marine Colloids Div., Rockland Maine) into the pad of the left hindpaw. Paw swelling was measured by using a plethysmometric device. Adjuvant arthritis was induced in female rats, body weight 90–160 g, by injecting 0.1 ml of complete Freund's adjuvant (0.5% suspension of Mycobact. tubercul., Institut für Impfstoffe Dessau, in paraffin oil) into the pad of

TABLE I
Influence of desferrioxamine on carrageenin paw edema. Desferrioxamine was injected immediately prior to edema induction

Dose mg/kg	% Edema inhibition 1 h	2 h	3 h	4 h	5 h	24 h	n
250 i.m.	17	4	19	9	17	n.d.	16
500 i.m.	16	17	32+	26+	34+	n.d.	8
1000 i.m.	41+	40+	29+	42+	37+	28+	8
125 i.v.	11	19	17	10	3	15	16
250 i.v.	49+	27+	20	23+	19	23	16
500 i.v.	64+	28+	35+	48+	32+	43+	8

+ Significantly different ($p < 0.05$) from controls according to Student's t-test.
n.d. = not determined.
Desferrioxamine did not influence the edema up to 125 mg/kg after i.p. injection.

the left hindpaw. Swelling of the injected paw was measured by using a sliding gauge. Desferrioxamine (Desferal[R], CIBA-GEIGY, Basel) was administered during days 1–3 in the primary phase, and, in other animals, from day 15 until day 18 in established secondary phase, once or twice daily.

RESULTS AND DISCUSSION

Desferrioxamine caused a significant and dose-dependent inhibition of carrageenin edema after intravenous and intramuscular administration with i.v. injection as the more effective route (Table I). The effects were not increased by injecting desferrioxamine 30 minutes before edema induction (data not shown). There was no anti-inflammatory activity of desferrioxamine up to the high dose of 1 g/kg (2 × 500 mg/kg) daily in adjuvant arthritis, neither in primary phase nor during established secondary arthritis (Table II). In contrast, an allergic synovitis of guinea pigs was significantly inhibited by only 100 mg/kg desferrioxamine via the i.p. route[6]. Desferrioxamine was not effective up to 125 mg/kg i.m., once daily, during 8 days in 6-sulfanilamidoindazole arthritis of rats (data not shown).

As mentioned above, radical-mediated tissue damage, e.g. after a site-specific Fenton reaction[7], is generally difficult to verify in vivo. Nevertheless, there is apparently hardly a reference for inflammatory processes which might be caused by iron-catalysed reactions in adjuvant arthritis. On the other hand, the antiinflammatory effect of desferrioxamine in carrageenin edema supports the idea of a partially

TABLE II
Influence of desferrioxamine on paw swelling in primary (2 d–4 d) and established secondary phase (17 d–19 d) of adjuvant arthritis. Intramuscular injection of 500 mg/kg, once or twice daily, from day 1 until day 3 and, in other animals, from day 15 until day 18, respectively. n = 8 per group

Group	Paw swelling; mm, $\bar{x} \pm SD$ 2 d	3 d	4 d	17 d	18 d	19 d
Control	2.1 ± 0.5	2.7 ± 0.6	2.8 ± 0.7	8.7 ± 1.3	9.6 ± 2.1	9.6 ± 1.5
Desferr. once daily	2.2 ± 0.7	2.9 ± 0.8	2.8 ± 0.7	8.7 ± 1.8	8.5 ± 1.8	8.3 ± 2.4
Desferr. twice daily	2.3 ± 0.4	3.2 ± 0.9	3.1 ± 0.8	8.5 ± 1.4	8.7 ± 1.9	8.7 ± 2.0

iron-mediated tissue damage via radical production in this acute model, just as in allergic synovitis of guinea pigs[6]. Other desferrioxamine effects, such as inhibition of iron-depending enzymes, e.g. lipoxygenases[8], could of course also explain anti-inflammatory activity of this iron III chelator.

References

1. I. Fridovich, *Science*, **201**, 875–880, (1978).
2. B. Halliwell, *Cell Biol. Int. Rep.*, **6**, 529–542, (1982).
3. L. Flohé, H. Giertz and R. Beckmann, Handbook of Inflammation, Vol. 5: The Pharmacology of Inflammation. I.L. Bonta, M.A. Bray and M.J. Parnham, eds., pp. 255–281, Elsevier, Amsterdam-New York-Oxford (1985).
4. J.M. McCord, *New Engl. J. Med.*, **312**, 159–163, (1985).
5. R. Hirschelmann and H. Bekemeier, Experientia **37**, 1313–1314, (1981).
6. D.R. Blake, N.D. Hall, P.A. Bacon, P.A. Dieppe, B. Halliwell and J.M.C. Gutteridge, *Ann. Rheum. Dis.*, **42**, 89–93, (1983).
7. A. Samuni, J. Aronovitch, D. Godinger, M. Chevion and G. Czapski, *Eur. J. Biochem.*, **137**, 119–124, (1983).
8. S. Zarnack, personal communication.

Accepted by Prof. H. Sies