In summary, following a single oral dose of DCA to laboratory rats, peak hepatic tissue DCA concentration occurred at 3 hr. When given chronically for 7 days, DCA caused activation of the pyruvate dehydrogenase complex which returned to basal activity 24 hr following the final dose. Hepatic tissue DCA concentrations were maximally increased at 3 hr following the final dose, and the drug was eliminated slowly over 72 hr with a half-life of 9.74 hr. Liver and muscle showed similar DCA tissue concentrations following chronic administration.

**Acknowledgements**—The author thanks Dr. Grant Wilkinson and Brenda McAllister for their assistance in determining DCA concentrations, Glenna Jarrett for technical assistance, and Barbara Page for preparing the manuscript. This project was supported in part by a grant from the Muscular Dystrophy Association.

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**Inhibition of carrageenin-induced rat footpad edema by systemic treatment with prostaglandins of the E series**

(Received 4 December 1981; accepted 25 March 1982)

One of the most widely used models for evaluation of anti-inflammatory agents is carrageenin-induced edema in the rat footpad [1]. This reaction consists of three distinct phases of mediator-induced vascular permeability changes. The initial phase, during the first 30 min after injection, results from the release of histamine and serotonin from host cells and is inhibited by anti-histamines [2]. The second phase, between 1 and 2.5 hr after injection, is attributed to the action of bradykinin since pretreatment of rats with histamine, serotonin, and bradykinin reduces edema. The third phase of persistent edema is complement-dependent and has been attributed to the local production of prostaglandins, especially of the E series, by inflammatory cells [3–6]. This phase of edema formation is inhibited by indomethacin and aspirin, and is potentiated by the local injection of vasodilatory prostaglandins such as PGE2 [7, 8]. However, additional studies suggest that stimulation of prostaglandin production may have inhibitory effects on carrageenin-induced edema [9]. Recent studies in our laboratory have shown that systemic treatment of rats with prostaglandins, especially of the E series, will inhibit vascular permeability changes induced by the vasoactive mediators histamine, serotonin, and bradykinin, compound 48/80 and the anaphylatoxin C3a [10]. In this report, we examine the effects of systemic prostaglandin treatment of rats with carrageenin-induced vascular permeability changes.

Carrageenin edema was induced by the intradermal injection of 0.1 ml of 1% carrageenin (viscariin 402) (Marine Colloids, Springfield, NJ), dissolved in phosphate-buffered saline (PBS), pH 7.4, into the hind paw of Sprague–Dawley rats weighing 200–250 g (Charles River Laboratories, Portage, MI). Separate groups of three to five rats were pretreated (subcutaneously) with prostaglandin 1 hr prior to carrageenin injection. Footpad thickness was measured at various times after carrageenin injection with a Mitutoyo micrometer. Prostaglandins (PGs) were provided by Dr. John Pike (Upjohn Co., Kalamazoo MI). Student's t-test (two tailed) was used to compare PG-treated animals with non-treated control animals.

The effect of systemic treatment of rats with 15-S-15-methyl PGE2 (15-M-PGE2) on carrageenin-induced footpad edema is shown in Fig. 1. When 15-M-PGE2 at a dose of 1 mg/kg was administered s.c. 1 hr prior to carrageenin injection, there was significant inhibition of rat footpad edema formation as compared to control values. Both the acute phase (47.1% inhibition at 1 hr, P < 0.001) of edema formation mediated by histamine, serotonin, and bradykinin and the later phase (61.0% inhibition at 6 hr, P < 0.001) which is inhibited by indomethacin and aspirin were reduced significantly. Inhibition of footpad edema formation by 15-M-PGE2 was dose dependent with significant inhibition (40.7% at 1 hr, P < 0.001 and 37.7% at 6 hr, P < 0.001) occurring at a dose of 0.2 mg/kg and only

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Fig. 1. Effect of systemic treatment of rats with 15-S-15-methyl PGE₁ on carrageenin-induced footpad edema. Groups of four rats received 15-M-PGE₁ at various doses s.c. 1 hr prior to injection of carrageenin into the rat footpad. Footpad thickness was measured at 1 hr intervals after carrageenin injection. The mean value for each group of four animals is shown ± the standard error of the mean. Key: (●) control; (△) 15-M-PGE₁, 0.04 mg/kg; (○) 15-M-PGE₁, 0.2 mg/kg; and (□) 15-M-PGE₁, 1 mg/kg.

slight inhibition of edema formation at a dose of 0.04 mg/kg.

The specificity of the inhibition of carrageenin-induced edema is shown in Fig. 2. When prostaglandins were administered 1 hr prior to carrageenin treatment at concentrations of 1 mg/kg, 15-M-PGE₁ showed the greatest inhibition of edema formation (see above) while PGE₁ (49.5% inhibition at 6 hr, P < 0.001) and PGE₂ (34.4% inhibition at 6 hr, P < 0.001) at the same concentration showed significant inhibition of only the later phase of edema formation. Treatment of rats with PGF₂α, a potent vasodilator [11], had no effect on carrageenin induced edema formation. The difference in activity between 15-M-PGE₁ and PGE₁ is most likely a result of the increased stability and resistance to hydrolysis by 15-hydroxy-prostaglandin dehydrogenase of the 15-methyl analog [12].

The time dependence of the inhibitory effect of 15-M-PGE₁ on edema formation is shown in Fig. 3. Significant inhibition of both the early and late phases of carrageenin-induced edema was observed when animals received carrageenin at 1 hr (see above) and 24 hr (99% inhibition at 1 hr, P < 0.001, and 41.3% inhibition at 6 hr, P < 0.001) after treatment with 15-M-PGE₁ (1 mg/kg, s.c.). However, when animals were challenged at 48 hr after 15-M-PGE₁ treatment, there was only minimal inhibition (12.6% inhibition at 6 hr) of edema formation.

The data presented here show that systemic treatment of animals with prostaglandins of the E series will inhibit carrageenin-induced edema in the rat footpad in both a dose- and time-dependent manner. In addition, the inhibitory effects of PGs on carrageenin-induced edema formation show at least partial specificity for PGs of the E series since PGF₂α had no effect.

Inhibition of the earlier phases of carrageenin-induced permeability changes by PGE₁ and PGE₂ is consistent with initial studies in which systemic treatment of rats with PGE₁ and PGE₂ inhibited edema formation induced by histamine, bradykinin, and serotonin [10] as well as other acute and chronic inflammatory reactions [4, 13–15]. The inhibition of edema formation at 3–6 hr after carrageenin treatment by PGE₁ and PGE₂ suggests that there are marked differences between the local and systemic effects of prostaglandins on acute inflammatory reactions. Several authors have shown that the local injection of prostaglandins of the E series will potentiate leakage of plasma proteins due to histamine, bradykinin, and carrageenin secondary to PGE-induced vasodilation [4, 7, 16–18]. However, the dose of locally administered PGE is frequently in the range of 1 μg, and it is unlikely that s.c. administration of 15-M-PGE₁ at 0.2 mg/kg or PGE₂ at 1.0 mg/kg resulted in comparable local concentrations 1 hr later. Therefore, the con-
Because of the anatomic location of epinephrine-forming neurons in rat brain, attention has been focused recently on their possible role in the central regulation of blood pressure [1-3]. The possibility that some antihypertensive drugs act by influencing epinephrine-forming neurons or receptors for these neurons in brain has also been suggested [2-5].

Recently, Beart et al. [6, 7] have reported that α-methylnorepinephrine and norepinephrine in brain

(Received 11 January 1982; accepted 13 April 1982)

Methylation of norepinephrine and α-methylnorepinephrine in brain

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