monstrated. D-*threo*-DOPS had no effect on the atrial rate and noradrenaline formation.

It has been reported that persistent blockade by α-MT of the synthesis of catecholamines may induce an adaptive change in their receptors thereby increasing sensitivity (Dominic & Moore, 1969; Moore & Dominic, 1971). If this is so, and assuming that the positive chronotropic effect is due to the noradrenaline formed from L-*threo*-DOPS by decarboxylase, the increase of atrial rate induced by L-*threo*-DOPS should be greater in atria from rats treated with α-MT. This was so with $20 \times 10^{-5}$ M L-*threo*-DOPS and atria from rats treated with α-MT (200 mg $kg^{-1}$, i.p.) compared with untreated rats. That is, supersensitivity to L-*threo*-DOPS as well as to exogenous noradrenaline was observed in atria after a single administration of α-MT.

The results suggest that L-*threo*-DOPS is converted by decarboxylase to noradrenaline in isolated atrium and this increases the atrial rate.

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# Mannitol and delayed hypersensitivity in the rat

J. P. TARAYRE*, P. VILAIN, H. LAURESSERGUES, *Department of Pharmacology, P. Fabre Research Centre, 17, avenue J. Moulin, 81100 Castres, France*

In therapeutics, mannitol, after intravenous administration, is used as an osmotic diuretic (Mudge, 1975) and also to reduce certain cases of cerebral oedema (Krayenbühl & Bühlmann, 1963; Lazorthes & Campan, 1972). It may also be used pharmaceutically as an excipient. We describe here its action when it has been administered for long periods in inflammatory models where delayed hypersensitivity plays an important role.

The experiments were on Sprague Dawley male rats. Mannitol was always injected at a dose of 23 mg $kg^{-1}$ subcutaneously. Control animals received, 0·9% NaCl by the same route.

Mannitol was first studied on polyarthritis produced by Freund's adjuvant (Table 1). The treatment was started on the 10th day of the reaction and was continued for 28 days. While the volume of the injected paw was not significantly modified, mannitol reduced inflammation in the non-injected hind paw and the involvement of other organs affected by secondary arthritis (fore paws, ears, tail and penis) was also reduced significantly. The weight changes were improved by treatment compared with arthritic controls. Furthermore, autopsy revealed restoration of the weight of the thymus and of the adrenal glands.

Mannitol was used in animals with pleurisy due to *Bordetella pertussis* (Dieppe, Willoughby & others, 1976). The technique was described (Tarayre, Delhon & Lauressergues, 1977). The results obtained after chronic treatment, starting 3 weeks before sensitization, are presented in Table 2. Mannitol significantly reduced the volume of the inflammatory exudate. The various white cell counts remained unchanged.

After single and chronic administration, mannitol did not modify acute inflammation induced by carrageenan in the paw and pleural cavity of the rat. After repeated injections, it did not reduce the increase in capillary permeability induced by histamine.

In the doses used subcutaneously, the action of

* Correspondence.

Table 1. *Action of mannitol on Freund's adjuvant polyarthritis.* Polyarthritis was induced by the injection of 0·6 mg *Mycobacterium butyricum* suspended in paraffin oil in the hind paw. The treatment started on the 10th day and continued to the 28th day when the rats were killed to examine thymus and adrenals. (I) Weight gain at +26 days (g). (II) Decrease of volume of uninjected hind paws at +24 days. (III) Thymus weight (mg), weight/100 g rat. (IV) Adrenals weight (mg), weight/100 g rat. Means are followed by the standard error.

| Groups | I | II | III | IV |
|---|---|---|---|---|
| Controls without arthritis | +117 ± 8 (n = 6) | — | 201 ± 23 | 16·3 ± 1·4 |
| Controls with arthritis | +36 ± 4 (n = 12) | — | 161 ± 13 | 28·4 ± 1·8 |
| Mannitol (23 mg kg$^{-1}$ day$^{-1}$) | +57 ± 4 ** (n = 12) | −40% * | 215 ± 11 ** | 19·2 ± 0·8 ** |

* $P$ <0·05 ** $P$ <0·01 compared with controls with untreated arthritis.

Table 2. *Action of mannitol on* B. pertussis *pleurisy.* Rats were sensitized by the injection of a 0·2 ml mixture (vol.: 50/50) of *B. pertussis* suspension (Institut Pasteur) + Complete Freund's adjuvant (Difco) into the dorsal side of the right fore paw and the right hind paw. After 12 days, 0·1 ml of the *B. pertussis* suspension was injected into the pleural cavity of the rats. 48 h later, the pleural exudate was collected, leucocytes were counted, and percentages of mononuclear and polynuclear leucocytes determined. Animals were treated 5 times a week during the 3 weeks before sensitization. Between the latter and the challenge, mannitol was given every day. The last injection of the compound was given 24 h after the challenge injection.

| Groups/Dose | Decrease in pleural exudate at +48 h | Decrease in leucocyte count | Percentage of leucocytes: Mononuclear | Percentage of leucocytes: Polynuclear |
|---|---|---|---|---|
| Controls — | — | — | 58 ± 1 (20) | 42 ± 1 (20) |
| Mannitol (23 mg kg$^{-1}$ day$^{-1}$) | −35%* | −17% | 59 ± 2 (19) | 41 ± 2 (19) |

$P$ <0·05 compared with controls.

mannitol does not appear directly linked to an osmotic effect as occurs during clinical use by intravenous injection. If this were so, its anti-inflammatory effect would be general. This is furthermore confirmed by the absence of effect on the hematocrit of the drug after various periods of treatment and on the concentrations of plasma proteins, plasma sodium, diuresis during saline overload and systolic blood pressure. Mannitol moreover is lacking in irritant properties which might cause a non-specific anti-inflammatory effect.

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