Interaction of *beta* Adrenergic Blockade and Certain Vasodilators in Dextran-Induced Rat Paw Edema. (30813)

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Epinephrine is a potent antagonist of the pedal edema induced in rats by subplantar injection of dextran(1). Conceivably this could be due to one or more of several known, discrete actions of epinephrine: (*a*) vasoconstriction, (*b*) vasodilation, or (*c*) effects on certain "metabolic" processes such as glycogenolysis and lipolysis. The vasoconstrictor action of epinephrine is believed to be mediated *via* the hypothetical *alpha* adrenergic receptors(2), while the vasodilator and metabolic effects are most probably a result of *beta* adrenergic receptor stimulation although species differences appear to exist(3).

Larsen and Lish(4) recently described the synthesis and *beta* adrenergic blocking activity of a series of phenethanolamines containing alkyl sulfonamide groups on the benzene ring. Three additional reports(3,5,6) further describe the pharmacologic and toxicologic properties of two compounds, MJ 1998* and MJ 1999,† in that series. In particular, Kvam *et al*(3) reported on the effects of these *beta* receptor blocking agents on certain metabolic responses to catecholamines. For example, in the intact rat the compounds blocked epinephrine-induced hyperglycemia, but did not alter the elevation of plasma free fatty acids (FFA) induced by either epinephrine, norepinephrine, or isoproterenol. However, both MJ 1998 and MJ 1999 could inhibit catecholamine-induced FFA release in isolated rat adipose tissue. On the other hand the *beta* blocking agents antagonized both the hyperglycemia and the increases in plasma FFA in the intact dog.

Since epinephrine effectively inhibits dextran-induced rat paw edema(1), it was of interest to determine whether *beta* adrenergic blockade could antagonize this action of epinephrine, and if so, whether it similarly affected "non-adrenergic" vasodilators.

Methods. Adult Wistar rats of either sex and weighing 140-160 g each were divided randomly into groups of 10 each. Certain groups received MJ 1999 orally one hour before a subcutaneous injection of epinephrine (as *l*-adrenaline, Eastman Kodak #3097). Others received only epinephrine. Fifteen minutes following the epinephrine injection all rats received subplantar injections of 0.1 ml of 6% dextran in physiological saline in the right hind paw, and 0.1 ml of saline contralaterally. One hour later the mean % of increase in edema of the dextran- over the saline-injected paws in each group was determined plethysmographically by mercury displacement(7).

The interactions of MJ 1999 and isoxsuprine or hydralazine were similarly examined. Also the effect of the *alpha* blocking drug, phentolamine, on inhibition by epinephrine was tested.

Results. The data in Table I indicate that MJ 1999 can antagonize the inhibition of dextran-induced edema of the rat paw by epinephrine. The degree of effect of the *beta* adrenergic blocking agent is dose-dependent and approaches completeness when used with a submaximal dose of epinephrine. With the 2 lower doses of subcutaneous epinephrine the presence of 100 times as much MJ 1999, given orally on a weight basis, prevented essentially all of the inhibition. However, with epinephrine doses of 0.1-1.0 mg/kg complete antagonism of their effects by MJ 1999 was not attained.

The antidextran action of the 2 vasodilators, isoxsuprine and hydralazine, was less clearly affected by MJ 1999 (Table II). Each of these 2 agents was less effective than epinephrine as an inhibitor of dextran-induced edema. Maximal inhibition of edema provided by isoxsuprine and hydralazine was 56% and 40%, respectively, while that produced by epinephrine might be as much as

* MJ 1998 = 4-(2-methylamino-1-hydroxypropyl) methanesulfonanilide HCl.

† MJ 1999 = 4-(2-isopropylamino-1-hydroxypropyl)methanesulfonanilde HCl.

TABLE I. Effects of Epinephrine and MJ 1999 on Dextran-Induced Edema in the Rat Paw.

Dose MJ 1999,* mg/kg p.o.	Edema response: Epinephrine dose, mg/kg, s.c.† 0 Mean‡ ± S.E.	.01 Mean ± S.E.	.01 % I‖	.032 Mean ± S.E.	.032 % I	.10 Mean ± S.E.	.10 % I	.32 Mean ± S.E.	.32 % I	1.0 Mean ± S.E.	1.0 % I
0	71.8 ± 1.01 (155)§	60.8 ± 3.00 (40)	15.3	45.9 ± 2.43 (20)	36.1	35.0 ± 1.98 (62)	51.3	19.7 ± 1.56 (20)	72.6	14.6 ± .86 (30)	79.7
1.0	78.6 ± 2.40 (30)	69.6 ± 3.08 (20)	3.1	45.9 ± 4.64 (10)	36.1	41.4 ± 3.01 (20)	42.3	47.4 ± 3.30 (20)	34.0	20.4 ± 2.16 (10)	71.6
3.2	79.3 ± 4.89 (20)			67.3 ± 2.83 (10)	6.3	52.4 ± 2.74 (10)	27.0	46.2 ± 3.89 (10)	35.7	28.1 ± 2.03 (10)	60.9
10.0	72.1 ± 1.43 (40)					55.2 ± 3.93 (10)	23.1	55.7 ± 3.40 (10)	22.4	31.0 ± 2.74 (10)	56.8

* Given as a suspension in 0.5% methocel 75 min prior to dextran.
† Given in 0.9% saline 15 min prior to dextran.
‡ Mean % increase in volume of dextran-injected paw *vs* saline-paw 60 min following subplantar dextran.
§ No. in parentheses = No. of rats in respective treatment group.
‖ % Inhibition = [1-(treated ÷ control response of 71.8)] × 100.

80%. MJ 1999 (10 mg/kg) prevented about one-half of the inhibition by isoxsuprine and about one-third of that provided by the higher dose of hydralazine. However, MJ 1999 did not affect the inhibition produced by the lower dose (5 mg/kg) of hydralazine.

Phentolamine, an *alpha* blocking agent, at a dose of 1 mg/kg was without effect on epinephrine inhibition by doses of 0.032 and 0.1 mg/kg of the catecholamine (Table II).

Discussion. That 3 "vasodilators" having differing mechanisms of action should antagonize dextran edema would suggest that vasodilation, rather than some adrenergically triggered metabolic event, was the property responsible for the common antiedemic effect. Under the conditions of these experiments much, if not all, of the inhibition of dextran-induced edema of the rat paw effected by epinephrine could be overcome by pretreatment of the rats with the potent *beta* adrenergic blocking agent, MJ 1999. The extent of the blockade was related, to a large degree, to the proportion of each amine. The specificity of the *beta* stimulating activity of epinephrine in this anti-inflammatory effect on dextran edema is seen by the lack of effect of phentolamine, an *alpha* blocking agent, on inhibition by epinephrine. This result is not totally consistent with work reported by Spector and Willoughby(8) who demonstrated reversal of the anti-inflammatory effect of iproniazid by concomitant administration of dibenamine, another *alpha* blocking agent, in thermal injury in rats. The inconsistency might be at least partially explained by the fact that Spector and Willoughby's work involved endogenous catecholamines, whereas this present study employed exogenous epinephrine.

The incomplete block by MJ 1999 of inhibition by either isoxsuprine or hydralazine is of interest in view of the possible mechanisms of their vasodilator actions. In this laboratory Drinnon and Yelnosky(9) have demonstrated that the vasodilator action of isoxsuprine does not depend primarily on *beta* stimulation. Similarly, it is felt that the vasodilator effect of hydralazine is largely mediated by a non-adrenergic action on vascular smooth muscle(10), with only minimal direct

TABLE II. Effects of MJ 1999 and Certain Vasoactive Amines on Dextran-Induced Edema of Rat Paw.

Treatment (mg/kg) s.c.*				Edema response†			
				Treatment B alone		Treatment A + B	
A‡		B§		Mean % increase ± S.E.†	% Inhibition‖	Mean % increase ± S.E.†	% Inhibition‖
phentolamine	(1)¶			75.5 ± 2.4¶ (20)††	(+5.2)		
"	(1)	epinephrine	(.032)	45.2 ± 3.9	37.1	44.3 ± 3.6	38.3
"	(1)	"	(.10)	33.1 ± 2.0	53.9	30.6 ± 3.0 (20)	57.4
MJ 1999	(10) orally**	isoxsuprine	(25)	31.7 ± 2.7	55.9	55.3 ± 3.6	22.9
"	(10) "	"	(100)	35.2 ± 6.9	51.0	57.1 ± 4.0	20.5
MJ 1999	(10) orally	hydralazine	(5)	53.5 ± 2.9 (20)	25.5	51.8 ± 3.6	27.9
"	(10) "	"	(20)	43.4 ± 3.6	39.6	63.2 ± 3.0	12.0

* All treatments were subcutaneous, except MJ 1999 (footnote **).
† Mean % increase of dextran-injected paws over saline-injected paws, 60 min following dextran ± standard error of mean.
‡ All A treatments given 75 min prior to dextran.
§ All B treatments given 15 min prior to dextran.
‖ [1-(treated response ÷ control response of 71.8) (Table I)] × 100.
¶ This group treated only with phentolamine 75 min prior to dextran.
** MJ 1999 given orally.
†† (#) = number of rats in respective group; # = 10 when not indicated.

stimulation of adrenergic β-receptors(11). The greater effect of MJ 1999 on isoxsuprine as compared to hydralazine is consistent with the greater *beta* receptor stimulating capacity of isoxsuprine. Of course, since the role of vasodilation in anti-inflammatory action is not clear, one cannot disregard the possibility that these two drugs exert an antidextran effect independent of their vasodilator properties. However, such an agent as MJ 1999 provides a tool for possibly more elaborate studies designed to study the role of both endogenous and exogenous biologically-active amines in pertinent physiopathologic mechanisms.

Summary. The antagonism by a potent *beta* adrenergic blocking agent, MJ 1999, of the inhibition of dextran-induced rat paw edema by epinephrine was demonstrated. MJ 1999 did not antagonize the inhibition by either isoxsuprine or hydralazine as effectively as that by epinephrine. The importance of the *beta* receptor stimulating component in epinephrine inhibition was further seen by the lack of antagonism by phentolamine, an *alpha* blocking agent.

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