INHIBITION OF HYPERSENSITIVITY OF DELAYED AND IMMEDIATE TYPES IN GUINEA PIGS BY METHYLENEDIPHOSPHONIC ACID

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The effect of subcutaneous injection of the immunosuppressive agent methylenediphosphonic acid (MDPA) on hypersensitivity of delayed and immediate types (HDT and HIT) was studied in guinea pigs. Administration of MDPA to the animals in a dose of 30 μg/g was found to inhibit HDT and HIT by 60-80% compared with the control.

KEY WORDS: *immunosuppression; hypersensitivity; methylenediphosphonic acid.*

The search for effective immunosuppressant agents of low toxicity with the aim of controlling the immune response deliberately is an important problem in experimental and clinical immunology. The writers showed previously [1] that methylenediphosphonic acid (MDPA), a structural analog of pyrophosphate, considerably inhibits the formation of antibody-secreting cells as detected by the method of Jerne and Nordin [5] in response to immunization of BALB/c and CC57W mice with sheep's red cells. This action can evidently be explained by the inhibitory effect of MDPA on the enzyme systems of the body which act as sources of energy or of substrates for protein biosynthesis, and in which inorganic pyrophosphate plays a part [2, 3].

In this investigation the action of MDPA on cellular immunity was studied with the aid of one model of the reaction of hypersensitivity of delayed type (HDT) [4].

EXPERIMENTAL METHOD

Experiments were carried out on noninbred male guinea pigs weighing 350-400 g. The animals were sensitized with a lysate of sheep's red cells in Freund's complete adjuvant (Difco). They were sensitized by injection of 0.1 ml of a mixture of equal volumes of Freund's complete adjuvant and lysate of sheep's red cells into the footpads of all four limbs in a dose of 40 μg protein per animal. The reacting dose of lysate (40 μg) was injected intradermally in 0.1 ml of physiological saline 10 days after sensitization. The intensity of the reactions was judged by two indices: the area of infiltration and the thickness of the skin fold at the site of the intradermal injection. By multiplying these two indices, the skin reaction could be quantified in conventional units. The volume of infiltration 4 h after injection of the reacting dose served as the index for the reaction of hypersensitivity of immediate type (HIT) and the volume of infiltration after 24 h minus the volume after 4 h as the index of HDT. Animals receiving an injection of physiological saline instead of the sensitizing dose or the reacting dose served as the control. In both cases HDT and HIT were negative. The third, basic control was the animals of series I, for which the values of HDT and HIT were taken as 100%. The experimental series II, III, IV, and V differed from series I in that the guinea pigs received subcutaneous injections of a 0.5% solution of MDPA at different times (depending on the scheme, in a dose of 30 μg of the

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TABLE 1. Effect of MDPA on Hypersensitivity of Delayed and Immediate Types in Guinea Pigs (in conventional units)

Type of reaction	Index	Series of experiments				
		I	II	III	IV	V
HDT	$M \pm m$	686±116	209±34	217±41	116±25	215±55
	n	15	13	15	10	10
	%	100	30,5	31,6	16,9	31,3
	P	—	<0,001	<0,001	<0,001	<0,001
HIT	$M \pm m$	199±39	162±23	74±27	48±15	102±23
	n	15	13	15	10	10
	%	100	81,4	37,0	24,0	51,0
	P	—	<0,5	<0,01	<0,001	<0,1

compound per gram body weight. In series II the animals received MDPA 8, 7, and 6 days before sensitization; in series III 8, 7, and 6 days before and also 2 and 3 days after sensitization; in series IV 2, 3, and 4 days after sensitization, and series V 1 day before, on the day of, and 1 day after sensitization.

EXPERIMENTAL RESULTS

The experimental results, given in Table 1, show that injection of MDPA into the animals considerably and significantly inhibited the development of HDT and also, to a lesser degree, of HIT. The action of MDPA was most effective when given between the sensitizing and reacting doses of the antigen. The HDT reaction is known to be an inflammatory reaction based on interaction between sensitized lymphocytes and the corresponding antigen, which develops relatively slowly. The development of HDP in time was compared in the control and experimental series. The inhibitory action of MDPA had virtually no effect on the dynamics of the hypersensitivity reactions.

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