Treatment of adjuvant arthritis in rats with the histidine decarboxylase inhibitor hypostamine

Many reports suggest a significant role for histamine in inflammatory and allergic diseases. Again, factors such as the so-called adjuvants, can enhance hypersensitivity states and inflammatory changes in some species of animals; such a factor was also found to increase histidine decarboxylase activity (Schayer & Ganley, 1961).

The widely used model of animal pathology, resembling in some respects human rheumatoid disease, is adjuvant arthritis in rats. This is characterized by disseminated inflammatory lesions of joints and skin of the animals.

The aim of the present work was to investigate the influence of the histidine decarboxylase inhibitor, hypostamine (Trioqualine) (Parrot & Laborde, 1959) on the course of adjuvant arthritis in rats. Additional experiments were also made to test inhibitory activity of hypostamine on histidine decarboxylase in rats.

The experiments were made on 3-month old rats of either sex, of inbred August strain and of randomly bred Wistar rats. The animals were injected with lyophillized tubercle bacilli of $H_{37}Rv$ strain suspended in liquid paraffin into the plantar surface of hind paw in amount of 0·5 mg bacilli per animal. Hypostamine, in daily doses of 250 mg/kg weight, was administered, orally, beginning 8 days after adjuvant injection to the 30th day of the experiment. The animals of control groups were treated with the suspensoid, i.e. 1·25% methylcellulose. Each group of animals consisted of 8 rats.

Immediately after the injection of adjuvant, transitory swelling of the paw was observed; the secondary symptoms of polyarthritis and skin lesions appeared after a latent period of 14–25 days in control Wistar rats and after 12–20 days in both control and hypostamine-treated August rats. The intensity of the disease was then evaluated by scoring according to a conventional 18 point pattern (Giełdanowski, Pelczarska & others, 1969).

The results of 36 days observation of Wistar adjuvant rats are shown in Fig. 1.

The information obtained from experiments on August rats is not reproduced graphically because the results were almost identical in both control and hypostamine-treated animals.

To test inhibitory properties of hypostamine on histidine decarboxylase activity in rats, examinations with liver as a source of the enzyme, were made (Telford &

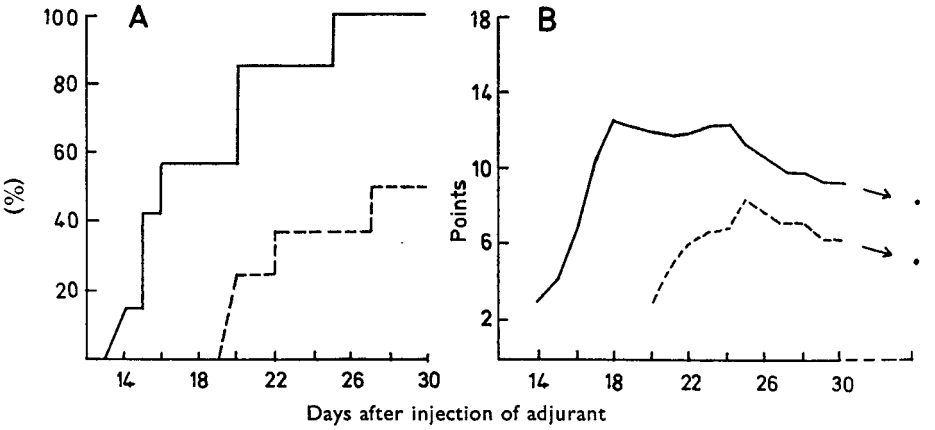

FIG. 1. A. Morbidity rate (%) in Wistar rats.

B. Intensity of symptoms. Average count of points (Giełdanowski & others, 1969) in animals affected with polyarthritis. ——— Control - - - - - Hypostamine-treated rats.

West, 1961). Food was withheld from male and female 3 month-old rats of the previously mentioned strains for 12 h. Next day one group of August rats and one group of Wistar rats were treated orally with a single dose of 250 mg/kg weight of hypostamine. The other two groups of animals were the controls. The animals were killed 3 h later and the livers were excised, cleaned, weighed, cut into small pieces and ground in a mortar with sand and Tyrode solution. The L-histidine zwitterion was prepared from commercial L-histidine monohydrochloride (Fluka) (Mackay & Shepherd, 1960).

Mixtures of supernatant of liver homogenate (800 mg/4 ml), L-histidine zwitterion (15 mg/1 ml) and phosphate buffer pH 8 (5·0 ml) with 1 drop of benzene were incubated for 3 h at 37°. The reaction was then stopped by reducing the pH of the solution to 4·0 with N HCl, and boiling for 3 min. After neutralizing the mixtures with N NaOH, their histamine content was measured on the guinea-pig ileum. Control mixtures containing no homogenate or no histidine were similarly treated and assayed.

The results are in Table 1.

As it has been shown in Fig. 1 hypostamine when administered in Wistar rats had a favourable effect upon the syndromes of adjuvant arthritis. On the contrary, in August rats no therapeutic effect of the drug was observed. These observations were supported by findings that hypostamine inhibited liver histidine decarboxylase in Wistar rats whereas this was not so with August rats.

It seems that genetic differences condition different mechanisms of action of the drug in the two strains of animal.

Table 1. *Influence of hypostamine on histidine decarboxylase activity*

Sex	Wistar					August	
	Control	Hypostamine	Inhibition (%)	t*	P*	Control	Hypostamine
Female ..	3·25 ±0·50	1·75 ±0·54	46·2	5·03	0·001	4·50 ±0·71	4·50 ±0·82
Male ..	3·25 ±0·50	2·12 ±0·25	34·8	5·65	<0·001	3·06 ±0·52	3·12 ±0·43

The histidine decarboxylase activity expressed as μg histamine formed per g tissue per 3 h.

* Data of statistical analysis according to Student's t test.

This evidence also draws attention to the question whether genetically defined, inbred strains of animals are a better choice for pharmacological investigations.

In my opinion, since inbred strains are not common under natural conditions, they are less useful for pharmacodynamic studies than randomly bred, or intentionally "not inbred" animals.

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