The effect of indomethacin on carrageenan pleurisy in inbred strains of rats

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Rat carrageenan pleurisy is a widely used model of acute inflammatory reaction which enables the comparative investigations of exudate formation and cell emigration. There is, however, controversy over the results obtained (Di Rosa, 1974; Vinegar, 1974). With the discrepancy in results in mind we set out to study the exudate formation and cellular sequence of events following intrapleural injection of carrageenan in Lewis and AVN inbred strains of rats. In our previous work both strains showed genetically determined opposite sensitivity for adjuvant-induced arthritis (Zídek & Perlík, 1971; Perlík & Zídek, 1973). In addition the efficacy of indomethacin to inhibit rat carrageenan pleurisy was tested.

Carrageenan pleurisy was induced in male Lewis and AVN inbred rats, 200–250 g, by intrapleural injection of 0·15 ml of 1·0 % carrageenan (Viscarin Marine Colloids) in saline. The animals were killed at intervals after the injection, pleural exudates collected, measured and total and differential cell counts were made. A single dose of indomethacin (5·0 or 10·0 mg kg^{-1}) was administered orally 30 min before intrapleural injection. Generally there were 6 rats in each group.

Fig. 1 shows changes in the volume of pleural exudate at 5 and 15 h after carrageenan injection. As can be seen, in the control group there was no substantial difference in exudate volume at both time intervals with the AVN strain. However, with the Lewis strain the exudate formation was markely increased at 15 h. Indomethacin at 5·0 and 10 mg kg^{-1} did not significantly change the exudate volume in the AVN strain whereas both doses

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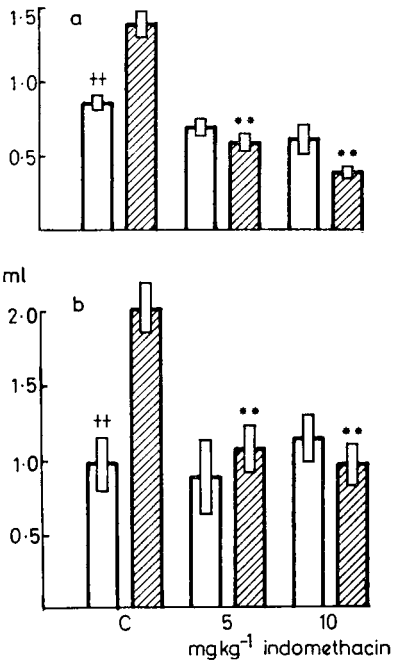

FIG. 1. Effect of indomethacin on carrageenan pleurisy (ml) in AVN (open columns) and Lewis (hatched columns) inbred strain of rats, a—after 5 h, b—after 15 h. Indomethacin was given 30 min before the intrapleural injection of 0·15 ml of 1·0% carrageenan in saline. Each group consists of 6 animals (mean ± s.e.m.) C—control., †† $P < 0.01$ significance between the strains. ** $P < 0.01$ significance of the indomethacin treatment versus control.

Table 1. *Effect of indomethacin on the cell counts in carrageenan pleurisy in AVN and Lewis inbred strain of rats.*

	Controls		Indomethacin 5 mg kg^{-1}		Indomethacin 10 mg kg^{-1}	
	AVN	Lewis	AVN	Lewis	AVN	Lewis
			5 h			
Neutrophils	100·4 ± 8·9†	145·3 ± 14·9	91·5 ± 12·9	80·3 ± 9·3**	67·7 ± 14·0	74·2 ± 5·4**
Lymphocytes	11·3 ± 1·3†	25·4 ± 5·7	13·9 ± 3·2	8·9 ± 1·9*	14·2 ± 3·7	9·2 ± 1·0*
Macrophages	7·2 ± 0·9††	14·7 ± 2·0	5·0 ± 0·9†	8·2 ± 1·1*	6·4 ± 1·4	8·7 ± 1·5*
Epithelial cells	7·1 ± 2·1	9·5 ± 1·8	6·1 ± 1·7	4·7 ± 1·0*	3·6 ± 0·9	4·5 ± 0·5*
Total cells	126·0 ± 10·7†	194·9 ± 15·0	116·5 ± 17·7	102·1 ± 11·4**	91·9 ± 18·7	96·6 ± 6·5**
			15 h			
Neutrophils	53·1 ± 7·5†	91·3 ± 13·5	57·3 ± 16·0	53·9 ± 12·1	47·0 ± 9·8	44·4 ± 5·6**
Lymphocytes	26·1 ± 2·2††	49·3 ± 4·5	30·1 ± 7·8	32·8 ± 8·9	25·0 ± 4·2	23·7 ± 3·4**
Macrophages	6·0 ± 1·6	11·1 ± 2·5	10·8 ± 4·0	9·7 ± 1·8	6·0 ± 1·3	7·7 ± 1·5
Epithelial cells	5·6 ± 1·2	6·3 ± 1·2	5·4 ± 2·6	3·4 ± 1·4	3·2 ± 0·6	5·1 ± 1·1
Total cells	90·8 ± 10·9††	158·0 ± 14·9	103·6 ± 29·6	99·8 ± 22·8	81·2 ± 15·1	80·9 ± 9·6**

Indomethacin was given 30 min before the intrapleural injection of 0·15 ml of 1·0% carrageenan in saline. Figures are mean number of cells ($\times 10^6$) calculated per single rat ±s.e.m. Each group consists of 6 animals.
† $P < 0.05$; †† $P < 0.01$ significance between the strains.
* $P < 0.05$; ** $P < 0.01$ significance of the indomethacin treatment versus control.

markedly decreased the formation of exudate in the Lewis strain at both times.

Table 1 summarizes the changes in the cell counts of the pleural exudate. In control animals the total number of cells at 5 h was greater than at 15 h. Differential cell counts showed that neutrophils were the predominant cells in both strains and at both times. However, after 15 h, the proportion of neutrophils to lymphocytes decreased in comparison with that at 5 h.

As with exudate formation, treatment with indomethacin decreased the cell number only in Lewis rats. This was still evident at 15 h after the 10 mg kg^{-1} dose.

The present results showed that in carrageenan pleurisy also there was a marked difference between strains in their sensitivity. This might partly explain the discrepancies in the results of different authors. The rats of the AVN strain appear to be much more resistant in this experimental model as was shown in our work with adjuvant-induced arthritis (Perlík & Zídek, 1973). Greater mobilization of the inflammatory cells in the Lewis strain may amplify and prolong the inflammation of this strain.

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On the relation between hypodipsia and anorexia induced by (+)-amphetamine in the mouse

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(+)-Amphetamine inhibits drinking when water is offered to thirsty rats which are nevertheless offered unrestricted access to food (Soulairac & Soulairac, 1970). However, its effect on the water intake of rats whose food is taken away immediately before water is given is less clear. Glick & Greenstein (1973) have reported that it fails to influence the water intake of such animals, whereas Nielsen & Lyon (1973) found that the presence or absence of food has little effect on the hypodipsic action of (+)-amphetamine in thirsty rats.

We have investigated the acute effects of (+)-amphetamine on drinking in water deprived mice because of the extensive use of mice in the screening of drugs for anorectic properties (Friedman, Weingarten & Janowitz, 1962; Clark, 1969), and because it would be useful to ascertain to what extent, if any, the anorexia produced by a drug such as (+)-amphetamine is secondary to hypodipsia or vice-versa.

Male albino mice, 20–25 g, of the CFLP-ICI strain 1, bred in our laboratories were caged in groups of 8 and housed at 25 ± 1°. They were fed on a conventional 41B cube diet (Spilsburys, Birmingham) and tap water was made available from standard feeder bottles with the nozzles all the same height (3 cm) above the floor of the cage.

Assessment of hypodipsic activity. The mice were deprived of water but not food for the 21 h, extending from 17.00 h till 14.00 h the following day when they were again allowed access to water. The effect of drugs on the total amount of water consumed by each group of 8 mice between 14.00 h and 15.00 h while having free access to food was then determined and expressed as a volume (ml) per unit body weight (kg), the mean water intake from 6 such groups being finally obtained. This was then compared with that obtained in a similar manner in mice treated with a saline control. The significance of any observed difference between the means of test and control groups in these and all subsequent experiments was determined by Student's *t*-test.

In a second set of experiments mice were similarly deprived of water, but their food was removed immediately before replacement of the supply of water. The effect of drugs on water intake in the absence of food between 14.00 h and 15.00 h was then determined and compared with that of a saline control.

The water intake measured over 1 h immediately following water deprivation was found to be 66·36 ± 3·74 ml kg^{-1} (group mean ± s.e.; n = 6) with food

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