suffice, by itself, for a chlorpromazine-like central action[8].

L. DECSI and J. MÉHES

Institute of Pharmacology, Medical University, Pécs (Hungary), January 1, 1958.

Zusammenfassung

Die Tranquilizer Miltown (Meprobamat) und Benactyzin beeinflussen den Gehirnzellstoffwechsel *in vitro* qualitativ wie Largactil, das heisst, sie hemmen die oxydative Phosphorylierung und gleichzeitig auch die ATPase-Aktivität. Demgegenüber hemmt das bloss über eine sedative Wirkung verfügende Captodiamin (Covatin) nur die oxydative Phosphorylierung und lässt die ATPase-Aktivität unbeeinflusst. Dies spricht dafür, dass zur Auslösung einer largactilartigen Wirkung beide oberen Hemmungsprozesse notwendig sind.

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Inhibitory Action of Trypsin and Trypsin-Inhibitors on Experimental Inflammation in Rats

Parenterally administered trypsin appears to possess important anti-inflammatory action in animal experiments[1] and in clinical therapy[2]. However, much confusion seems to exist in our knowledge of the mechanism of its action and many facts point to the possibility that this action might be rather an indirect one. We have attempted to bring some light into this problem.

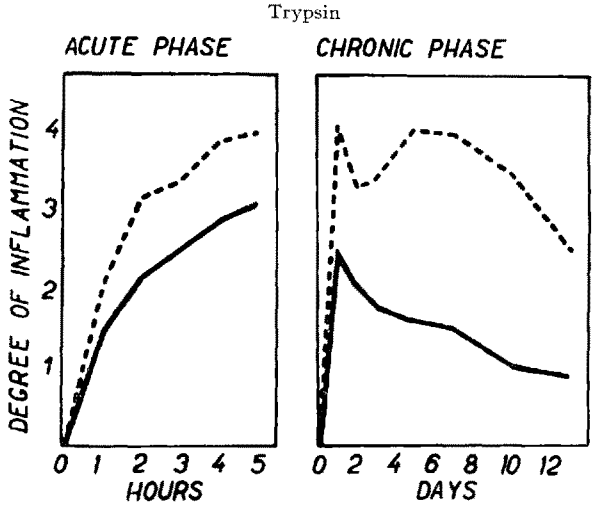

Fig. 1. – Anti-inflammatory action of intramuscular trypsin on kaolin-induced inflammation in rats. Both lines are mean values of responses in 10 animals. (Broken line: control).

To accomplish this, we reinvestigated first the anti-inflammatory action of a suspension of trypsin in oil applied intramuscularly in doses of 20 mg/kg to rats. The first injection was given 2 h before the induction of inflammation and the others followed every third day, 6 injections being given in all. The experimental inflammation was induced by subaponeural injection of 10% sterile kaolin suspension into the hind paw[3]. The evaluation of inflammation was based on the measurement of differences in the volume of the paw, differences in the diameter of the metatarsophalangeal joint and differences in abscess formation[4] (Fig. 1).

Trypsin revealed a statistically significant antiphlogistic influence in the acute phase of inflammation 5 h after administration of kaolin. Trypsin inhibited even more significantly the chronic phase of inflammation characterized by abscess formation which lasts more than a week.

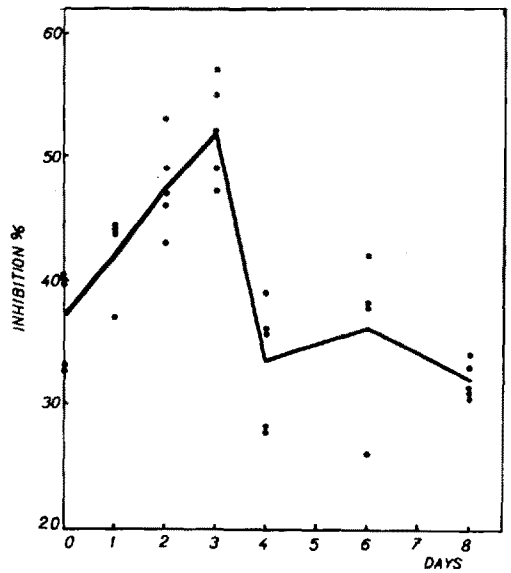

Fig. 2. – Plasmatic trypsin-inhibitory activity after intramuscular application of trypsin.

Subsequently we have tested the influence of parenteral trypsin on trypsin-inhibitory activity of rat serum in an attempt to confirm the experiments of GROB[5]. The degree of inhibition was expressed in percent of the trypsin activity after incubation with serum (Fig. 2). Trypsin suspension was applied in one dose (0·5 mg/kg) which is nearly in the range of clinical dosage. We noted, even after this low dose, a significant increase in the trypsin-inhibitors, the maximum being attained on the third day approximately. The original level of inhibitors was then quickly restored.

Evidence from this experiment led us to adopt a concept that the inhibitors of trypsin could provide for the mediation of the anti-inflammatory action of trypsin. Endogenous trypsin could furthermore participate in the defensive reaction of the organism against the proteolytic enzymes activated during the inflammation. These enzymes might be responsible for the greater part of basic elements of inflammation releasing locally active products

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[5] D. GROB, J. Gen. Physiol. *26*, 405 (1943).

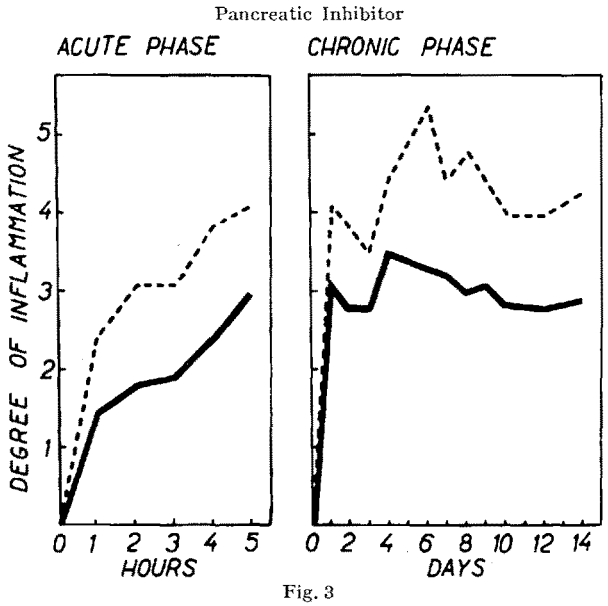

Fig. 3

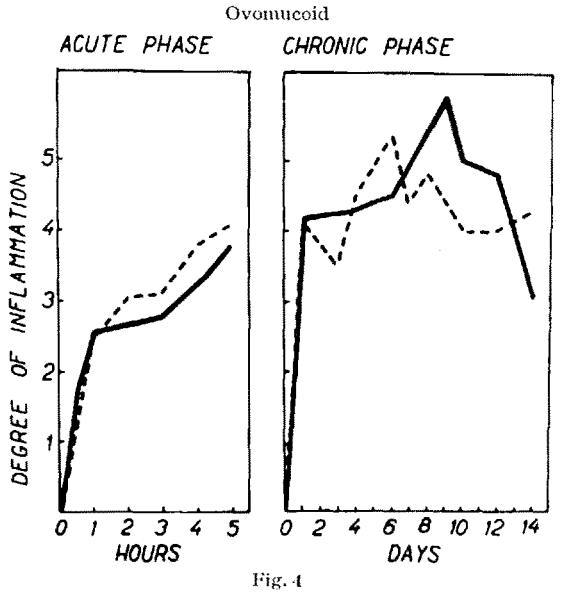

Fig. 4

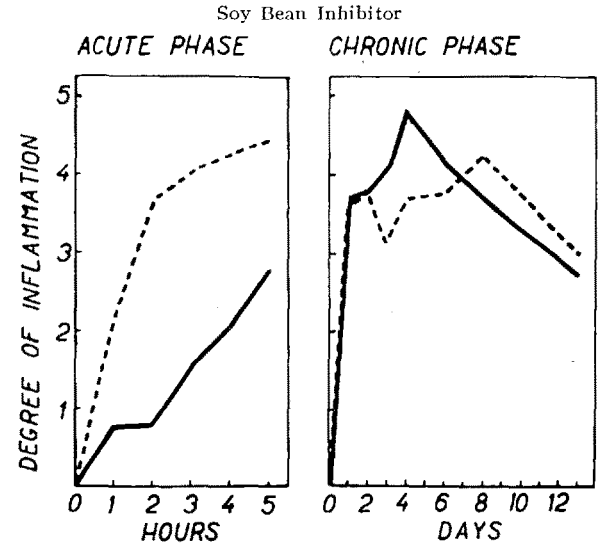

Fig. 5

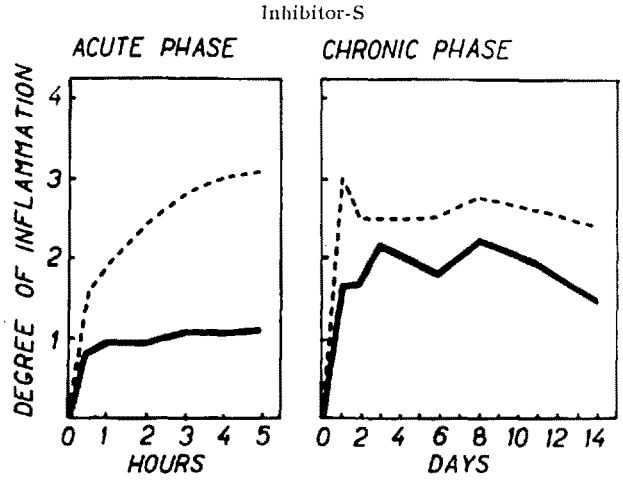

Fig. 6

Fig. 3, 4, 5, 6. – Anti-inflammatory action of trypsin-inhibitors on kaolin-induced inflammation in rats. Both lines are mean values of responses in 10 animals (broken line: control).

of protein breakdown, e.g. leucotaxin[6], bradykinin[7], pain-producing substance[8].

This concept was greatly substanciated by our experiments proving strong antiphlogistic action of several naturally occuring trypsin-inhibitors (Fig. 3, 4, 5, 6).

The inhibitors (pancreatic trypsin-inhibitor, soya bean trypsin inhibitor, inhibitor S and ovomucoid) were applied in 6 intraperitoneal injections (50 mg/kg). The first injection was given 20 min before the induction of inflammation, the second 6 h after and the others followed daily. 3 inhibitors (pancreatic, soya-bean and inhibitor S) revealed a highly significant inhibition of experimental inflammation whereas ovomucoid was ineffective. The inhibitors influenced particularly the acute phase of inflammation. As compared with the drugs of the phenylbutazone type, at least two inhibitors (soya-bean and inhibitor S) showed much higher antiphlogistic activity.

The inhibitors were proved highly active even in other types of experimental inflammation (the inflammation of the rabbits eye induced by mustard oil, skin inflammation in the rabbit induced by the same agent and generalized dextran edema in rats). These data and the results of the study of antiphlogistic action of chymotrypsin and its inhibition, which were quite analogous to the results with trypsin, will be dealt with in detail in another paper.

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Pharmaceutical and Biochemical Research Institute, Prague, November 26, 1957.

Zusammenfassung

Die entzündungshemmende Wirkung von einigen in der Natur vorkommenden Trypsin-Inhibitoren wurde an Ratten mit experimenteller Kaolin-Arthritis nachgewiesen. Die entzündungshemmende Wirkung von Trypsin könnte demzufolge auf eine durch die Applikation von Trypsin bedingte, reaktive Mobilisierung endogener Protease-Inhibitoren zurückgeführt werden.

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