trodes placed on both temporal regions of the skull. The effect of a single electroshock, i.e. tonic-clonic convulsions was complete in all cases. Animals were decapitated 1 min after the last convulsion. The details concerning the procedure of obtaining the samples of various regions of the brain, as well as the methods used for determinations of deoxyribonucleic (DNA) and ribonucleic acids, have been already indicated in the previous paper[1].

Results are presented in the Table. The samples of all investigated regions showed a pronounced decrease in the RNA content. No quantitative differences in the decrease of RNA could be found between the animals which received one electroshock, and those which received four successive electroshocks applied with an intershock interval of 7 min. The values of DNA observed in the various regions of the CNS after electroshock were found to be within the range of those obtained in normal animals.

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Zusammenfassung

Beim Elektroschock kommt es zu bedeutenden Erniedrigungen der Konzentration von RNA in verschiedenen kortikalen und subkortikalen Teilen des zentralen Nervensystems der Katze, während sich die Konzentration von DNA in normalen Grenzen hält.

The Action of Tranquilizing Drugs on Brain Metabolism

In a previous paper[1], we reported experiments indicating a complex biochemical mechanism to be involved in the central effects of Chlorpromazine and other central ganglionic blocking agents. Two inhibitory processes have been demonstrated as necessary for a chlorpromazine-like pharmacological action: (a) uncoupling of oxydative phosphorylation and (b) simultaneous inhibition of ATPase activity.

Chlorpromazine has been reported to have beneficial effects in some psychotic disturbances[2]. The same holds for Miltown (Meprobamat)[3] and Benactyzin[4], while Captodiamin (Covatin), a substance with an even more pronounced «narcobiotic» effet than Chlorpromazine[5], was found to have only a sedative action[6].

The present work was undertaken to investigate: (a) whether these drugs with chlorpromazine-like action influence brain metabolism in a similar way as chlorpromazine, and (b) whether the metabolic effects of Captodiamin differ from those of Chlorpromazine, Benactyzin and Miltown.

Oxydative phosphorylation and ATPase activity have been measured on rat brain homogenates, by the technique already described[7].

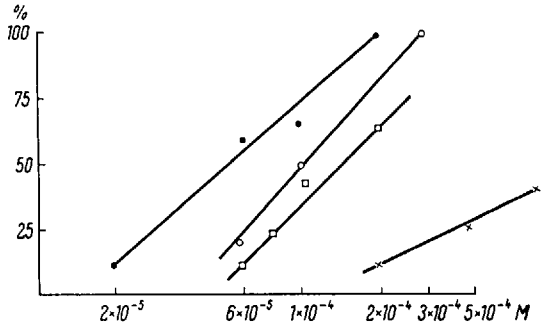

Fig. 1. – Inhibition of oxydative phosphorylation. Decrease in P/O ration as compared to controls plotted against the log of concentrations. ●–●–● = Captodiamin; ○–○–○ = Chlorpromazine; □–□–□ = Benactyzin; x–x–x = Miltown.

Figure 1 shows the effects of Chlorpromazin, Benactyzin, Miltown and Captodiamin on oxydative phosphorylation. All these compounds were found to have an uncoupling effect, the ID_{50} being $1{\cdot}05 \times 10^{-4}$ *M* for Chlorpromazine, $5{\cdot}5 \times 10^{-5}$ *M* for Captodiamin, $1{\cdot}6 \times 10^{-4}$ *M* for Benactyzin and $1{\cdot}1 \times 10^{-3}$ *M* for Miltown.

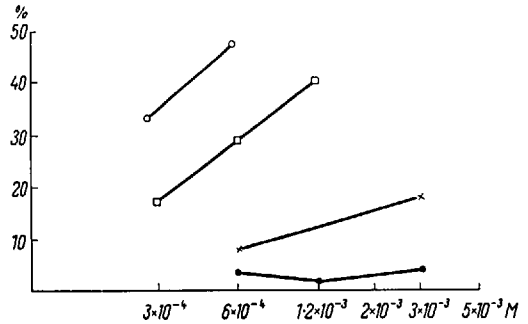

Fig. 2. – Inhibition of ATPase activity. Decrease in activity as compared to controls plotted against the log of the concentrations. ●–●–● = Captodiamin; ○–○–○ = Chlorpromazine; □–□–□ = Benactyzin; x–x–x = Miltown.

Figure 2 shows the effect of these drugs on the ATPase activity. Chlorpromazine, Benactyzin and Miltown exhibited a more or less pronounced inhibitory action, while Captodiamin was ineffective even in very large concentrations.

Benactyzin and Miltown thus influence the brain metabolism in the same way as Chlorpromazine, i.e. they inhibit both oxydative phosphorylation and ATPase activity. Captodiamin, on the contrary, inhibits only oxydative phosphorylation and leaves ATPase activity unchanged. This observation could be interpreted as indicating that uncoupling of oxydative phosphorylation may be involved in the 'action narcobiotique', but it does not

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

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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.

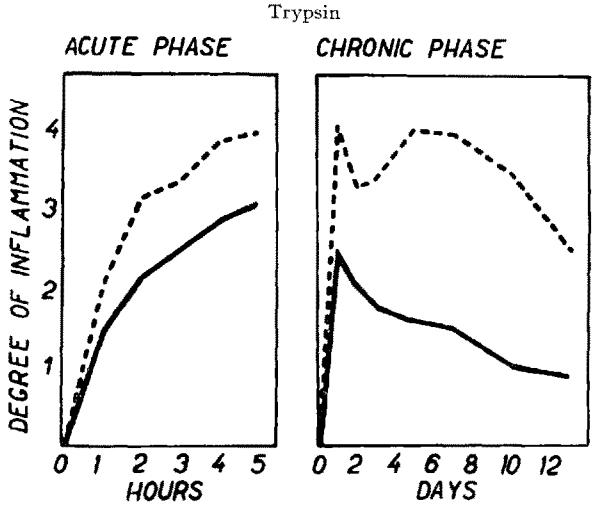

Fig. 1. – Anti-inflammatory action of intramuscular trypsin on kaolin-induced inflammation in rats. Both lines are mean values of responses in 10 animals. (Broken line: control).

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.

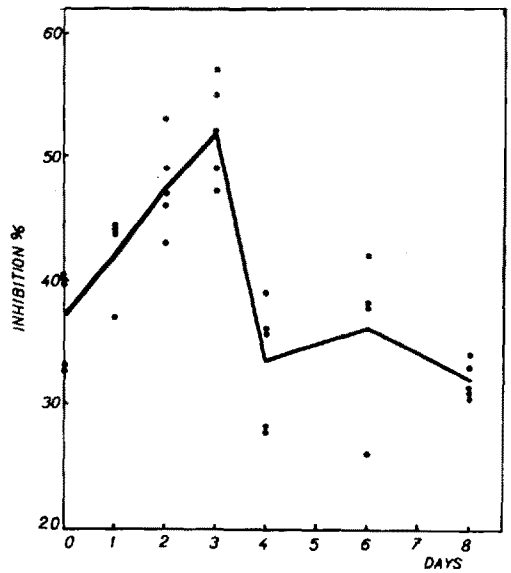

Fig. 2. – Plasmatic trypsin-inhibitory activity after intramuscular application of trypsin.

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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