2.0 mM there are only small differences in the degree of inhibition caused by both drugs.

The action of perathiepine and chlorpromazine on various enzyme systems is summarized in Table II. As can be seen, both drugs have only little effect on the rat brain hexokinase and glucoso-6-phosphatase. The influence of both drugs on the Mg^{++}-activated adenosinetriphosphatase in brain mitochondria and in 10,000 g supernatant is in general of a similar degree. In contrast to this, perathiepine seems to be a more potent inhibitor of the enzyme contained in 10,000 g supernatant.

Similarly, perathiepine is evidently a stronger inhibitor of brain mitochondrial 2,4-dinitrophenol stimulated adenosinetriphosphatase. Finally, the influence of perathiepine and chlorpromazine on the $Mg^{++}Na^{+}$-activated, K^{+}-stimulated adenosinetriphosphatase in 10,000 g supernatant (so-called 'NaKA'[6-8]) was studied. This enzyme differs from other adenosinetriphosphatases by its organ and cellular localization and by the sensitivity to strophantine and various cations[9,10]. NaKA is an essential constituent of the sodium pump, a system responsible for the transport of sodium and potassium across the cell membrane against the concentration gradient, which has a decisive importance for the excitability of the nervous system[11].

The activity of this enzyme is completely inhibited by chlorpromazine at 0.2 mM and more. The inhibition caused by perathiepine, although also very strong, does not reach the degree of the latter drug, and even at 0.4 mM about 10% of initial activity is detectable.

It may be concluded that, regardless of some minor quantitative differences, the action of both drugs upon the reactions studied here is in general of similar nature. The most outstanding features of this action are (1) relative ineffectiveness towards glycolytic enzymes, (2) inhibition of the oxidation of pyruvate, (3) strong inhibition of NaKA. This last effect may be considered as most important for pharmacology.

Zusammenfassung. Die Wirkung des Thymolepticums Prothiaden [10-(4-Methylpiperazino)-10,11-dihydrobenzo(b,f)thiepin] auf die Oxydation des Pyruvats, Oxoglutarats und Succinats sowie auf die Aktivität der Hexokinase, Glucoso-6-phosphatase und Mg^{++}-aktivierten, DNP-aktivierten und $Mg^{++}Na^{+}$-aktivierten, K^{+}-stimulierten Adenosintriphosphatase (NaKA) wurde untersucht und mit der Wirkung von Chlorpromazin verglichen. Im allgemeinen weisen beide Substanzen ähnliche Eigenschaften auf, welche in einer relativen Unwirksamkeit gegenüber glykolytischen Enzymen, Hemmung der Pyruvatoxydation und starker NaKA-Hemmung bestehen.

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Catalysis and Inhibition of the Oxidative Degradation of Deoxyribonucleic Acid by Catalase Showing Maximum Catalytic Effect in Pico-Molar Concentrations

As is known, catalase not only decomposes hydrogen peroxide but it can also exert a peroxidatic function with certain acceptors when hydrogen peroxide is released slowly[1,2]. It can further act as a non-specific hematin catalyst[3]. The experimental results presented in the following give evidence that the oxidative degradation of deoxyribonucleic acid (DNA) is catalysed by very low concentrations of catalase. When the concentration of catalase is increased, the catalytic effect decreases and is even inverted into a protective effect.

The experimental conditions and analytical methods used have been described before[4]. The DNA used contained about 0.01% iron. The solution of DNA was prepared with 10% aqueous sodium chloride containing 0.033 M/l phosphate buffer, pH 7, and 0.002 M/l sodium pyrophosphate. The specific viscosity of the 0.1% DNA solution was 0.71. Catalase was from Boehringer (Mannheim) and ferrichloride from Merck (Darmstadt), both of analytical grade. The experiments and the viscosity measurements were carried out at 37 °C.

Figure 1 shows the specific viscosity of the DNA solution after 1000 h storage under oxygen with the addition of different amounts of catalase or of ferrichloride. The results indicate that there is a maximum decrease of the viscosity when the solution contains $2 \cdot 10^{-12}$ M/l of catalase. Surprisingly, the catalytic effect becomes smaller not only with decreasing but also with increasing catalase concentrations and the effect almost disappears when 10^{-6} M/l or more of catalase are present. A similar type of curve is obtained when iron-III-chloride is added in place of catalase, although the effect is substantially smaller. Again, the maximum effect is obtained with about $2 \cdot 10^{-12}$ M/l of the additive.

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Figure 2 presents the specific viscosity of the DNA solution 90 h after the addition of 0.0005 M/l hydrogen peroxide (curve 2) or of 0.0005 M/l 1-methyl-2-benzyl-hydrazine-phosphate (curves 1 and 3). The latter compound is a cytotoxic agent[5] which is oxidized by molecular oxygen under formation of about the equimolar amount of hydrogen peroxide[4]. The amount of catalase or of iron-III-chloride added simultaneously with the above-mentioned compounds is indicated on the abscissa.

Curve 1 shows that the effect on DNA of the cytotoxic compound which slowly generates hydrogen peroxide is substantially modified by catalase. A strong promoting effect is observed with catalase concentrations of about $2 \cdot 10^{-12}$ M/l, whereas in concentrations higher than about 10^{-11} M/l catalase acts as an inhibitor of DNA degradation[6]. Iron-III-chloride has no enhancing effect on DNA degradation by the cytotoxic compound (curve 3). When the cytotoxic compound is replaced by the equimolar amount of hydrogen peroxide, catalase acts only as inhibitor (curve 2).

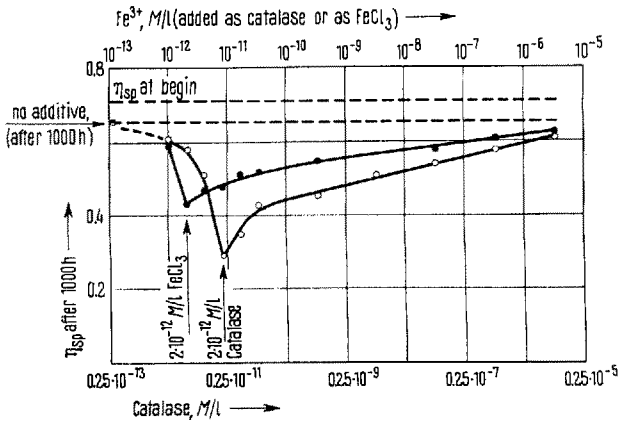

Fig. 1. Effect of catalase and of Fe-III-chloride on the specific viscosity of a 0.1% DNA solution after 1000 h storage under oxygen at 37 °C. Circles: specific viscosity as a function of the concentration of catalase. Dots: specific viscosity as a function of the concentration of added ferrichloride.

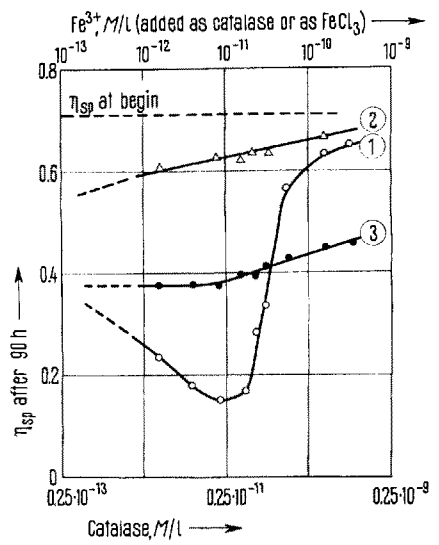

Fig. 2. Specific viscosity of a 0.1% DNA solution 90 h after addition of 0.0005 M/l 1-methyl-2-benzyl-hydrazine phosphate (MBH) or of 0.0005 M/l hydrogen peroxide: effect of catalase and of Fe-III-chloride. Curve 1: effect of catalase on the specific viscosity of a DNA solution containing MBH. Curve 2: effect of catalase on the specific viscosity of a DNA solution containing hydrogen peroxide. Curve 3: effect of Fe-III-chloride on the specific viscosity of a DNA solution containing MBH.

The experimental results demonstrate the catalytic effect of very low concentrations of catalase on DNA degradation by molecular oxygen and by a cytotoxic methyl-hydrazine derivative. The concentration of catalase is critical with respect to the catalytic effect, which decreases and is even inverted into an inhibitory action with increasing amounts of catalase. The catalysis may be explained by a peroxidatic effect[1,2] and/or hematin catalysis[3], and the inhibition by catalatic action[2]. Competition between catalatic and peroxidatic reactions of catalase and the increase of the catalatic reaction with increasing catalase concentration is known[2]. The experimental results with DNA presented here show an inversion of catalysis into inhibition in a much lower range of catalase concentration than in the work previously described, which had been carried out with specific acceptors for the catalase-hydrogen peroxide complex[2]. The results presented may indicate the possibility of a complex formation between catalase and DNA[7]. They may further be interpreted as evidence for an intermediate formation of hydrogen peroxide and/or organic hydroperoxides in the course of the degradation of DNA by molecular oxygen[8].

Zusammenfassung. Es wird gezeigt, dass eine $2 \cdot 10^{-12}$ molare Katalase-Lösung den durch Luftsauerstoff sowie durch ein Wasserstoffperoxid-lieferndes Cytostaticum bewirkten – nicht aber den durch zugesetztes Wasserstoffperoxid verursachten – Abbau von Desoxyribonucleinsäure (DNS) wesentlich verstärkt. Mit *steigender* Katalase-Konzentration wird dieser Effekt immer kleiner und verschwindet schliesslich. Im Falle des Cytostaticums wird der DNS-Abbau durch Katalase-Konzentrationen über 10^{-11} M/l inhibitiert. Dieser Übergang von Katalyse zu Inhibition wird auf die Fähigkeit der Katalase zu peroxydatischer bzw. häminkatalytischer Wirkung einerseits und zu katalatischer Wirkung andererseits zurückgeführt, wobei mit steigender Katalase-Konzentration eine Verschiebung zugunsten der katalatischen Reaktion erfolgt.

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