dem $X^2$-Test erfolgten statistischen Berechnungen hinsichtlich der einzelnen beurteilten Kriterien zusammengestellt.

*Diskussion.* Aus den Ergebnissen geht hervor, dass die EAE durch ε-ACS wirksam gehemmt wird, wobei eine Abhängigkeit von der applizierten Dosis zu bestehen scheint. Die wirksame Dosierung liegt an der oberen Grenze der vom Kaninchen parenteral tolerierten[19]. Dabei dürfte auch der Häufigkeit der Zufuhr eine Bedeutung zukommen, da NILSSON et al. die rasche Elimination des Wirkstoffes nach intravenöser Gabe nachgewiesen haben[14].

Weniger eindeutig gibt sich eine unter ε-ACS reduzierte Antikörpersynthese zu erkennen. Immerhin weisen die in Tabelle II enthaltenen Daten in diese Richtung. Demgegenüber war die Beeinflussung der granulomatösen Reaktion am Injektionsort des Antigens eindrücklich. Das unterschiedliche Verhalten der beiden letztgenannten Parameter weist auf die besondere Bedeutung der zellständigen Immunität bei der EAE hin. Eine ähnliche Wirkung auf die Granulationsbildung wird auch bei Verwendung von Nebennierenrinden-wirksamen Stoffen immer wieder beschrieben[4]. Es liegt deswegen nahe, die Hemmwirkung der ε-ACS bei verzögerter Immunreaktion mit dem antiphlogistischen Effekt der Corticosteroide in Parallele zu setzen. Darüber hinaus lässt sich eine Beeinträchtigung der Proteinsynthese durch die stoffwechselfremde Aminosäure denken[16].

Der durch unsere Untersuchungen am Beispiel der EAE erneut erbrachte Nachweis einer Hemmwirkung auf die verzögerte Immunreaktion bei weitgehender Atoxizität[16] legt den Gedanken an eine klinische Verwendung dieser Substanz bei hyperergischen Zuständen auch im Bereiche des Zentralnervensystems nahe.

*Summary.* The effect of ε-aminocaproic acid on EAE of rabbits was investigated. A partial inhibition, dependent on the dose administered by intravenous injection, can be proved. The formation of antibodies is not significantly impaired, whereas an inhibition of local granulomatosis is obvious. The results obtained can be interpreted as an inhibition of delayed immune reaction.

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## Increased Inactivation of Polysaccharide Phosphorylase in Liver Homogenates from Rats Treated with 3,5,3'-Triiodo-L-thyronine[1]

It has long been known that treatment with large doses of thyroid hormone leads to depletion of glycogen and ATP from the liver[2–6]. Loss of liver glycogen is often accompanied by an increase in PPh activity. Nevertheless rat liver PPh activity is significantly decreased after administration of several doses of T-3[7].

Since active Phosphorylase *a* requires ATP for its formation from inactive Phosphorylase *b*[8–10], it was thought that a lowering of ATP could result in a failure of the active enzyme to be maintained at its normal level. However, previous experiments in this laboratory have failed to reveal a significant difference between the ability of liver homogenates from normal and T-3 treated rats to activate inactive Phosphorylase *b*.

The decrease in liver PPh activity following T-3 administration may be the result of (1) an actual increase in IE activity (which transforms Phosphorylase *a* into *b*), or (2) a greater proteolitic breakdown of the enzyme. Both of these possibilities have been investigated in the present study.

*Methods.* Thirty-six male albino rats fed *ad libitum* and weighing 180–230 g were used. They were distributed into 3 groups of 12 rats each (6 T-3 treated and 6 controls). T-3 in a mild alkaline solution was administered intraperitoneally in doses ranging from 500 μg/kg body weight (1st group) to 100 μg/kg (2nd group) and 50 μg/kg (3rd group). The injections were given daily for three consecutive days. Control rats received daily injections of the vehicle (5 ml/kg). The animals had access to food and water to within 8 h of the time of sacrifice.

24 h after the last injection, the rats were killed by decapitation. Following rapid removal, the liver was homogenized with cold 0.9% KCl solution in a Potter all-glass homogenizer to give a concentration of 100 mg wet tissue per ml. PPh activity was assayed according to SUTHERLAND and WOSILAIT[11]. The results are expressed as mg of Pi produced from Glucose-1-phosphate per g wet tissue in 8 min at 37°C. Pi was determined by the method of BRIGGS and ZAMBOTTI[12–13]. IE activity was estimated by measuring the decrease in PPh activity which occurred when liver homogenates were incubated with an equal volume of 0.02 *M* Tris buffer (ph 7.4) at 37°C for 4 min. 'Proteolitic' inactivation was determined by the fall in PPh activity which occurred when liver homogenates were incubated at 37°C for 10 min with an equal volume of 0.02 *M* Tris buffer (pH 7.4) containing 0.2 *M* KF, which at this concentration almost completely inhibits IE.

[1] Dedicated to Prof. A. v. MURALT on the occasion of his 60th birthday. – The following abbreviations are used: ATP, adenosine triphosphate; PPh, polysaccharide phosphorylase; IE, inactivating enzyme or phosphorylase phosphatase; Tris, Tris (hydroxymethyl) aminomethane; Pi, inorganic phosphate; T-3, 3,5,3'-triiodo-L-thyronine.

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*Results.* Table I presents the effects of T-3 at three dose levels on liver PPh activity and its inactivation upon incubation in the absence of fluoride.

T-3 administration resulted in a significant decrease in the liver PPh activity. From the above results, there appears to be some relationship between the amount of T-3 administered and the decrease in liver PPh observed.

When liver homogenates are incubated at 37°C with an equal volume of 0.02 *M* Tris buffer (pH 7.4) a very rapid fall in PPh activity occurs. IE, which in the absence of fluoride promotes such an *in vitro* inactivation, appears to be greatly stimulated in liver homogenates from T-3 treated rats.

A slower but eventually significant fall in liver PPh activity was observed also when the homogenates were incubated at 37°C with Tris buffer (pH 7.4) in the presence of 0.1 *M* KF. Since fluoride at this final concentration effectively inhibits IE activity, the decrease in PPh could be attributed to proteolitic degradation of the enzyme molecule (Table II).

The results listed in Table II indicate that T-3, even when administered in relatively small doses (50 µg/kg body weight), markedly stimulates the inactivation of PPh which takes place in the presence of 0.1 *M* fluoride.

*Discussion.* The present studies indicate that T-3 administration induces a decrease in rat liver PPh activity and stimulates its *in vitro* inactivation due both to IE and to proteolitic degradation.

A simple and attractive interpretation of the above results would be that the decrease in liver PPh activity is dependent on an increased IE. In this case a greater transformation of Phosphorylase into the inactive *b* form could explain the fall in PPh activity. However, recent experiments in our laboratory indicate that, in the liver of the control and T-3 treated rats, Phosphorylase exists predominantly in the *a* form. Moreover, the administration of epinephrine (which stimulates Phosphorylase *a* formation) did not restore the decreased liver PPh activity after T-3 treatment. This would indicate that in intact animals the activation of the enzyme greatly prevails over the inactivation, and that IE activity, even when stimulated after T-3 treatment, cannot elevate the low Phosphorylase *b* concentration.

The above considerations could mean that the decrease of PPh is dependent on a low concentration of the enzyme itself in the hepatic tissue. This conclusion would indicate that T-3 administration can inhibit the biosynthesis of the enzyme or stimulate its proteolitic splitting. The lowering of ATP content[5,6] could explain a decreased biosynthesis of the enzyme, whereas the results listed in Table II are consistent with an increased breakdown.

Table I. PPh and IE activities in liver homogenates from control and T-3 treated rats

| Group | No. of rats | Daily treatment | Liver PPh (mg Pi/g/8 min) before incubation | Liver PPh (mg Pi/g/8 min) after incubation | IE |
|---|---|---|---|---|---|
| I | 6 | None | 10.5 ± 0.54 | 7.5 ± 0.42 | 3.0 |
| | 6 | T-3 (500 µg/kg) | 6.8 ± 0.66 | 1.7 ± 0.28 | 5.1 |
| II | 6 | None | 10.8 ± 0.48 | 7.7 ± 0.60 | 3.1 |
| | 6 | T-3 (100 µg/kg) | 7.5 ± 0.62 | 2.7 ± 0.35 | 4.8 |
| III | 6 | None | 11.2 ± 0.50 | 8.4 ± 0.44 | 2.8 |
| | 6 | T-3 (50 µg/kg) | 8.7 ± 0.56 | 4.3 ± 0.32 | 4.4 |

Liver homogenates were diluted with an equal volume of 0.02 *M* Tris buffer (pH 7.4); PPh activity was determined before and after 4 min incubation at 37°C. IE was estimated by the decrease in PPh activity upon incubation at 37°C in the absence of fluoride. Average control and T-3 treated values are given ± SE.

Table II. Inactivation of liver PPh from normal and T-3 (50 µg/kg) treated rats in the presence of fluoride

| Treatment | No. of rats | Liver PPh (mg Pi/g/8 min) before incubation | Liver PPh (mg Pi/g/8 min) after incubation | Inactivation |
|---|---|---|---|---|
| None | 6 | 11.2 ± 0.5 | 9.1 ± 0.6 | 2.1 |
| T-3 | 6 | 8.7 ± 0.5 | 5.4 ± 0.7 | 3.3 |

Liver homogenates were diluted with an equal volume of 0.02 *M* Tris buffer (pH 7.4) containing 0.2 *M* KF; PPh activity was determined before and after 10 min incubation at 37°C. Average control and T-3 treated values are given ± SE.

*Riassunto.* L'attività polisaccaride fosforilasica presente negli omogenati di fegato dei ratti trattati per 3 giorni con T-3 è sensibilmente diminuita; sono invece nettamente aumentate, in assenza di fluoruro, la trasformazione della forma *a* in *b* e, in presenza di fluoruro, l'inattivazione irreversibile dell'enzima. Nel fegato degli animali ipertiroidei la diminuzione dell'attività polisaccaride fosforilasica non sarebbe però dovuta all'esaltata inattivazione, ma alla minore concentrazione dell'enzima stesso.

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## Induction of Tumors in Rats by Subcutaneous Implants of Surgical Sponges[1]

It has been demonstrated repeatedly that experimental subcutaneous implantation of a wide variety of plastics and other substances, especially in the form of films, frequently gives rise to neoplasms[2–4]. Nevertheless, it appears to be widely assumed that polyvinyl alcohol surgical sponges (Ivalon), when implanted into living animals, are relatively inert, are well tolerated by adjacent tissues, and are without carcinogenic activity[5]. Most unfavorable reports on the use of Ivalon sponges as prostheses have found them to be unsatisfactory for reasons other than for non-tolerance or carcinogenicity[6].

On the basis of previously unpublished microscopic observations by MILLISER, we have long felt that polyvinyl sponge implants are not as inert as is generally supposed. Giant cells have been observed in all implants after the first few days. Erosion of the sponge substance (lysis? phagocytosis?) has seemed to take place and has appeared to be more prominent in the older implants. We therefore decided to examine sponge biopsies after long periods of implantation.

Male Holtzman rats, 5–6 weeks of age and weighing 150–200 g, were each implanted in June, 1960, with 2 circular polyvinyl alcohol sponges (Ivalon), 20 mm in diameter and 3–4 mm thick. The technique of implantation was the same as that previously described[7] except