

The Immediate Response of Thyroidectomized Rats to Small Doses of Thyroxine

According to the generally accepted view, thyroxine increases O_2 -consumption in the intact animal only with considerable delay. Usually no rise in the rate of metabolism is observed before 24 hours have elapsed. Sporadic observations¹ recording earlier effects are either inconsistent and conflicting, or were obtained under highly unphysiological conditions, and were achieved in common with most investigations, only through employment of very large doses. The immediate action of thyroxine injected into the lateral ventricle of the brain was shown to be due to the solvent and to be abolished by curarization². Sós³ found that thyroxine is followed in rabbits by immediate central excitation, yet a rise of basal metabolism could be observed only after 24 hours. This delayed action of thyroxine was not easy to understand, for on the O_2 -consumption of isolated tissue very high dilutions of thyroxine (10^{-12} to 10^{-16}) have an immediate effect⁴. An explanation of the delayed effect of thyroxine in the intact animal was furnished by MANSFELD⁵, whose experiments suggested that thyroxine was taken up by the central nervous system and conducted through the nerves to the periphery⁶.

In an earlier communication⁷ it could be demonstrated that thyroidectomized animals are much more sensitive to thyroxine, and especially to single doses of thyroxine, than normal rats. A single dose of 2 micrograms was followed within 24 hours by a rise of O_2 -consumption of approximately 20 per cent. The fact that a fraction of the doses hitherto employed was effective within 24 hours in the thyroidectomized animal served as stimulus to investigate more closely the response to such small and even smaller doses of thyroxine.

Methods. Adult male rats, well accustomed to estimation of O_2 -consumption in a somewhat modified Belák-Illényi apparatus⁸, and deprived of food for 12 hours were used, thyroidectomy having been performed at least one week, and in some cases as long as a few months, earlier. O_2 -consumption was determined at least in two, in many cases in four or more 20-min. periods prior to the administration of thyroxine and was followed up several hours afterwards, usually two 20-min. estimations being performed per hour. In a number of cases O_2 -consumption was observed in a similar manner the day before and the day after the thyroxine experiment, the period of food deprivation being necessarily reduced in these tests. Activity of the

animals was closely observed, and estimations in the course of which the animals were restless were discarded. The observations were made between the middle of September and the end of April. The curves represent the deviations from the normal rate of metabolism, i.e. 800 calories per square meter body surface, which was assumed to be $10 \cdot kg \frac{1}{3}$.

Results and discussion. Figures 1 and 2 serve as typical examples for a fair number of observations. It can be seen, that as little as 0.1 microgram of thyroxine is

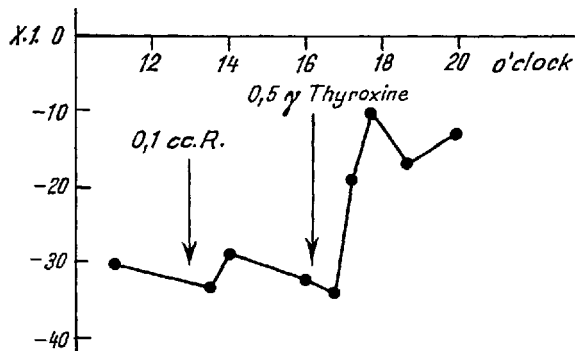


Fig. 1. – 1st Oct., 1948. At 13:00 0.1 cc. Ringers solution, at 16:10 0.5 γ thyroxine. Rat No. 1. 260 g.

followed by a marked rise of O_2 -consumption. The doses employed ranged from 0.1 to 10 micrograms and were in most cases between 0.1 and 1.0 microgram. One of the factors determining the immediate response to thyroxine seems to be the initial rate of metabolism. Out of 18 experiments with a basal rate below -20% only one failed to respond with a rise of O_2 -consumption,

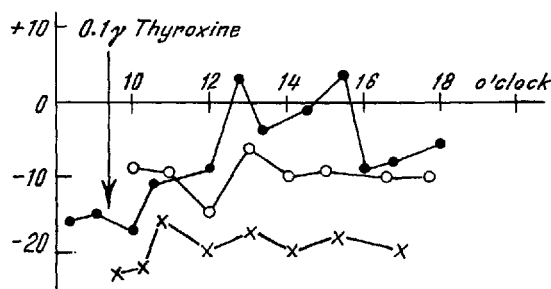


Fig. 2.

○—○ 17th Jan., 1949, receives no thyroxine.
●—● 18th Jan., 1949, 0.1 gamma of thyroxine.
x—x 19th Jan., 1949, receives no thyroxine. Rat No. XI. 200 g.

out of 9 experiments with an initial rate between -10 to -20% a response was missed also only in one instance, the dose being 0.1 microgram in both cases, while on the other hand out of 7 observations with an initial rate of metabolism higher than -10% no response was obtained in 4 (0.1 to 5.0 micrograms). It seems therefore that the initial rate of metabolism may be one of the factors playing a role in the determination of the immediate response to thyroxine.

The absence of delay in the response of the rate of metabolism of the intact animal following the administration of thyroxine is contrary to the present conception of the action of thyroxine and therefore great care has to be taken in its interpretation, the more so as Sós (l.c.) has shown that the usual large doses of thyroxine (1–2 mg) increase the muscular activity of rabbits for the first five hours following its administration, while

¹ G. ROESLER, Arch. exp. Pathol. und Pharmacol. 155, 114 (1930). – B. ISSEKUTZ and B. ISSEKUTZ, Jr., Arch. exp. Pathol. und Pharmacol. 177, 442 (1933); Klin. Wschr. 13, 1060 (1934). – D. RAPORT and A. CANZANELLI, Amer. J. Physiol. 97, 553 (1931). – C. A. KASSIL, E. BERKOWITCH, and T. PLOTITSYNA, Bull. Biol. Méd. expér. U.S.S.R. 9, 263 (1940).

² E. MÉSZÁROS, Ung. physiol. Ges.; Berichte ges. Physiol. 131, 228 (1943).

³ J. SÓS, Arch. exp. Pathol. u. Pharmacol. 192, 78 (1939).

⁴ G. AHLGREN, Klin. Wschr. 3, 667 (1924). – U. S. EULER, Klin. Wschr. 12, 671 (1933). – G. MANSFELD, Klin. Wschr. 14, 884 (1935). – T. VEREBÉLY, Klin. Wschr. 11, 1705 (1932).

⁵ G. MANSFELD and G. HORVÁTH, Pflügers Arch. 235, 520 (1935). – G. MANSFELD, Arch. exp. Pathol. u. Pharmacol. 193, 241 (1939).

⁶ In the meanwhile MANSFELD reported, that 0.5 mg thyroxine increases O_2 -consumption of anæmic normal and anæmic thyroidectomized rats within 2 hours (Kísérletes Orvostud. 1, 39 [1949]).

⁷ I. ANDIK, L. BALOCH, Sz. DONHOFFER, and Gy. MESTYÁN, Exper. 5, 211 (1949).

⁸ S. BELÁK and A. ILLÉNYI, Biochem. Z. 281, 27 (1935).

no rise in the rate of metabolism could be found before 24 hours elapsed. The apparatus used by us for estimation of O_2 -consumption permits observation of the animal, but does not exclude restricted movements. As restlessness could serve as a simple explanation for increased O_2 -consumption, the animals were observed carefully. In many cases they slept curled up during the whole 20-minutes period during which O_2 -consumption was measured. Increased muscular activity as a possible cause of the observed rise of O_2 -consumption may therefore be excluded.

Another possibility which had to be considered was that the observed rise in the rate of metabolism was founded on an indirect effect exerted by thyroxine on the pituitary in accordance with experiments which led MANSFELD¹ to the postulation of a hypophyseal "heating hormone".

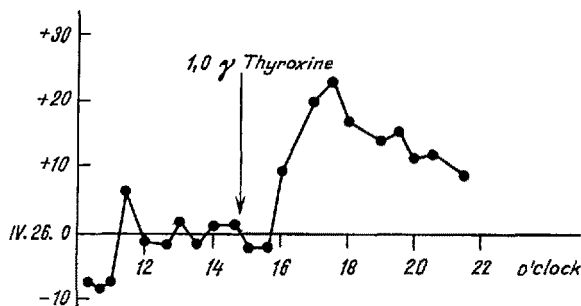


Fig. 3. – Hypophysectomized rat No. 6. 200 g. 1.0 γ of thyroxine at 14:15.

Fig. 3 shows that this is not the case. The same small doses of thyroxine which have been shown to be effective in the thyroidectomized rat are followed by a similar response in the hypophysectomized animal. The complete removal of the pituitary was verified by autopsy. It may be therefore concluded that in the reported experiments the immediate response to thyroxine is not based on a mechanism similar to the one demonstrated by MANSFELD. Immediate response to similar doses of thyroxine were obtained also in normal rats, yet these are less regular and uniform and show seasonal changes, and will therefore have to be dealt with in a separate communication.

The significance of responses obtained by such small doses of thyroxine is evident, for these are well within the range of those stored by the normal thyroid, which therefore may be assumed to pour out thyroxine in the same order of magnitude upon various stimuli without delay.

A detailed account will be published elsewhere.

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Zusammenfassung

In Versuchen, die Mitte September bis Ende April ausgeführt wurden, konnte nachgewiesen werden, daß kleinste Thyroxingaben (0,1–1,0 γ) an der schilddrüsenlosen Ratte mit niedrigem Stoffwechsel binnen zweier Stunden eine oft mehrere Stunden anhaltende Steigerung des O_2 -Verbrauchs um 20% verursachen. Dieser Befund steht im Gegensatz zu der üblichen Auffassung, daß

Thyroxin am intakten Tiere nur nach einer Latenz von etwa 24 Stunden wirke. Erhöhte Aktivität der Tiere kann zur Deutung ausgeschlossen werden. 1,0 γ Thyroxin bewirkt an der hypophysektomierten Ratte eine ähnliche Stoffwechselsteigerung wie an schilddrüsenlosen Tieren. Hieraus muß gefolgert werden, daß die beobachtete rasche Wirkung des Thyroxins nicht auf einem hypophysären Heizhormon (nach MANSFELD) beruht. Die Bedeutung der Versuche liegt darin, daß die angewandten Thyroxindosen den von der normalen Schilddrüse gespeicherten Wirkstoffmengen entsprechen. Es darf daher angenommen werden, daß Thyroxin in gleichen Quantitäten auch von der normalen Drüse auf verschiedene Reize ohne Verzögerung ausgeschüttet werden kann.

Atmungshemmung durch niedrigen Blutdruck

Im Jahre 1945/46 hat BUCHER¹ gezeigt, daß die Tätigkeit des Atmungszentrums deutlich gehemmt ist, wenn der arterielle Druck im Zentralnervensystem (ZNS) nur noch etwa 35 mm Hg beträgt, und daß bei einem Druck von nur etwa 10 mm Hg das Atmungszentrum überhaupt keine inspiratorischen Impulse mehr ausgibt. Daß der daraus resultierende Atmungsstillstand tatsächlich «druckbedingt» ist, und nicht etwa nur Folge der begleitenden Hypoxämie des Zentrums ist, konnte dabei weitgehend gesichert werden.

Wir haben uns die Aufgabe gestellt, zu prüfen, ob eventuell das beschriebene Phänomen unter bestimmten Umständen auch schon in wesentlich höheren Druckbereichen auftreten könnte und demzufolge gegebenenfalls praktisch-klinisch berücksichtigt werden müßte. Dazu haben wir an Kaninchen untersucht, bei welchem arteriellen Druck die spontane Atmungstätigkeit aufhört, wenn a) das Atmungszentrum unter der Einwirkung eines an sich schon depressiv wirkenden Pharmakons, wie beispielsweise des Morphins, steht, und b) umgekehrt das Atmungszentrum unter der Einwirkung eines zentral atmungsanregenden Pharmakons, wie beispielsweise des Coramins, steht.

Methode. Die Kaninchen werden in Urethannarkose präpariert wie in Lit. 1 beschrieben, d. h. – kurz zusammengefaßt – nachdem die beiden Aa. vertebrales okkludiert worden sind, wird der ganze Hals etwa in der Mitte vollkommen fest umschnürt mit Ausnahme der vorher frei präparierten linken A. carotis, der beiden Vv. jugulares, der beiden Vagi und der Trachea. Damit ist das ZNS nur noch durch die linke Carotis mit Blut versorgt, was indes zu einer ansehnend normalen Atmungstätigkeit genügt. Die Atmung wird als Pneumogramm, der Druck im ZNS mittels einer in den kopfwärts gelegenen Stumpf der rechten Carotis eingebundenen endständigen Kanüle registriert. Infolge der zwischen der rechten und linken Carotis bestehenden interarteriellen Verbindungen ist dadurch eine zumindest relative Aussage über das Verhalten des Druckes im ZNS möglich.

Der eigentliche Versuchsgang gestaltet sich folgendermaßen: Die linke Carotis wird abgeklemmt (0 in Tabelle). Dadurch sinkt der Druck im ZNS stark ab und von einer gewissen Druckhöhe an steht auch die Atmung still. Nach ca. 20 Sekunden wird durch Entfernen der Klemme das ZNS wieder an den allgemeinen Kreislauf angeschlossen. Um möglichst genaue Werte ermitteln zu können, wird der Versuch in der Regel in je 2–3minütigen Intervallen 2–3mal wiederholt. Anschließend wird entweder 3 mg/kg Morphin oder 60 mg/kg Coramin i. v. injiziert und 5 Minuten später wieder verfahren wie oben beschrieben.

Die Resultate sind in der beigegebenen Tabelle zusammengestellt. Das praktisch wohl wichtigste Ergebnis

¹ G. MANSFELD, *Die Hormone der Schilddrüse und ihre Wirkungen*, p. 151 (Benno Schwabe, Basel 1943).

¹ K. BUCHER, *Helv. physiol. et pharmacol. acta* 3, 469 (1945); 4, 77 (1946).