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STUDIORUM PROGRESSUS

The Relation Between Activity and Blood Flow in the Thyroid Gland[1]

By U. SÖDERBERG*

Since the famous remark by KING[2] that the nourishment of the thyroid gland 'does not seem to be the main intention of its vascular supply', a great number of experiments have been performed measuring blood flow as an index of thyroid activity. Thus, OSSOKIN, WATTS, and GUNNING[3] introduced the measurement of venous outflow from the gland, a method which has been adapted to the technique described below. The discovery of the iodine metabolism at the beginning of this century was a beautiful confirmation of KING's suggestion as it showed that the intimate contact between thyroid cells and the circulating blood was an effective arrangement for filtering off the small amounts of iodide present in the blood. Synthesis and transportation of a few micrograms of thyroid hormone per day to the systemic circulation would probably have been managed at a much reduced rate of blood flow.

The introduction of radioactive isotopes of iodine in thyroid physiology[4] concentrated the main interest on direct measurements of the level of iodine in the gland and earlier circulatory studies seem to have been forgotten. However, it is still of considerable importance to collect information about the relation between blood flow and uptake of iodine for a correct understanding of the regulation of thyroid functions. Although the iodide clearance of the thyroid has been determined indirectly from the thyroid increment of radioactivity and blood concentration of radioiodide by e.g. BROWN-GRANT *et al.* and BROWN-GRANT and GIBSON[5] and thyroid blood flow has been calculated from the thyroid A–V difference of radioiodine and indirect clearance determinations (POCHIN[6]) no sincere attempt at direct measurement of thyroid blood flow and A–V difference simultaneously seems to have been reported in the literature.

The technique to be described was also found accurate enough for measuring the release of labelled thyroid hormone. As it could be demonstrated that rate of secretion of hormone did not correlate with rate of blood flow, isolated measurements of the content of hormone in arterial and thyroid venous blood that have been previously reported give very little information of thyroid activity. The present experiments have shown that the combining of the measurement of venous outflow from the gland with assay of inorganic radioiodide and protein bound radioiodine in the systemic arterial blood and in the venous blood from the thyroid gland made it possible to record much more rapid changes than those seen in previously reported experiments in which changes in the total content of radioiodine in the thyroid or in the circulating blood are followed.

As the indices used here for thyroid functions were particularly sensitive to short term reactions, special attention was directed towards the somewhat obscure effects of nervous activity and blood catechols on the thyroid which have been described by several authors[7].

Methods. Experiments were performed on 18 cats and 66 rabbits under light to moderate anaesthesia ('Nembutal', 'Pentothal', chloralose or urethane). A few cats were *encéphale isolé* or decerebrated. The femoral vein was cannulated for intravenous infusions, one femoral artery for blood pressure recordings with an electromanometer and the other femoral artery for taking blood samples. In some cases the electroencephalogram and other vegetative variables than those described below were also registered.

The animals were completely heparinized. A thin polyethylene cannula was introduced into the largest thyroid vein and all the other veins from the gland were then ligated. The thyroid tissue was dissected as free as possible from its surroundings and covered with mineral oil or cotton. Each drop of blood from the free end of the cannula gave a signal to an electric ordinate recorder registering blood flow (see Legend to Fig. 1) and fell on a slowly running strip of filter paper. These strips were then dried and afterwards analyzed for radioiodine by a scintillation counter. Drops of arterial blood were examined in a similar way. Known volumes of venous and arterial blood were also repeatedly tested for radioactivity to permit accurate determination of the relation between the two series of drops. Thus, blood flow and arterio-venous concentration difference could be continuously recorded with a fairly high degree of accuracy and with good temporal resolution, the latter being related to time interval between drops. After corrections for the volume of the recording system had been done, these two factors, blood flow and A–V difference, provided all data necessary for the calculation of the rate of uptake of iodine and the rate of release of hormonal radioiodine. No distinction has been made here between the various thyroid hormones[8], and, for simplicity, it is assumed that there is a uniform labelling of the hormones in most of the cases.

After a short period of recording the thyroid blood flow, one or several tracers of radioiodine was injected intravenously. For determinations of the rate thyroid hormone secretion, the tracer was administered 1 to 3 days before the acute experiment, so that the hormone was labelled with radioiodine. Since the blood drop technique permitted repeated measurements of the radioactivity of all the blood samples, several isotopes of iodine with different half-lives could be used simultaneously. Consequently, both the rate of uptake of iodine and release of hormone could be measured in the same ex-

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[2] T. W. KING, Guy's Hosp. Rep. *1*, 429 (1836).

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[5] K. BROWN-GRANT, C. VON EULER, G. W. HARRIS, and S. REICHLIN, J. Physiol. *126*, 1 (1954). – K. BROWN-GRANT and J. G. GIBSON, J. Physiol. *127*, 328 (1955).

[6] E. E. POCHIN, Lancet *259*, 41, 84 (1950).

[7] See e.g. W. B. CANNON and M. CATTELL, Amer. J. Physiol. *41*, 39, 58, 74 (1916) – H. B. FRIEDGOOD and W. B. CANNON, Endocrinology *26*, 142 (1940).

[8] J. GROSS and R. PITT-RIVERS, Biochem. J. *53*, 652 (1953). – J. ROCHE, S. LISSITZKY and R. MICHEL, C. R. Acad. Sci., Paris *232*, 2047 (1952). – A. TAUROG, J. D. WHEAT and I. L. CHAIKOFF, Trans. Amer. Goiter Ass. 228 (1955).

periment and studied in relation to each other and to blood flow. Figure 1 illustrates the results of such an experiment. It shows the influence of 4 μg adrenaline on the secretion of thyroid hormone labelled with I^{131} (half-life 8 days) and uptake of I^{132} (half-life 2·33 h)[9]. The multitracer technique was also used for differentiating diffusion of iodine from 'active' uptake.

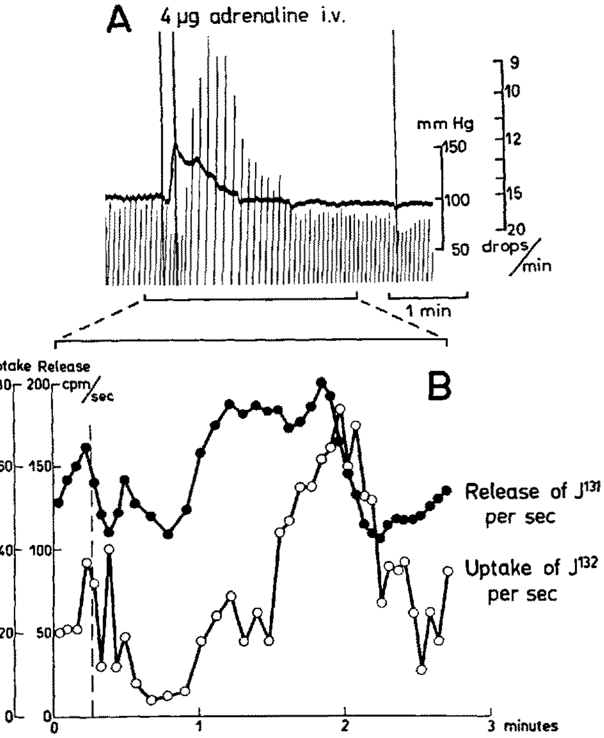

Fig. 1.—Male rabbit. 2·5 kg. Nembutal and chloralose. *A* Blood pressure from the femoral artery (heavy horizontal line) and blood flow from a cannula in a large thyroid vein (steeply rising lines). Each drop of blood from the free end of the thyroid cannula makes a signal which rapidly carries the spot of the mirror galvanometer to the base of the record from which it returns at slower speed so that a steeply rising line is recorded. The length of these lines is directly proportional to time-interval between drops. By joining the upper ends of these lines one obtains a curve inversely proportional to thyroid blood flow (cf. calibration on the right). *B* Rate of uptake of I^{132} (open circles) and rate of release of hormone labelled with I^{131} (filled circles). Calibration on the left in counts per min per s (cpm/s) i.e. radioactivity taken up or released per unit time. The time relation between *A* and *B* is illustrated by horizontal bars between the figures. Vertical broken line in *B* at the onset of adrenaline injection. Adrenaline injected intravenously (4 μg) constricts thyroid vessels with short latency, increases rate of release of hormonal I^{131} with short latency and increases rate of release of hormonal I^{131} with a latency somewhat less than 1 min. Rate of uptake of I^{132} is reduced initially but is then increased above the initial level. Secretion of thyroid hormone was induced by administration of large doses of exogenous thyrotropic hormone ('Actyron').

Results. In a large series of experiments where circulatory changes in the thyroid were elicited by central or peripheral nervous stimulations or by administration of hormones or drugs, it was found that the rate of uptake of iodine was largely proportional to the blood flow through the gland. Thus, the arterio-venous concentration difference of inorganic radioiodide was often found to be roughly constant during considerable length of time also when there were moderate changes in blood flow. During severe vasoconstrictions the A–V difference fell and it increased during large dilatations. The uptake was somewhat augmented when the animals were breathing pure oxygen and decreased during inhalation of gas mixtures rich in carbon dioxide or poor in oxygen. The rate of uptake was, however, less reduced after large doses of antidiuretic hormone than one would have expected from the vasoconstriction. Another exception from the simple relationship was observed in animals pretreated with heavy doses of thyrotropic hormones (TSH)[10] after administration of adrenaline or after sympathetic stimulation. Under these conditions, there was often a period of increased rate of uptake during the recovery from the stimulation (Fig. 1). This effect was obtained with a latency as short as a few minutes after the injection of the thyrotropic hormone and is, in fact, the earliest effect of injected TSH so far known. It does not seem to be closely related to the well-known long-latency effect of TSH on iodine accumulation. Corresponding to the known inhibition of the release of TSH from the anterior pituitary, following 1 to 3 days after the administration of large amounts of thyroxine (EULER and HOLMGREN[11]), there was a strong reduction of the rate of uptake of iodine (down to zero). However, at the same time the thyroid blood flow was largely unaffected.

In order to release the radioiodide that was trapped by the thyroid gland but not yet utilized, thiocyanate or a heavy dose of NaI^{127} was administered. It was thereby observed that the turnover rate of iodine within the gland was generally reduced during the acute experiments, probably by influence of the anesthetics.

The rate of secretion of thyroid hormone, in contrast to the rate of uptake of inorganic iodide, was found to follow what was believed to be the titre of endogenous TSH or administered exogenous thyrotropic hormone regardless of the blood circulation through the gland. Consequently, the thyroid V–A concentration difference of labelled thyroid hormone increased considerably during periods of vasoconstriction and decreased during vasodilatation. Secretion of hormone and vasomotor activity were generally not parallel. The release of thyroid hormone, maintained by the TSH, could be modified by various means. Thus, injection of adrenaline, noradrenaline or acetylcholine, electrical stimulation of the cervical sympathetic trunk or the peripheral end of the cut superior laryngeal nerve were as a rule followed by a transient increase of the release of labelled hormone per unit time, as is also seen in Figure 1 (filled circles). A brief nerve stimulation generally produced a much more long-lasting effect on the rate of release of thyroid hormone than a single injection of adrenaline, noradrenaline or acetylcholine regardless of the vasomotor response to the same stimulus. These observations permit one to suggest the existence of nerve fibres that can markedly change the rate of output of thyroid hormone in response to a given input of TSH. This suggestion was verified by experiments where the veins from either of the two isolated halves of the gland were cannulated. If one half of the gland was acutely denervated and the peripheral end of the cut superior laryngeal nerve stimulated there was an increase of the rate of release of hormone into the vein from that half of the thyroid gland. The other half, with intact innervation, could be stimulated to increased secretion by nervous reflexes or by drugs acting via the central nervous system as in Figure 2 were the release is elicited by 2-brom-lysergic acid diethylamide, 'BOL-148'

[9] I^{132} was obtained by the courtesy of Dr. L.-G. LARSSON and Dr. J. EINHORN, Radiumhemmet, Karolinska Sjukhuset, Stockholm (Sweden).

[10] TSH, 'Actyron', was kindly supplied by A. B. Ferring, Malmö (Sweden)

[11] C. VON EULER and B. HOLMGREN, J. Physiol. *131*, 125 (1956).

(Cerletti and Rothlin[12]). Adrenaline injected intravenously had inconstant effects in the animal of Figure 2. In another rabbit a heavy spontaneous 'arousal reaction' was followed by a more pronounced increase in the thyroid hormone release from the intact half of the gland than from the acutely denervated one. This indicates that nervous influence on the thyroid may be even more important than the effect of an increase of blood catechols during 'arousal'. Such experiments can, however, only be performed in animals in which the vascular anatomy is extremely favourable.

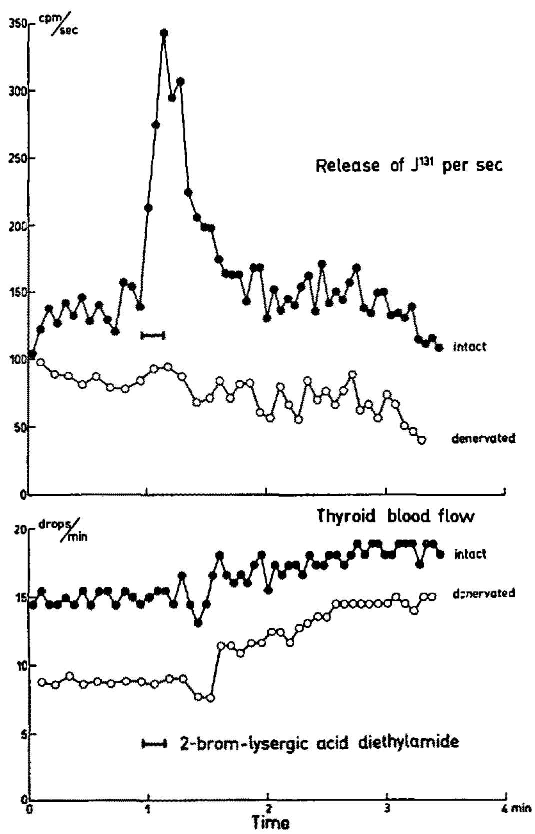

Fig. 2. – Male rabbit. 3·0 kg. Nembutal. Hormone secretion induced by exogenous TSH ('Actyron'). *Upper part:* Rate of release of hormonal I^{131} as in Figure 1*B* from intact and acutely denervated halves of thyroid. *Lower part:* Rate of venous outflow from the same halves. Brom-lysergic acid diethyl amide ('BOL-148') increases rate of release by more than a 100% in the intact half of the gland. Blood flow increases slightly in both halves. Blood pressure (not reproduced in the figure) showed slight transient fall.

It has thus been found that rate of uptake of iodine and rate of release of thyroid hormone may be widely independent of each other in the acute experiment. More experimentation has, however, to be done to permit an analysis of the long-time dependence that evidently exists.

The results show that changes in thyroid activities may be more rapid than was expected and that thyroid activity may be a useful index of vegetative changes both in physiological and pharmacological experiments even in animals subjected to small operations under anesthesia.

[12] A. Cerletti and E. Rothlin, Nature *176*, 785 (1955). – E. Rothlin, J. Pharm. Pharmacol. *9*, 569 (1957). – The autor is indebted to Sandoz AG., Basel (Switzerland) for 'BOL-148'.

Nervous and hormonal stimuli have been shown to have marked effects on thyroid hormone secretion. However, these effects are due to changes in the responsiveness to TSH and cannot be demonstrated in the absence of the pituitary hormone. The uptake of TSH by the thyroid gland may also be related to thyroid blood flow governed both by nerves and hormones.

A detailed description of this work will be presented in the near future[13].

Note added during correction of proof: Since this paper was sent to the Editor, a description of measurement of thyroid blood flow from thyroid I^{131} clearance and *A–V* difference in the rabbit has been presented in Amer. J. Physiol. *192*, 268 (1958) by E. F. Monkus and E. P. Reineke. Their work beautifully supports the view that thyroid blood flow and the effect of TSH do not always go hand in hand. In a group of rabbits with mean acinar cell height of 4·7 μ the *A–V* difference was 25%, in another group with mean cell height of 7·9 μ the *A–V* difference averaged 57%.

Zusammenfassung

An 18 Katzen und 66 Kaninchen wurde die Beziehung zwischen Schilddrüsendurchblutung, Aufnahme von Jod in die Schilddrüse und Abgabe von Schilddrüsenhormon untersucht. Das anorganische und das an Eiweiss gebundene Jod wurde im arteriellen und im venösen Blut der Schilddrüse mit Hilfe radioaktiver Isotopen bestimmt. Die Durchblutung wurde als Frequenz der von dem freien Ende einer in der Schilddrüsenvene befindlichen Kanüle fallenden Tropfen registriert. Es zeigte sich, dass die Geschwindigkeit der Jodaufnahme im wesentlichen proportional der Durchblutung ist, während die Geschwindigkeit der Abgabe von hormonalem Jod durch das thyreotrope Hormon der Hypophyse (TSH) bestimmt wird. Nervöse und hormonale Reize führen auf dem Weg über Durchblutungsänderungen innerhalb kurzer Zeit zu einer Veränderung der Aufnahmegeschwindigkeit und beeinflussen ausserdem die Hormonabgabe durch Änderung der Empfindlichkeit der Schilddrüse gegenüber dem TSH. Die Aufnahme von TSH in die Schilddrüse hängt wahrscheinlich von der Durchblutung ab. Bromlysergsäurediäthylamid, das an der intakten Schilddrüse die Abgabe von hormonalem radioaktivem Jod erhöht, ist an einer akut denervierten Schilddrüsenhälfte ohne Wirkung; daraus kann geschlossen werden, dass die Schilddrüsennerven eine fördernde Wirkung auf die Hormonfreisetzung haben.

[13] U. Söderberg, Acta physiol. Scand. *42*, Suppl. 147, (1958).

CONSTRUCTIONES

An Experiment in the Design of a Scientific Conference

The purpose of this note is to report on a conference design that differed somewhat from the traditional plan of scientific meetings, and on its possible value for similar scientific conferences.

As science progresses, as the number of scientists increases and as scientists become more specialized, the problem of communication among scholars becomes more and more pronounced. The large scientific conventions and the international congresses that several decades ago