98. TISSUE METABOLISM OF BRAIN CORTEX AND LIVER AFTER HYPOPHYSECTOMY AND TREATMENT WITH THYROTROPHIC HORMONE

BY LESLIE DUNDONALD MACLEOD¹ AND MAX REISS

From the Burden Neurological Institute, Stapleton, Bristol

(Received 18 April 1940)

THE experiments described in this paper were carried out to determine the effect of hypophysectomy and hyperthyroidism (induced by the thyrotrophic hormone of the anterior lobe of the pituitary) on the metabolism of the cerebral cortex measured *in vitro*, and to compare this tissue with another organ, namely liver.

Up to now comparatively little work has been done from this point of view and, so far as brain is concerned, we know only the paper of Cohen & Gerard [1935] who reported that 16–19 days' treatment with thyroid powder resulted in an increase in respiratory activity of rats' brain measured in whole brain brei. As regards liver, it has already been found that injection of thyrotrophic hormone produced an increased O_2 uptake of liver and kidney. Hypophysectomy was shown to reduce the O_2 consumption of liver slices about 27% [Reiss *et al.* 1933, 1, 2]. The latter fact was confirmed by Victor & Andersen [1938].

Methods

Our experiments were carried out on male rats, some normal, some 3–10 weeks after hypophysectomy. The operation was performed by the paratracheal route and its completeness was checked before use of the animals (*a*) by the lack of increase in weight, (*b*) by atrophy of the gonads and (*c*) in some cases by the appearance of the sudanophobic zone in the adrenal cortex of one of the suprarenal glands which had been removed for examination [Reiss *et al.* 1936]. After killing, the sella turcica was examined to ensure that the hypophysis had been fully removed.

The tissue respiration was measured in cerebral cortex and liver slices according to the methods of Warburg. O_2 uptake was determined by the direct method employing Ringer solution according to Warburg. It may be mentioned that a higher respiration rate for brain slices may be obtained in phosphate-Ringer, especially if Ca is omitted altogether, but we prefer to use for the direct method Ringer solution as follows: 96 parts 0.15 *M* NaCl, 2 parts 0.15 *M* KCl, 2 parts 0.15 *M* $CaCl_2$, 2 parts 0.15 *M* $NaHCO_3$, 2 parts 10% glucose.

Normal and hypophysectomized rats were treated with thyrotrophic hormone. The material used was a preparation containing 20 guinea-pig units per mg. and was not purified so far that it would not produce antihormonal reactions, but it was free from gonadotrophic and corticotrophic factors.

Results

Reference to Table 1 shows that in the case of the unoperated animals treated with thyrotrophic hormone, the O_2 consumption of liver begins to show an increase as compared with normal controls on the second day after starting

¹ Working with Medical Research Council Grant.

the treatment, and reaches maximal values 4–6 days after treatment begins. The cerebral cortex of these animals, on the other hand, shows no appreciable effect up to the third day. From the fourth day onwards an increase was observed in some cases, but this effect was not constantly apparent.

Effect of thyrotropic hormone on metabolism of brain and liver slices

Table 1. *Unoperated rats*

Treatment units	Duration days	Brain		Liver	
		Q_{O_2}	Q_G^{Na}	Q_{O_2}	Q_G^{Na}
—	—	— 8.6	19.6	— 13.0	1.3
—	—	— 5.8	22.7	— 11.2	1.1
—	—	— 5.7	17.0	— 12.7	1.5
—	—	— 7.8	21.9	— 11.5	1.9
—	—	— 8.8	19.8	— 13.2	1.6
100	1	— 7.3	21.1	— 11.7	1.8
100	1	— 6.7	21.0	— 11.4	0.7
100	1	— 5.4	18.5	— 12.3	1.8
300	2	— 6.6	17.0	— 14.3	1.2
300	2	— 7.8	21.7	— 13.2	2.2
300	2	—	—	— 12.2	2.4
400	3	— 7.9	16.1	— 13.2	1.8
400	3	— 5.5	—	— 13.2	2.7
400	3	— 7.0	19.4	— 13.0	2.8
400	3	— 7.3	—	— 13.3	4.5
500	4	— 10.2	21.0	— 14.4	2.2
500	4	— 8.7	19.5	— 15.1	3.0
500	4	— 9.2	17.4	— 14.0	1.7
600	4	— 9.1	23.0	— 23.0	5.4
700	5	— 13.2	20.2	— 11.6	2.0
800	6	— 7.5	23.2	— 15.1	2.3
800	6	— 9.8	25.3	— 23.0	3.1
800	6	— 8.2	—	— 17.4	1.3

Table 2. *Hypophysectomized rats*

Treatment units	Duration days	Brain		Liver	
		Q_{O_2}	Q_G^{Na}	Q_{O_2}	Q_G^{Na}
—	—	— 7.2	25.7	—	3.0
—	—	— 7.9	25.5	— 9.0	5.2
—	—	— 7.1	23.9	— 6.6	3.1
—	—	— 9.4	27.6	— 9.3	2.5
—	—	— 7.5	26.3	— 9.9	3.7
250	5	— 16.9	23.3	— 16.0	3.0
500	5	— 8.5	25.1	—	1.4
500	5	— 7.2	22.7	— 13.3	—
600	6	— 8.9	14.4	— 10.8	1.2
600	6	— 11.3	—	—	—
800	8	— 10.2	—	—	—
800	8	— 11.2	14.9	— 11.8	2.3
2400	16	— 6.4	25.9	— 7.8	2.2
2400	16	— 7.2	19.1	— 11.8	2.8
2400	16	— 6.5	29.2	— 12.1	2.0

After hypophysectomy (Table 2) the O_2 consumption of liver shows a distinct diminution as compared with normal controls, while that of brain is not affected. The anaerobic glycolysis of brain appears to be somewhat (*ca.* 25%) increased after hypophysectomy. When the hypophysectomized animals were treated with thyrotrophic hormone, the O_2 uptake not only of the liver but of the

cerebral cortex was increased. This latter effect occurs more regularly than in the case of the unoperated animals already mentioned.

The anaerobic glycolysis of brain which showed an increase after hypophysectomy began to decrease after 5-8 days' treatment with thyrotrophic hormone. After 16 days' treatment the effect on brain cortex was no longer evident.

DISCUSSION

It can easily be understood why the O_2 consumption of brain in intact animals should be less subject to endocrinological influence than the liver, the former organ being much more constant in its function than the latter. Also the greater ease with which, in the hypophysectomized animal, the O_2 consumption of the brain could be increased by treatment with thyrotrophic hormone might find an explanation in the fact that, after hypophysectomy, the system of inter-regulation of the various ductless glands is disturbed; whereas in the normal animal attempts to increase the function of one gland will bring compensatory mechanisms into play. It has already been shown that the hypophysectomized animal is much more thyroxine-sensitive than the normal [Reiss & Fischer-Popper, 1936].

The fact that the O_2 consumption of the brain cortex is decreased again after 16 days' treatment with thyrotrophic hormone can perhaps best be explained on the assumption that the so-called "antihormones" are being developed.

As regards the increased rate of anaerobic glycolysis of cerebral cortex slices following hypophysectomy, we are not yet in a position to give an explanation.

SUMMARY

After hypophysectomy there is no significant decrease of O_2 consumption by brain slices (contrary to the behaviour of liver slices of the same animal) but an increase in anaerobic glycolysis of about 25 %.

After treatment of hypophysectomized rats with thyrotrophic hormone, the O_2 consumption of brain was found to be increased, as compared with normal unoperated animals, between 5-8 days after commencement of treatment. The liver O_2 uptake was restored or slightly increased above the normal. After 16 days' treatment, the effect on brain was no longer apparent, and that on liver less marked, due presumably to the development of the so-called "antihormones".

After treatment of normal unoperated animals with thyrotrophic hormone, the O_2 consumption of brain was much less markedly increased than in the case of hypophysectomized animals.

REFERENCES

- Cohen & Gerard (1935). *Proc. Soc. exp. Biol., N.Y.*, **32**, 1446.
- Reiss, Balint, Oestreicher & Aronson (1936). *Endokrinologie*, **18**, 1.
- & Fischer-Popper (1936). *Endokrinologie*, **18**, 92.
- Hochwald & Druckrey (1933, 1). *Med. Klinik*. p. 1112.
- — — (1933, 2). *Endokrinologie*, **13**, 1.
- Victor & Andersen (1938). *Amer. J. Physiol.* **122**, 296.