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THYROID AND HYPERGLYCAEMIA PRODUCED BY ADRENALINE AND NORADRENALINE

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The hyperglycaemia produced in rabbits by subcutaneous injection of adrenaline has often been stated to be augmented by thyroid feeding. There have been repeated suggestions that the destruction of adrenaline in the body, in some organs at least, depends on the action of the enzyme amine oxidase, and Burn (1952a) has recently emphasized findings which are consistent with this idea. The possibility thus arose that the augmentation of adrenaline hyperglycaemia by thyroid feeding might be due to a diminution in the amount of amine oxidase in the liver. Spinks and Burn (1952) found that a fall in amine oxidase took place after two weeks of thyroid feeding; and, further, that the operation of thyroidectomy, both in rabbits and in rats, was followed by a rise in the amount of amine oxidase in the liver.

The fall in liver amine oxidase was not large, and it was impossible to say with certainty that it accounted for the increase in adrenaline hyperglycaemia. Now noradrenaline is less effective than adrenaline in causing hyperglycaemia, as was first shown by Schümann (1949). Noradrenaline is also less effective than adrenaline in constricting the vessels of the rabbit ear, in dilating the pupil of the cat's eye, and in contracting the nictitating membrane : Burn and Robinson (1951) explained these observations by their finding that noradrenaline is more readily oxidized by amine oxidase than is adrenaline. Such an explanation would attribute the smaller hyperglycaemic action of noradrenaline to more rapid destruction by amine oxidase in the liver. Thus, thyroid feeding might be expected to augment noradrenaline hyperglycaemia to a greater extent than it augments adrenaline hyperglycaemia

Experiments have therefore been carried out to determine :

(1) the dose-response curve for the hyperglycaemia produced by adrenaline in normal rabbits ;

(2) the amounts of adrenaline and noradrenaline equiactive in producing hyperglycaemia in normal rabbits ;

(3) the effect of thyroid feeding on the hyperglycaemia produced by amounts of (*a*) adrenaline, (*b*) noradrenaline, which were roughly equivalent in normal rabbits ;

(4) the effect of thyroid feeding on the amine oxidase in rabbit livers ;

(5) the effect of small doses of ephedrine—which is known to inhibit amine oxidase—on the hyperglycaemia produced by adrenaline.

METHODS

Rabbits of various breeds and both sexes were taken at random from stock. Their weight varied from 1.5–2.5 kg. They were fed on a mixed diet of bran and whole cereal with addition of some cabbage. For thyroid feeding, dried thyroid was given by stomach tube for a period of 14 days with 1–2 days' interval, so that the daily intake amounted to 200 mg. irrespective of body weight.

Determination of Blood Sugar.—For an experiment six rabbits were kept without food for 18 hr. Blood was removed from the ear veins, mixed with small amounts of potassium oxalate, and the blood sugar estimated by a combination of Somogyi's (1930) method of precipitating the proteins with Hagedorn-Jensen's (1923) method of sugar estimation. Each determination was done in duplicate and the mean calculated. For the estimation of the initial value 2 × 0.5 ml. blood was removed; after the subcutaneous injection of adrenaline or noradrenaline 2 × 0.1 ml. blood was taken at intervals of 1, 2, 3, 4, and 5 hr. and the samples pooled. In half of the rabbits adrenaline was tested on the 13th day of thyroid-feeding, and noradrenaline on the 15th day. In the other half the order was reversed. The means were taken to be valid for the 14th day. A corresponding cross-over method was applied in the control experiments before thyroid feeding began. With one exception not more than two experiments were done within a week. All values refer to L-adrenaline and to L-noradrenaline.

Determination of Amine Oxidase.—Rabbits were stunned by a blow on the head and bled to death. The left liver lobe was removed immediately and tested at once or kept at −10° C. for not more than two days. For the manometric determination the method described by Spinks and Burn (1952) was adopted which consisted of the incubation of 50 mg. homogenized liver suspended in phosphate buffer (*p*H 7.4) with M/50 tyramine in the presence of M/100 semicarbazide and N-KOH (in the centre well). The oxygen uptake was measured for 30 min. and plotted in 5-min. intervals. The uptake between the 5th and 20th min. after tipping was measured and calculated as μl. O_2/100 mg. liver/15 min.

RESULTS

Dose-response Curve for Adrenaline.—The effect of a given amount of adrenaline or noradrenaline was measured by subtracting the initial blood sugar from the mean value during the five hours after injection, and expressing this difference as a percentage of the initial blood sugar. In order to find a suitable way to measure an increase in sensitivity, the relation between dose and response was determined. The details of the experiments are given in Table I. Fig. 1 relates the mean effect in six normal rabbits to each of five doses of adrenaline, plotted on a logarithmic scale. Statistical calculation showed that the regression line did not depart significantly from linearity. Over this dose range doubling the dose always increased the response by 41.3%.

TABLE I

HYPERGLYCAEMIC ACTION OF ADRENALINE IN NORMAL RABBITS EXPRESSED AS PERCENTAGE BLOOD SUGAR INCREASE

Rabbit	Dose of Adrenaline (s c.) in μg /kg.				
	30	60	120	240	480
1	7·3	11·6	49·1	59·8	161·7
2	29·8	51·2	48·9	90·6	158·6
3	17·3	76·5	72·7	165·1	227·0
4	7·3	78·7	77·1	154·2	178·2
5	3·5	19·8	93·4	104·8	162·0
6	4·9	41·8	80·0	128·6	210·8
Mean	11·7	46·6	70·2	117.2	183·1

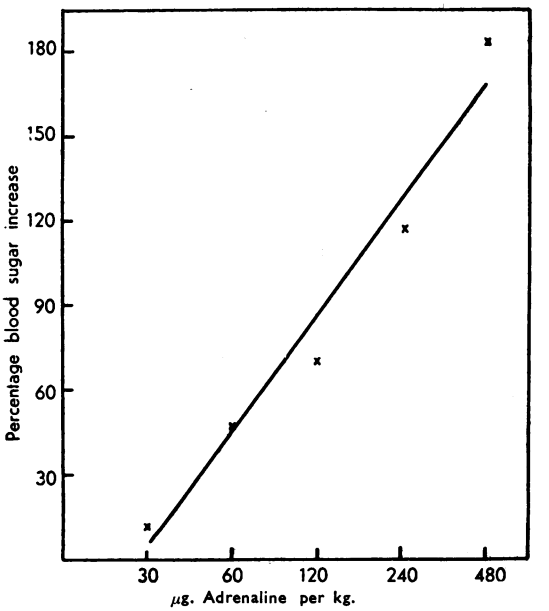

FIG. 1.—Dose-response curve for hyperglycaemic action of adrenaline in 6 normal rabbits. Each cross represents mean response of all rabbits.

Adrenaline and Noradrenaline Equivalence.—Since Ellis (1951) found that the dose-response curve for noradrenaline was parallel to that for adrenaline, a dose-response curve for noradrenaline was not determined on so many rabbits as was that for adrenaline. Experiments in four rabbits showed that the mean percentage blood sugar rise was 24.1 for 125 μg./kg., 35.8 for 250 μg./kg., and 57.9 for 500 μg./kg.

The relation between the hyperglycaemic effect of adrenaline and noradrenaline was determined from observations in 14 rabbits which were tested both with 60 μg./kg. adrenaline and with 250 μg./kg. noradrenaline. These doses were chosen because they produced effects of a similar order. The results are given in Table II (rabbits Nos. 7–20). The mean effect of the injection of

TABLE II

HYPERGLYCAEMIC RESPONSE TO 60 μg./kg. ADRENALINE AND TO 250 μg./kg. NORADRENALINE BEFORE AND AFTER 14 DAYS OF THYROID FEEDING

The response is expressed as the percentage blood sugar increase

Rabbit	Adrenaline			Noradrenaline		
	Before	After	Difference	Before	After	Difference
7	19·0	33·6	+14·6	26·6	20·6	−6·0
8	39·7	61·5	+21·8	36·0	42·4	+6·4
9	34·1	93·1	+59·0	51·5*	58·4	+6·9
10	20·1*	83·8	+63·7	29·3*	19·6	−9·7
11	110·6*	117·3	+6·7	97·4*	96·9	−0·5
12	79·0*	146·2	+67·2	63·6*	49·5	−14·1
13	145·3*	134·3	−11·0	105·0*	73·2	−31·8
14	79·6*	96·5	+16·9	39·0*	63·8	+24·8
15	73·4*	92·3	+18·9	28·2*	21·0	−7·2
16	78·4	86·5	+8·1	32·2	30·7	−1·5
17	44·4	63·2	+18·8	51·1*	21·8	−29·3
18	64·2	101·6	+37·4	68·2*	38·8	−29·4
19	93·2	112·8	+19·6	46·3*	22·3	−24·0
20	39·8	56·3	+16·5	25·7*		
21				35·3*	37·2	+1·9
22				24·9*	18·7	−6·2
23				25·6	21·7	−3·9
24				22·8	26·0	+3·2
25				34·2*	19·7	−14·5
Mean	65·8	91·4	+25·6	45·4	37·9	−7·5

* Mean of two experiments.

adrenaline was a blood-sugar rise of 65.8%, and that of the injection of noradrenaline was a blood-sugar rise of 50%. The difference between these two effects was 15.8%. Since an increase of 41.3% was produced by doubling the dose, it follows that the logarithm of the difference in potency between the doses of adrenaline and noradrenaline used was $\frac{15.8}{41.3} \times \log 2$, which is 0.115%. Hence the difference in potency between the doses of adrenaline and noradrenaline used was 1.3. Thus 1 μg. adrenaline was equal to 5.43 μg. noradrenaline in hyperglycaemic action.

Effect of Thyroid Feeding.—The effect of administering dried thyroid for 14 days is shown in Table II, where the change in the hyperglycaemic response is shown to 60 μg./kg. adrenaline in 14 rabbits, and in the hyperglycaemic response to 250 μg./kg. noradrenaline in 18 rabbits. The hyperglycaemic response to adrenaline increased in 13 out of the 14 rabbits, while that to noradrenaline increased in 5 out of 18 and decreased in 13 out of 18. The mean change in the hyperglycaemic response to adrenaline was an increase in the blood-sugar rise of 25.6%, so that the effect of 60 μg./kg. adrenaline in the rabbits after thyroid feeding was equivalent to that of 85 μg./kg. in the same rabbits before. The mean change in the hyperglycaemic response to noradrenaline was a decrease of 7.5% in the blood-sugar rise. Thus 250 μg./kg. noradrenaline had an effect in the rabbits after thyroid feeding equivalent to 220 μg./kg. in the same rabbits before. These changes in sensitivity to adrenaline and to noradrenaline were both significant (for adrenaline $P<0.01$; for noradrenaline $P<0.05$).

The experiments thus showed that the difference in the hyperglycaemic action of adrenaline and of noradrenaline was exaggerated and not diminished by thyroid feeding for 14 days. Whereas in the control observations the mean ratio for equiactive amounts of adrenaline and noradrenaline was 1 to 5.44 ± 1.12, in the thyroid-fed animals the mean ratio was 1 to 9.78 ± 1.13.

The mean loss of weight due to thyroid feeding was 270 g., and did not exceed 500 g. in any one rabbit. There was no correlation between the loss of weight and the increase in sensitivity to adrenaline.

Changes During Thyroid Feeding.—When thyroid feeding was prolonged beyond two weeks Burn and Marks (1925) found that the hyperglycaemic response to adrenaline decreased ; this change appeared to be due to the exhaustion of the liver glycogen reserve, as described by Cramer and Krause (1913).

Thus there were two phases in the effect of thyroid feeding on adrenaline hyperglycaemia, and it seemed probable that there were also two phases in the effect on noradrenaline hyperglycaemia. The change from one phase to the other might not coincide for the two substances, and the fall in the hyperglycaemic response to noradrenaline on the fourteenth day of thyroid feeding might have been preceded by a rise at an earlier stage. Experiments were therefore done to determine the responses to 250 μg./kg. noradrenaline on the third, seventh, and eleventh days of thyroid feeding. The results are given in Table III. They

TABLE III

HYPERGLYCAEMIC ACTION OF NORADRENALINE EXPRESSED AS PERCENTAGE BLOOD SUGAR INCREASE ON SUCCESSIVE DAYS OF THYROID FEEDING

Rabbit	Days of Thyroid Feeding				
	0	3	7	11	14
16	32·2	82·4	51·6	28·4	30·7
17	51·1*	35·8	38·7	25·6	21·8
18	68·2*	75·6	67·7	48·4	38·8
19	46·3*	64·8	79·6	86·0	22·3
20	25·7*	33·9	33·6	34·2	0
24	22·8	45·2	38·3	26·0	0
Mean	41·1	56·3	51·6	41·5	28·4

* Mean of two experiments.

show that the hyperglycaemia in five out of the six rabbits was increased during the first week and decreased in the second. Only one rabbit (No. 17) showed a decreased sensitivity to noradrenaline throughout the experiment. The individual maximal responses were observed between the third and the eleventh day, and Fig. 2 shows that the maximal mean effect was obtained on the third day, the difference from the controls being +15.2%.

In another group of four rabbits tested with 250 μg./kg. noradrenaline on the third day only, three showed an increased response, while one was less sensitive than before thyroid-feeding. The mean increase of response of all ten rabbits on the third day of thyroid-feeding was 14.3% ; this was significantly different from the controls ($P<0.05$). Thus the decrease in sensitivity to noradrenaline observed on the fourteenth day of thyroid-feeding was preceded by a significant increase in sensitivity during the first week.

To compare the change in sensitivity to noradrenaline with that to adrenaline, five out of the six rabbits in Table III were given 60 μg./kg. adrenaline on the seventh and fourteenth day. The

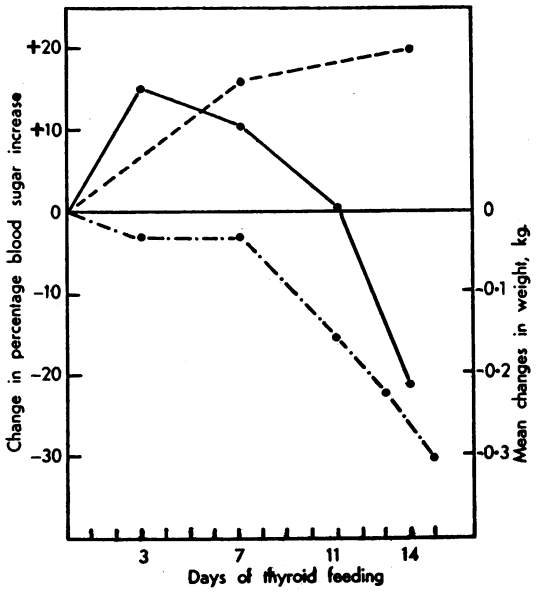

FIG. 2.—Changes in percentage blood sugar response to adrenaline and noradrenaline during thyroid feeding. Mean of controls taken as 0. The mean response of 6 rabbits to 250 μg./kg. noradrenaline (solid line) was increased during the first week and decreased during the second. The mean response of 5 of these 6 rabbits to 60 μg./kg. adrenaline (broken line) increased gradually. The loss of weight (dot–dash) appeared during the second week.

mean responses gradually increased, as shown in Fig. 2.

From the seventh day onwards the rabbits began to lose weight (Fig. 2). The onset of loss in weight appeared to coincide with the decrease in sensitivity to noradrenaline.

Relationship of Initial Blood Sugar to Hyperglycaemic Response.—Hemmingsen and Marks (1932) showed that the percentage blood-sugar reduction after insulin increased with increasing initial value of the blood sugar. The opposite was found to be true for the adrenaline and noradrenaline hyperglycaemia. The higher the initial blood-sugar value, the lower was the response to a given dose. A correlation between the initial blood sugar and the response to 60 μg./kg. adrenaline was observed in 41 experiments in normal rabbits, and was found to be highly significant ($P<0.001$), the regression coefficient being 1.838 ± 0.418. This meant that the magnitude of a response to a given dose of adrenaline depended on the initial blood-sugar value. The same relationship was observed for 250 μg./kg. noradrenaline and 30 μg./kg. adrenaline. In Fig. 3 the control rabbits were arranged in different groups according to their initial blood-sugar values, and the mean responses to 30 and 60 μg./kg. adrenaline and to 250 μg./kg. noradrenaline were plotted. The resulting curves were not parallel, the slope being steeper for 60 μg./kg. adrenaline than for 30 μg./kg. adrenaline. 250 μg./kg. noradrenaline, which had an intermediate action, showed an intermediate slope. Thus it was concluded that the slope of the curves did not depend on the nature of the substance injected but on its mean effect.

Thyroid-feeding seemed to affect this relationship. As adrenaline was more effective after thyroid-feeding the curve representing the response

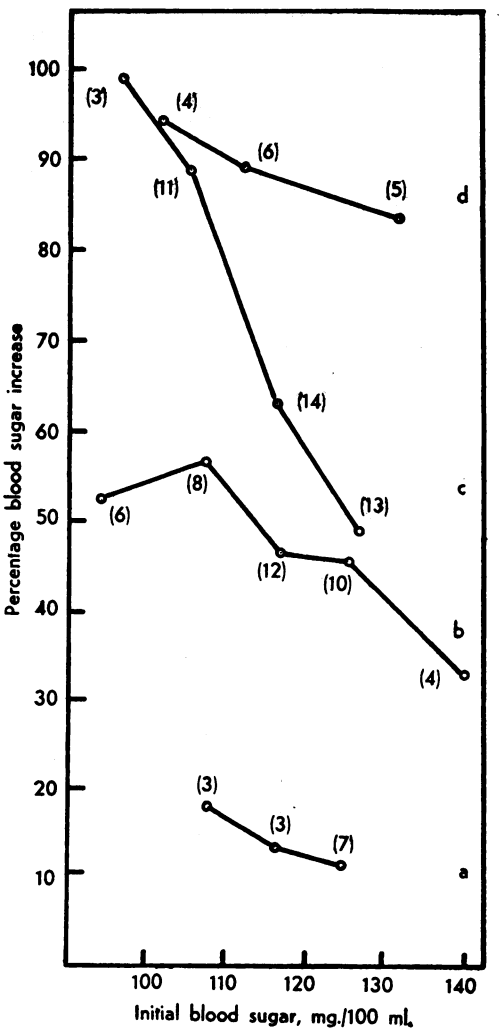

FIG. 3.—Relationship between initial blood sugar value and hyperglycaemic response to (*a*) 30 μg./kg. adrenaline, (*b*) 250 μg./kg. noradrenaline, and (*c*) 60 μg./kg. adrenaline in normal rabbits, and (*d*) to 60 μg./kg. adrenaline after 14 days of thyroid feeding. Numbers in brackets denote number of estimations made. For further details see text.

to 60 μg./kg. adrenaline after thyroid-feeding was expected to be steeper than that of the controls. It was, however, nearly horizontal (Fig. 3*d*), so that there was no correlation between initial blood-sugar value and response after thyroid-feeding. As this curve represented only a limited number of experiments, the difference between its slope and the slope of that for the controls (Fig. 3*c*) was not significant.

These results showed that a comparison of responses without consideration of the initial blood-sugar value might lead to error. Care was therefore taken to ensure that the mean responses calculated in Tables I–IV referred to approximately similar mean initial blood-sugar values. Thus, for instance, the mean initial blood-sugar value observed in the experiments with adrenaline before thyroid-feeding was 115.5 mg./100 ml. and after thyroid-feeding was 114.2 mg./100 ml. The corresponding values for the responses to noradrenaline were 115.5 mg./100 ml. and 114 mg./100 ml. These differences were too small to affect the results shown in Table II.

Changes in Amine Oxidase Activity of the Liver after Thyroid-feeding.—The determination of the amine oxidase activity of the livers of 14 control and 20 thyroid-fed rabbits confirmed the results of Spinks and Burn (1952), since amine oxidase activity fell from 96.5±3.68 μl. O_2/100 mg. liver/15 minutes in the controls, to 86.55±3.09 μl. O_2/100 mg. liver/15 minutes after thyroid-feeding. Thus by thyroid-feeding the amine oxidase activity of the liver was reduced to 89.6% of the value for the controls, a small but significant fall ($P<0.05$).

The Action of Ephedrine on Adrenaline Hyperglycaemia.—Since ephedrine is known to inhibit the action of amine oxidase (Blaschko, Richter, and Schlossmann, 1937), ephedrine should augment the hyperglycaemic action of adrenaline, if this is limited by the amine oxidase present. Ellis (1951) found that ephedrine in amounts as great as 25 mg./kg. did not alter the blood-sugar level of the rat, and Riechert and Schmieder (1941) found no change during three hours after subcutaneous injection of 10 mg. ephedrine into rabbits.

In a series of experiments on nine rabbits a single dose of 1 mg./kg. ephedrine was given subcutaneously 15 minutes before giving 60 μg./kg. adrenaline. No difference between the response to adrenaline and to adrenaline plus ephedrine was observed.

As the effect of this single dose of ephedrine probably did not last for more than one hour, a second series of 12 rabbits was tested in a different way: 1 mg./kg. ephedrine was given subcutaneously 15 minutes prior to 60 μg./kg. adrenaline, and the same dose of ephedrine was repeated 60, 120, and 180 minutes afterwards. As Table IV shows, the combination of adrenaline and ephedrine in this series was more effective than adrenaline alone in 11 of 12 rabbits. The mean increase in response was +31.7% ($P<0.02$), the mean initial blood-sugar value being approximately the same in both groups. Thus when a certain ephedrine level was maintained for more than three hours the effect of adrenaline was significantly potentiated. In the presence of ephedrine, 60 μg./kg. adrenaline had the same hyperglycaemic effect as 96 μg./kg. alone. This potentiation can be compared with the effect of thyroid-feeding, after which 60 μg./kg. adrenaline had the same effect as 85 μg./kg. before.

TABLE IV

THE POTENTIATION OF THE HYPERGLYCAEMIC ACTION OF ADRENALINE BY EPHEDRINE

Figures are percentage blood sugar rise

Rabbit No.	Adrenaline	Adrenaline plus Ephedrine	Difference
26	59·5*	114·9	+55·4
27	58·6	74·3*	+15·7
28	40·7*	164·9	+124·2
29	62·0	101·7*	+39·7
30	91·0	45·2*	−45·8
31	100·8	120·2	+19·4
32	24·1	51·6	+27·5
33	53·8*	109·6	+55·8
34	49·6*	67·6	+18·0
35	61·9	98·5	+36·6
36	71·0	92·4	+21·4
37	45·0*	57·2	+12·2
Mean	59·8	91·5	+31·7

* Mean of two experiments.

The amine oxidase activity of the 12 rabbit livers of the experiments of Table IV was determined and a calculation was made to see whether there was any correlation between amine oxidase activity and (*a*) the response to the test dose of adrenaline, (*b*) the potentiating effect of ephedrine. No correlation was, however, found.

The Ratio of Equi-effective Doses of Adrenaline and Noradrenaline on the Isolated Rabbit Duodenum Before and After Thyroid-feeding.—To find if thyroid-feeding affected the ratio of equiactive amounts of adrenaline and noradrenaline on the isolated rabbit duodenum in the same way as it affected the ratio of doses producing the same hyperglycaemia, the ratio was determined on the isolated duodenum of six control and six thyroid-fed rabbits. Table V shows that it did not change, and that the mean ratio agreed with

TABLE V

RATIO OF EQUIACTIVE AMOUNTS OF ADRENALINE AND NORADRENALINE ON ISOLATED STRIPS OF DUODENUM TAKEN FROM CONTROL RABBITS AND FROM RABBITS AFTER 14 DAYS OF THYROID-FEEDING

Controls	After 14 Days of Thyroid-feeding
1 : 1·11	1 : 0·85
1 : 0·6	1 : 0·9
1 : 0·9	1 : 4·0
1 : 1·1	1 : 1·0
1 : 1·3	1 : 1·5
1 : 1·25	1 : 0·42
Mean 1 : 1·01	1 : 1·11

the 1:1 value found by West (1947) and by Luduena, Ananenko, Siegmund, and Miller (1949). The minimal effective doses were not tested, but adrenaline and noradrenaline appeared to be more effective after thyroid-feeding, since a comparable relaxation of the intestine was obtained with about one-third of the normal dose.

DISCUSSION

The hyperglycaemia produced in rabbits by the subcutaneous injection of adrenaline is generally accepted as being a direct action of adrenaline on the liver. Miculicich (1912) showed that it was absent after the injection of ergotoxine, and this was confirmed by Burn (1915). Previous statements that thyroid-feeding increases adrenaline hyperglycaemia have now been confirmed, by determining a dose-response curve for adrenaline, and then using a large group of rabbits for a study of the effect of thyroid-feeding. The administration of 0.2 g. thyroid daily augmented the hyperglycaemic response to adrenaline, so that at the end of two weeks the response to 60 μg./kg. was equivalent to the response to 85 μg./kg. initially.

One explanation of this increased effect would be that thyroid-feeding led to a fall in the enzyme which destroys adrenaline. While the steps in the breakdown of adrenaline are not yet generally agreed, there is increasing evidence that amine oxidase is concerned. The work of Schayer and his colleagues (see Schayer and Smiley, 1953) on the fate of C^{14} labelled epinephrine has led them to the conclusion that amine oxidase plays a major role in epinephrine metabolism in the intact animal. Amine oxidase is present in the liver, and Spinks and Burn (1952) found that in rabbits fed with thyroid extract for 14 days there was a significant fall in the amine oxidase in the liver. Their observations have been confirmed in these experiments, and this suggests that the increase in adrenaline hyperglycaemia may indeed be due to the decline in the amount of the enzyme. Further support was gained for this view by finding that ephedrine potentiated adrenaline hyperglycaemia when 1 mg. was given before adrenaline and at hourly intervals after. This agreed with Gaddum and Kwiatkowski's findings in blood vessels, nictitating membrane, and frog heart (1938).

The mean potency of noradrenaline in raising the blood sugar was found to be 18% of that of adrenaline. The effect of thyroid-feeding was to increase its mean hyperglycaemic action more rapidly than that of adrenaline during the first three days; but by seven days the increase in the adrenaline effect was the greater, and by two weeks the noradrenaline effect had declined below the initial value. This result did not support the expectation, outlined earlier, that thyroid-feeding would augment noradrenaline hyperglycaemia more than it augmented adrenaline hyperglycaemia. It pointed to a difference in the action of the two substances. While adrenaline breaks down muscle glycogen to form lactic acid which is then converted to liver glycogen in the lactic acid cycle (see Soskin, 1941), noradrenaline does not have this action (Bearn, Billing, and Sherlock, 1951; Russell, personal communication). The work of Geiger and Schmidt (1928) showed that the breakdown of muscle glycogen can play a part in the hyperglycaemic effect of adrenaline. They treated dogs for several days with phloridzin until the liver glycogen was greatly diminished. They found that adrenaline was still able to produce a rise of blood sugar, this being accompanied by a complete loss of muscle glycogen. Thus, while the blood-sugar response to noradrenaline depends on the liver glycogen only, that of adrenaline probably depends on muscle glycogen as well.

How great a fall in amine oxidase would be required to affect the adrenaline response is unknown. Evidence was obtained by Nachmansohn (1952) that conduction in nerve ceased only when almost the whole of the cholinesterase present was inhibited, and that the inhibition of a small proportion of the cholinesterase had no effect on function. Observations in other tissues show that this is not a general rule. A concentration of eserine 4×10^{-8} g./ml. causes a prompt increase in the tone of a loop of rabbit duodenum (Burn, 1952b) and a concentration of eserine 10^{-8} causes the rate of isolated rabbit auricles to become slower (Burn and Kottegoda, 1953). *In vitro* experiments by Miss H. Shelley have shown that when ACh is used as a substrate the cholinesterase in the auricles was inhibited 15.4% by eserine 3×10^{-8} g./ml. and was not appreciably affected by half this concentration.

Another explanation for the hypersensitivity to adrenaline produced by thyroid feeding must be mentioned. The observed relationship of initial blood sugar and response to a given dose of adrenaline may be due to two or more factors. The utilization of glucose by extra hepatic tissue has been found to increase greatly with a rise in the blood sugar level. On the other hand, the liver maintains the blood sugar at a normal level by increasing the intake and decreasing the output of glucose (Soskin, 1941). These two different regulating mechanisms may well account for the smaller response to a given dose of adrenaline at a high initial value.

The fact that after thyroid feeding the response to adrenaline does not depend on the initial blood sugar suggests an impairment of one or both of these regulating mechanisms. The effect of thyroid hormone on the utilization of glucose by extra hepatic tissues is unknown, while both the anterior pituitary hormones and insulin control the maintenance of the normal blood sugar level by the liver (Soskin, 1941). As thyroid hormone affects both the anterior pituitary and the β cells of the pancreas (Houssay, Foglia, and Martinez, 1946), it is possible that the increased adrenaline hyperglycaemia is due to changes in the mechanisms which control the blood sugar.

Summary

1. A dose-response curve has been determined for the hyperglycaemic action of adrenaline in normal rabbits. The response bore a linear relation to the log dose.

2. The dose-response curve for noradrenaline was parallel to that for adrenaline; noradrenaline was found to have 18% of the action of adrenaline.

3. The mean hyperglycaemic response to 60 μg./kg. adrenaline was increased by feeding 0.2 g. thyroid daily for 14 days so that it became equal to the response to 85 μg./kg. before thyroid feeding.

4. The mean hyperglycaemic response to 250 μg./kg. noradrenaline was increased by feeding 0.2 g. thyroid daily during the first three days to a greater extent than was the adrenaline response. Thereafter the noradrenaline response diminished, and at the end of 14 days was less than the initial response.

5. The response to adrenaline in normal rabbits was found to depend on the height of the resting blood sugar. In thyroid-fed rabbits the response to adrenaline was independent of the height of the resting blood sugar.

6. Ephedrine potentiated adrenaline hyperglycaemia to about the same extent as did thyroid feeding when 1 mg. was injected 15 min. before the adrenaline and at hourly intervals for 3 hr. after.

7. Thyroid feeding produced a fall of liver amine oxidase to 89.6% of the control value, this fall being significant, and approximately the same as that previously found.

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