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COMPENSATORY REACTIONS TO A LACK OF METABOLIZABLE GLUCOSE

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SUMMARY

1. Following the injection of adrenaline into rats pre-treated with thyroxine, there is a pronounced and prolonged increase in their oxygen consumption. On this basis a method is described for following increases in the rate of secretion of adrenaline in response to physiological stimuli in rats.

2. Using this method the onset and the cessation of the increased rate of secretion of adrenaline during insulin induced hypoglycaemia has been found to correspond to a blood glucose concentration of approximately 40 mg/100 ml.

3. 3-Methylglucose (3-*O*-methyl-D-glucopyranose) is shown to cause a marked and sustained increase in the blood glucose concentration.

4. This action of 3-methylglucose can be accounted for by an increase in the rate of secretion of adrenaline, as it is accompanied by a rise in oxygen consumption in thyroid treated rats and is prevented by interruption of the central nervous connexions of the adrenal medulla.

5. These findings can be explained by 3-methylglucose's acting upon the receptor which reacts to insulin hypoglycaemia by bringing about the secretion of adrenaline. It is shown that the effective stimulus to this receptor is not a low blood glucose concentration. The stimulus is possibly a depressed rate of utilization of glucose by the receptor tissue.

INTRODUCTION

In a classical series of experiments, Cannon, MacIver & Bliss (1924) showed that when, under the influence of insulin, the blood glucose concentration fell below a certain critical value a secretion occurred from the adrenal medulla. This could be prevented by cutting the splanchnic nerves. It has subsequently been shown that the secretion from the adrenal medulla evoked by hypoglycaemia is adrenaline and that the

output of noradrenaline is little affected (Hökfelt, 1951; Euler & Luft, 1952). This selective release of adrenaline would appear to be an emergency response to hypoglycaemia and not an element in the normal homeostasis of the blood glucose, for it ceases when the blood glucose concentration rises above the level at which it is initiated and before the blood glucose returns to normal (Armin & Grant, 1959).

The inference from these studies is that there exists somewhere in association with the nervous system a receptor that is sensitive to the presence of glucose and which responds when the blood glucose falls below a certain minimum concentration by promoting the secretion of adrenaline. The experiments here presented concern the nature of the stimulus to which such a receptor or sensitive tissue reacts. In particular, they show that the mechanism that promotes an increased secretion of adrenaline can come into action at blood glucose concentrations above normal, thereby demonstrating that the effective stimulus is not a low concentration of glucose in the blood *per se* but rather a state in which glucose is unavailable to a sensitive tissue.

In some of the following experiments use has been made of a previous observation that permits the demonstration of the secretion of adrenaline in the intact, unoperated animal; namely that in rats, previously treated with thyroxine, the injection of adrenaline is followed by a conspicuous and prolonged rise in oxygen consumption (Himsworth, 1960).

METHODS

Animal techniques. Female rats of a laboratory albino stock were used in all experiments. Food but not water was removed from the cages on the evening before an experiment.

Thyroxine was administered in the drinking water to rats whose average weight was 140 g. The water consumption by cages of six rats was noted and the concentration of Na L-thyroxine in the drinking water was adjusted from 10 to 15 mg/l. so that each animal received an estimated 2–3 mg of thyroxine over 10 days. This dose did not cause any obvious change in the animals and they did not lose weight.

The apparatus for the measurement of the oxygen consumption of individual rats held six animals and was built in two parts. The respiration chambers and the spirometers were in separate units. The design of the spirometer unit conformed closely to that described by Holtkamp, Ochs, Pfeiffer & Heming (1955). The six respiration chambers were made of 4 in. (10·2 cm) diameter brass tube. They were closed at one end and let into the side of a brass water trough. The water in the trough was circulated by a propeller and maintained at a constant temperature (26–27° C) by a thermostatically controlled heater. The chambers contained a sheet of perforated brass on which the rats stood and beneath which was a tray containing a carbon dioxide absorbent ('Durasorb'). The open ends of the respiration chambers were closed by Perspex covers and sealed with greased rubber rings. A pipe let into the closed end of the chamber was connected to a spirometer by a plastic tube. The total internal volume of each of the spirometer respiration chamber units was approximately the same. As conditions were constant in all experiments no correction was made for physical factors, e.g. water saturation and atmospheric pressure. The oxygen consumption

of each rat was not corrected for surface area for if there is no great variation in body weight the observed oxygen consumption is the most accurate figure for purposes of comparison (Chiu & Hsieh, 1960).

The following procedure was used in all experiments where the oxygen consumption of the animals was measured. On at least two occasions during the 10 days over which thyroxine was given the animals were placed for several hours in the apparatus so that they might become familiar with it. The rats were placed in the respiration chambers on the morning of the 11th day after an overnight fast. No readings were made for at least 1 hr. The basal oxygen consumption was then recorded in 5 min periods over 1 hr, the results being expressed as ml./5 min. Each rat was next given two injections, one subcutaneous (0·1 ml.) and one intraperitoneal. Adrenaline (50 μg) and insulin (0·25 u.) were given subcutaneously, glucoses (600 mg) were given intraperitoneally. If no active substance was given by either route an injection of saline was given. Immediately after the injections the animal was returned to the respiration chamber. Recording of the oxygen consumption was started 2 min after the injections were given. The first reading after this was invariably artificially low because of alteration in the temperature within the respiration chamber owing to its having been opened.

Blood samples were taken immediately after the rapid induction of anaesthesia with ether either from the tail or after cutting the common carotid artery in the neck. If this procedure was carried out swiftly it was found that the anaesthetic did not influence the blood glucose concentration. Blood was taken on only one occasion from each animal.

Urine collections were made from a group of eight rats in a metabolism cage on top of a funnel fitted with a faeces deflector. At the end of each collection period the sides of the funnel were washed with distilled water, the urine and washings being collected in a single flask. Sulphadimidine (250 mg) was added to each flask to prevent the growth of *Escherichia coli* because this organism is capable of metabolizing 3-methylglucose (Czáky & Glenn, 1957). Sulphadimidine does not interfere with the subsequent estimation of 3-methylglucose.

In some animals both adrenal glands were transplanted in order to sever the nervous connexions of the medulla. A single dorsal incision was made under ether anaesthesia. Each gland was removed, cleaned of fat and transfixed with a single atraumatic cat gut suture, with which it was then sewn to the surface of the ipsilateral ovary. (In a very few instances the gland was placed in a fascial pocket near the femoral canal.) These animals were given saline (0·9 g NaCl/100 ml.) instead of drinking water for 10 days after the operation. They were given no ACTH or steroid replacements. No animals with adrenal gland transplants were used for experiments until 6 weeks had elapsed from the time of operation.

Acute experiments were carried out under anaesthesia with pentobarbitone sodium (5 mg/100 g body wt. I.P. with supplementary doses of 2·5 mg as required). In some of these experiments the spinal cord was divided. The level and completeness of the transection of the cord were checked by examination at autopsy. In no acute experiments were any blood samples taken within 1 hr of the induction of anaesthesia or the completion of all operative procedures. Blood samples in these experiments were taken either from the tail or, if the arterial blood lactate concentration was being measured, through a polythene catheter in the common carotid artery.

Chemical methods. Blood and plasma samples for sugar determinations were diluted in saline and the proteins precipitated with zinc sulphate and sodium hydroxide. The blood glucose was estimated by a glucose oxidase–peroxidase method. 3-Methylglucose is not a substrate for glucose oxidase (Keilin & Hartree, 1948) and does not affect the reaction of the enzyme with glucose. The total amount of aldosaccharide was measured as described by Hyvärinen & Nikkilä (1962). This method is claimed to be specific for glucose (in the absence of 3-methylglucose). A direct comparison of the two methods over a range of blood glucose concentrations (10–150 mg/100 ml.) showed a linear relationship between the results obtained by the two methods but the values obtained by the glucose oxidase technique were

lower by a constant factor (glucose [*aldosaccharide*] = 1·02 glucose [*glucose oxidase*] + 11·5; $r = 0{\cdot}955$). The blood 3-methylglucose concentration was determined by the difference between the results obtained by the two methods, allowance being made for this factor and the proportionately slightly greater intensity of colour developed by 3-methylglucose in the aldosaccharide estimation.

Blood lactate concentration was measured, after protein precipitation with 0·6 M perchloric acid, by an enzymic method (Boehringer).

The plasma water content was determined in the manner described by Dicker (1948). The haematocrit was measured using a Hawksley micro-haematocrit centrifuge.

All chemical determinations were carried out in duplicate.

Statistical methods. Results are expressed as the mean ± standard error of the mean (S.E.M.). The variance was analysed where appropriate and the probability (P) derived from tables of the F distribution.

Chemicals. 3-Methylglucose (3-*O*-methyl-α-D-glucopyranose) was purchased from Koch-Light Laboratories Ltd.

RESULTS

The subcutaneous injection of 50 μg adrenaline caused an immediate increase in the oxygen consumption of each of a group of five rats given thyroxine. This increase was maximal 1 hr after the injection and persisted for 2 hr (Fig. 1). The injection of saline subcutaneously into six comparable animals had no effect, the oxygen consumption being unchanged from that measured during the control period. If the oxygen consumption recorded for each 5 min period between 15 and 75 min after the injection of adrenaline is compared with the same measurements made during the control period of 1 hr, it is found that the observed increases are highly significant both for individual animals ($P < 0{\cdot}001$ in each case) and for the grouped results from all the rats taken together ($P < 0{\cdot}001$).

The subcutaneous administration of 0·25 u. insulin to six rats, prepared in the same fashion, was followed, after a delay of 20 min, by a marked and sustained rise in their consumption of oxygen (Fig. 2). Comparison of the oxygen consumption by these animals during the control period with that during the hour from 90 to 150 min after the injection of insulin shows that the increase is statistically significant ($P < 0{\cdot}01$) in five out of the six animals and for the grouped results from all six animals ($P < 0{\cdot}001$). The blood glucose concentration was measured in a comparable series of animals given the same amount of insulin. The onset of the rise in the consumption of oxygen above the mean for the control period and the return to that level some 4 hr later were found to correspond to blood glucose concentration of about 40 mg/100 ml.

It has been shown that this effect of insulin upon the oxygen consumption of rats given thyroxine is entirely prevented by the administration of glucose (Himsworth, 1960). This finding was confirmed.

The preceding series of experiments were repeated using rats with established adrenal gland transplants. These animals were both heavier

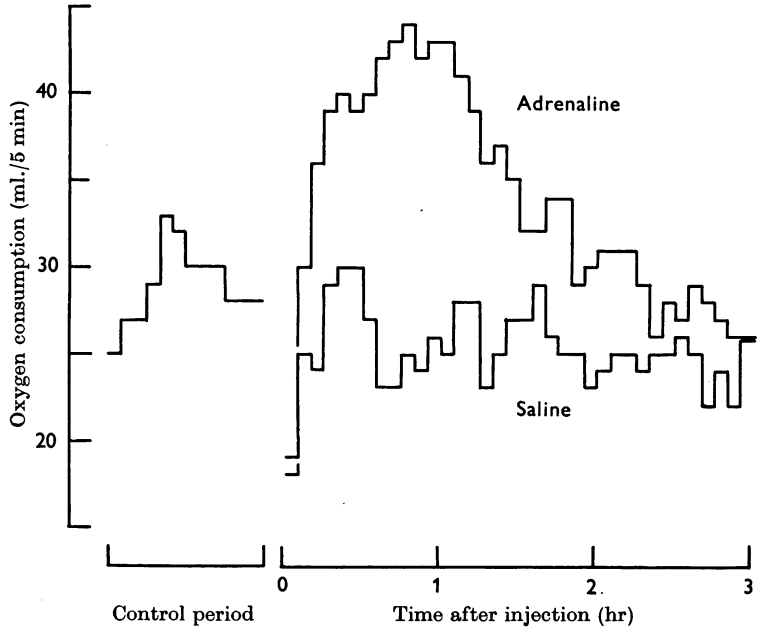

Fig. 1. The effect of adrenaline (50 μg, subcutaneously) upon the oxygen consumption of rats fed with thyroxine. The mean oxygen consumption for a group of five rats is compared with the mean oxygen consumption of a group of six rats given a control injection of saline.

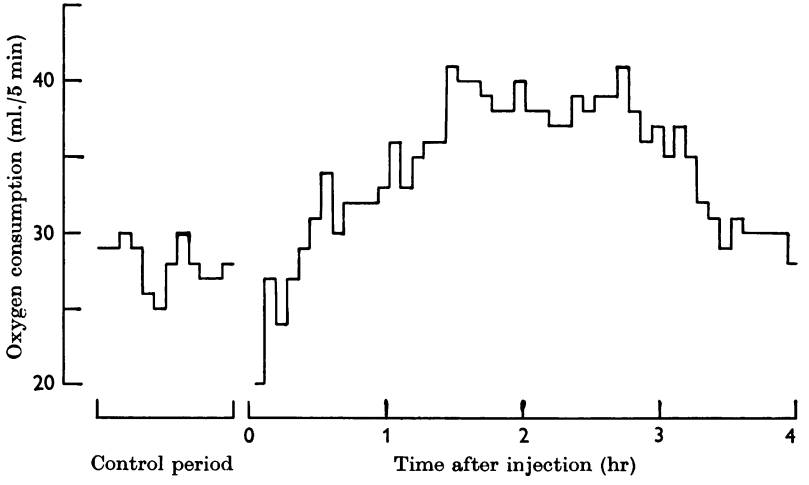

Fig. 2. The effect of an injection of insulin (0·25 u. subcutaneously) upon the mean oxygen consumption of six rats prepared with thyroxine.

(average weight 170 g) and older than the unoperated animals, used in foregoing experiments, with which they are therefore not completely comparable. Following the subcutaneous injection of 50 μg adrenaline into these operated animals, which had also been given thyroxine, the oxygen consumption rose from a mean control value of $27{\cdot}8 \pm 0{\cdot}3$ to $32{\cdot}8 \pm 1{\cdot}7$ ml./5 min in the period from 15 to 75 min after the injection. The difference between the two periods was significant for the grouped

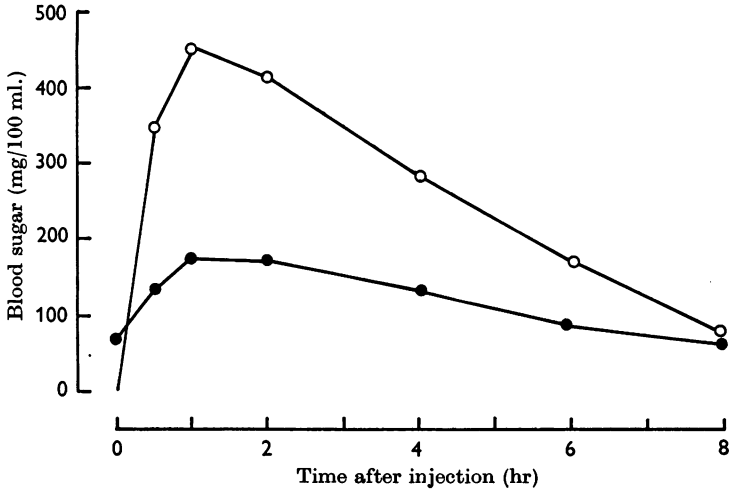

Fig. 3. The effect of a single injection of 3-methylglucose (600 mg, I.P.) upon the blood concentrations of glucose (●) and 3-methylglucose (○) of normal fasted rats. Each point is the mean of not less than three determinations.

results ($P < 0{\cdot}001$) and for six out of eight of the individual animals ($P < 0{\cdot}01$ in each such case). The administration of 0·25 u. insulin subcutaneously to nine of these operated rats, which had also been pre-treated with thyroxine, failed, however, to cause an increase in their oxygen consumption ($28{\cdot}6 \pm 0{\cdot}1$ ml./5 min in the control period and $28{\cdot}1 \pm 2{\cdot}1$ ml./5 min in the hour starting 30 min after the injection of insulin, $P > 0{\cdot}5$). Furthermore, these rats were found to be very sensitive to the action of insulin for three convulsed in the course of the experiments. The same dose of insulin in smaller unoperated rats never produced convulsions.

The effects of 3-methylglucose. The intraperitoneal injection of a substantial dose (600 mg) of the non-metabolizable sugar 3-methylglucose into fasted rats (average weight 140 g) caused a pronounced rise in the blood glucose concentration (Fig. 3). This was maximal 1 hr after the injection when the blood glucose had increased from the fasting level of $67 \pm 2{\cdot}7$ to $177 \pm 10{\cdot}0$ mg/100 ml. At the same time the blood 3-methylglucose concentration reached its maximum (454 ± 45 mg/100 ml.).

3-Methylglucose is excreted unchanged in the urine. Following the intraperitoneal administration of 600 mg 3-methylglucose to a group of rats (average weight 150 g) in a metabolism cage 90 % was recovered from the urine within 24 hr. This renal excretion of 3-methylglucose was not accompanied by the appearance of glucose in the urine. Thirty per cent of the dose was excreted in the 2 hr after the injection. The excretion of 3-methylglucose causes a considerable diuresis. A rise in the haematocrit occurs due partly to this diuresis and partly to the accumulation of fluid in the peritoneal cavity. Since in the presence of 3-methylglucose the usual relationship between the concentration of glucose in the red cells and in the plasma water is disturbed, the over-all blood glucose concentration no longer closely reflects the concentration of glucose in the extracellular fluid. These changes are shown in Table 1.

It was found that 3-methylglucose had no effect upon the blood glucose concentration of rats with adrenal transplants. The fasting blood glucose in such animals (average weight 185 g) was $75 \pm 2{\cdot}9$ mg/100 ml. (13 observations). One hour after the intraperitoneal injection of 3-methylglucose (400 mg/100 g body weight) the blood glucose concentration was $79 \pm 1{\cdot}0$ mg/100 ml. while the blood 3-methylglucose concentration was 319 ± 18 mg/100 ml. (10 observations). Two hours after injection the blood concentrations of the two sugars were $76 \pm 3{\cdot}8$ and 255 ± 23 mg/100 ml. respectively (7 observations). Throughout the period when the blood 3-methylglucose concentration was greatest these animals were abnormally quiet, occasionally prostrated, but never unconscious.

These latter experiments suggested that the rise in the blood glucose concentration after the administration of 3-methylglucose was consequent upon a secretion from the adrenal medulla. The brief but clear rise in the oxygen consumption of thyroxine treated rats which followed the intraperitoneal injection of 3-methylglucose (600 mg) supported this conclusion (Fig. 4). This rise in oxygen consumption, confined to the half an hour after the administration of 3-methylglucose, is significant when the results are considered as a whole ($P < 0{\cdot}001$) and in four out of seven animals in the group ($P < 0{\cdot}01$ in each case). The intraperitoneal injection of the same amount of glucose had no effect upon the consumption of oxygen by comparable animals. 3-Methylglucose did not modify the action of adrenaline upon rats previously given thyroxine. The rise in oxygen consumption that follows the subcutaneous injection of 50 μg adrenaline into such rats was unaffected by the simultaneous intraperitoneal injection of 600 mg 3-methylglucose.

3-Methylglucose caused a rise in the blood glucose concentration of normal rats prepared with thyroxine which was comparable both in degree and in duration with that in normal rats not so treated.

TABLE 1. The effect of an intraperitoneal injection of a hypertonic solution of 3-methylglucose (900 mg in 3 ml. water) upon the concentrations of sugars in the arterial blood, plasma water and red blood cells, and upon the haematocrit of normal rats (average weight 189 g). Blood samples were taken 2 hr after the injection of 3-methylglucose. The concentrations of glucoses in the plasma water were calculated from the known concentration of each glucose in the plasma and the plasma water content. The amount of each glucose in the red cell fraction of the blood was derived from the difference between the blood concentration and the glucose content of the plasma fraction

		Blood		Plasma water		Red blood cell		
	Number of animals	Glucose (mg/100 ml. blood)	3-Methyl-glucose	Glucose (mg/100 ml. plasma water)	3-Methyl-glucose	Glucose (mg/100 ml. blood)	3-Methyl-glucose	Haematocrit
Control rats	7	63 ± 2·2	—	111 ± 3·4	—	6 ± 0·9	—	45 ± 0·5
3-Methylglucose injected rats	6	117 ± 9·4	260 ± 9·5	268 ± 20·0	429 ± 23·0	−2 ± 2·7	66 ± 6·8	51 ± 0·8

The effect of intraperitoneally administered 3-methylglucose upon the blood glucose was not affected by continuous anaesthesia with pentobarbitone sodium and the rise in the blood glucose was accompanied by a rise in the arterial blood lactate concentration (Table 2). Nor did the method of parenteral administration of 3-methylglucose seem to determine its hyperglycaemic action. The slow intravenous infusion of 3-methylglucose into anaesthetized rats also caused a rise in the blood glucose. In

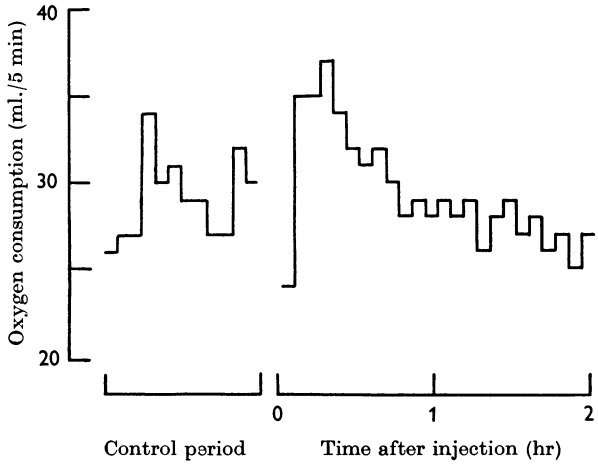

Fig. 4. The effect of an intraperitoneal injection of 3-methylglucose (600 mg) upon the mean oxygen consumption of a group of seven rats prepared with thyroxine.

TABLE 2. The effect of 3-methylglucose upon the arterial blood glucose and lactate concentrations in rats anaesthetized with pentobarbitone sodium. Blood samples were taken 1 hr after the intraperitoneal injection of 3-methylglucose (600 mg)

	Number	Average weight (g)	Blood glucose (mg/100 ml. ±S.E.M.)	Blood 3-methyl-glucose (mg/100 ml. ±S.E.M.)	Blood lactate (mg/100 ml. ±S.E.M.)
Control animals	4	174	64±6·3	—	4·2±0·6
3-Methyl-glucose injected animals	6	177	186±5·4	497±29	10·6±1·3

these experiments the maximum blood glucose concentration was not reached until 30 min after the end of the infusion by which time the blood 3-methylglucose concentration had fallen well below its maximum level. A typical experiment is shown in Fig. 5.

The response to 3-methylglucose was found to be practically abolished if the spinal cord of anaesthetized rats was cut above the level of the sym-

pathetic outflow (Table 3). Transection of the cord below this level did not affect the rise in blood glucose concentration after the administration of 3-methylglucose (compare Tables 2 and 3). The lack of response in the animals in which the cord had been cut at the higher level is therefore unlikely to be due to a state of 'spinal shock' resulting from the operation.

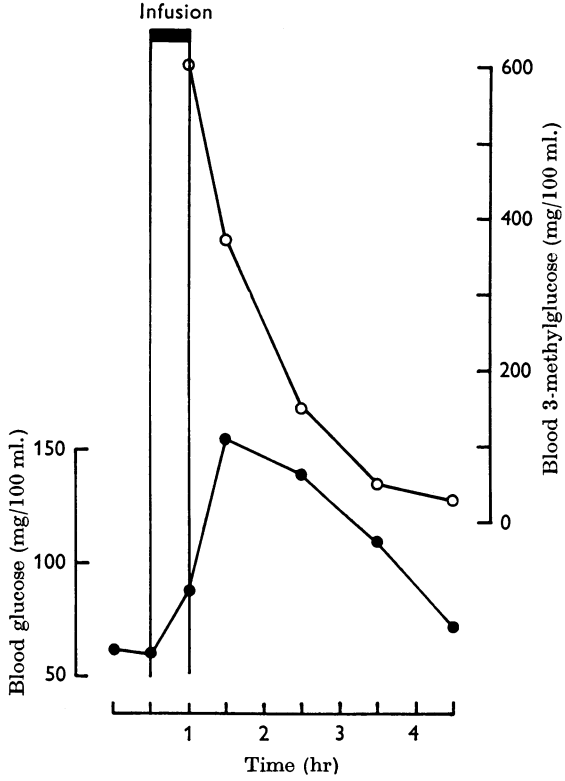

Fig. 5. The effect of an intravenous infusion of 3-methylglucose (900 mg in 3 ml. water over 30 min) upon the blood glucose concentration of a fasted rat (wt. 180 g) anaesthetized with pentobarbitone sodium.

DISCUSSION

The first of these experiments simply demonstrates that the technique of sensitizing animals with thyroxine to the effects of adrenaline provides a preparation in which the secretion of adrenaline from the adrenal gland in response to physiological stimuli can be revealed in the intact unoperated animal. It therefore provides a tool that can be used to investigate the stimuli that provoke such a secretion in relation to the regulation of glucose metabolism. The injection of adrenaline into rats previously given thyroxine causes an immediate and conspicuous rise in

TABLE 3. The effect of 3-methylglucose (400 mg/100 g body wt. I.P.) on the blood glucose concentration of rats with transection of the spinal cord at one of two levels. Blood sugar concentrations as mg/100 ml. ± S.E.M.

				Time (min after injection of 3-methylglucose)					
				−30	0	60		120	
Level of transection	Number of animals	Average weight (g)	Injection	Blood glucose	Blood glucose	Blood glucose	Blood 3-methyl-glucose	Blood glucose	Blood 3-methyl-glucose
T2–5	6	178	None	72 ± 3·8	70 ± 3·5	64 ± 2·8	—	62 ± 1·7	—
T2–5	6	176	3-Methyl-glucose	76 ± 1·3	72 ± 2·1	88 ± 4·3	476 ± 26	83 ± 6·5	543 ± 47
L3	4	171	3-Methyl-glucose	67 ± 2·7	66 ± 2·0	163 ± 6·3	417 ± 33	190 ± 5·5	406 ± 31

oxygen consumption. This rise is not due to the injection procedure for the injection of saline into comparable animals is not followed by a similar disturbance. The injection of a quantity of insulin sufficient to cause marked hypoglycaemia but without coma or convulsions, is followed after an interval by a rise in the consumption of oxygen in rats previously given thyroxine. This effect is prevented by the administration of glucose (Himsworth, 1960). It is inferred from these results and from the absence of similar changes after insulin in thyroxine treated rats in which the adrenal medulla had been severed from connexion with the nervous system by transplantation, that the rise in oxygen consumption following insulin is due to a release of adrenaline consequent upon hypoglycaemia, and that those other hormones whose rate of secretion is affected by hypoglycaemia do not influence the oxygen consumption of these animals. These results are in accord with other studies demonstrating the secretion of adrenaline during insulin induced hypoglycaemia.

In rats sensitized with thyroxine the onset and cessation of the period of increased consumption of oxygen after insulin correspond to a blood glucose concentration of approximately 40 mg/100 ml. This is the level at which the release of adrenaline during insulin hypoglycaemia in such animals starts and stops. This figure is somewhat below that given by Armin & Grant (1959) who found that the critical level in rabbits although variable was generally 50–70 mg/100 ml.

Administration of 3-methylglucose sufficient to produce a high concentration in the plasma water is followed by a rise in the concentration of glucose in the same medium. The relatively smaller rise in the concentration of glucose in the whole blood is due to a combination of two factors. First, the absence of glucose from within the red cells in the presence of 3-methylglucose, and, secondly, the increased proportion of red cells in the whole blood as shown by the rise in haematocrit. That the rise in glucose concentration is not accounted for by a decrease in its peripheral utilization is shown by the failure of the blood glucose to rise after 3-methylglucose is given to rats whose adrenal glands have been transplanted and who, in consequence, are unable to mobilize glucose by secreting adrenaline. In these latter animals there is a small increase in the concentration of glucose in the plasma water which is counterbalanced by an increase in the haematocrit. These changes are described and their significance discussed in another paper (Himsworth, 1968). The supposition that this hyperglycaemic response to 3-methylglucose is largely due to the release of adrenaline is supported both by the coincident increase in the blood lactate concentration and by the demonstration of a significant rise in the consumption of oxygen by rats sensitized by thyroxine to adrenaline in the period immediately following the injection of 3-methylglucose. That this

release of adrenaline is not due simply to the effect of a hypertonic injection is shown by the absence of any rise in the consumption of oxygen by rats treated with thyroxine following the injection of the same volume of a solution of glucose of equal concentration. Nor can such a release of adrenaline be secondary to the reduction in blood volume, as indicated by the increase in haematocrit, for a rise in the blood glucose concentration occurs during and after the intravenous infusion of 3-methylglucose when there is no abstraction of fluid into the peritoneal cavity. The rise in the concentration of glucose in both the blood and plasma water of normal animals that develops in the presence of high concentrations of 3-methylglucose is therefore the consequence of some effect of 3-methylglucose itself.

It has also been demonstrated that interruption of the central neurological connexions of the adrenal medulla by division of the spinal cord above the level of the sympathetic outflow also prevents the characteristic change in the blood glucose concentration caused by the administration of 3-methylglucose. The rise in the blood glucose produced by 3-methylglucose is therefore mediated by the same final pathway as the sympathetic response to hypoglycaemia.

If, as seems likely, 3-methylglucose acts on the same mechanism as hypoglycaemia to promote the secretion of adrenaline, it can be inferred that the effective stimulus for the secretion of adrenaline by the adrenal gland is not a low concentration of glucose in the blood or extracellular fluid as in the presence of 3-methylglucose adrenaline secretion occurs at or above the fasting blood glucose level (e.g. 67 mg/100 ml.) and well above the threshold for adrenaline release during insulin induced hypoglycaemia. Can the known biological properties of 3-methylglucose throw any further light upon the nature of this stimulus?

The available evidence indicates that 3-methylglucose is biochemically inert. It cannot be phosphorylated by brain hexokinase (Sols & Crane, 1954) and after being given to animals is excreted unchanged in the urine (Campbell & Young, 1952). Although 3-methylglucose cannot directly interfere with the enzymatic processes of glucose metabolism it has been shown *in vitro* to be capable of reducing the rate at which glucose is oxidized by adipose tissue. This phenomenon has been attributed to a reduction in the rate of entry of glucose into the cells due to competition by 3-methylglucose for the carrier mediated glucose transfer system of the cell surface (Crofford & Renold, 1965). The affinity of 3-methylglucose for glucose transfer systems appears to equal that of glucose in those tissues where this has been tested (Morgan, Regen & Park, 1964). A high concentration of 3-methylglucose in the blood and extracellular fluid might therefore be expected to restrict the amount of glucose entering the

various tissues of the body by competing with glucose for the carrier systems. The brain would be especially vulnerable to such a restriction for it can derive energy only by the oxidation of glucose. Further there is evidence, in dogs, that the system which facilitates the transfer of glucose from the blood into the brain tissue is saturated at a blood glucose concentration of 70 mg/100 ml. (Crone, 1965). It is shown in the following paper that the rate of oxidation of glucose by fasting rats with adrenal transplants is depressed by 3-methylglucose to such a degree that the oxidation of glucose by the brain must be reduced (Himsworth, 1968). Furthermore, it has been suggested that the receptor which controls the release of adrenaline during hypoglycaemia is situated within the hypothalamus (Dunér, 1953). If this interpretation of the present experiments is correct the factor determining the release of adrenaline after the administration of 3-methylglucose is a failure to maintain a minimum rate of glucose utilization within the receptor tissues.

The preceding discussion has been concerned with the situation which exists when a large concentration of 3-methylglucose is present in the blood. If only relatively small amounts of this sugar were present sufficient glucose might reach the receptor to prevent the release of adrenaline. This may explain why in some earlier experiments no increase in the blood glucose concentration was observed after the administration of 3-methylglucose (Campbell & Young, 1952). In these earlier experiments a mean blood 3-methylglucose concentration of only 80 mg/100 ml. was obtained while the blood glucose concentration in the control rats was 104 mg/100 ml. These experiments show, however, that the presence of 3-methylglucose itself does not cause the secretion of adrenaline.

The method by which 3-methylglucose provokes a release of adrenaline may, in principle, be similar to that by which another glucose analogue, 2-deoxyglucose, produces a similar effect.

The administration of 2-deoxyglucose (in a quarter the dose used for 3-methylglucose in the present experiments) to rats causes an increased rate of secretion of adrenaline with consequent hyperglycaemia (Hökfelt & Bydgeman, 1961). This effect is thought to be due to an inhibition of glucose metabolism, for 2-deoxyglucose can be phosphorylated, enter into and block the glycolytic pathway (Brown, 1962). It has been suggested that 2-deoxyglucose interferes with the utilization of glucose by the brain and that this interference activates the release of adrenaline (Hökfelt & Bydgeman, 1961).

The inference to be drawn from these sets of data—insulin hypoglycaemia and the hyperglycaemic actions of 3-methylglucose and 2-deoxyglucose—is that a failure to maintain the rate of glucose utilization by the receptor tissues above a certain minimum is an effective stimulus to

some sensitive tissue in the nervous system which initiates the secretion of adrenaline by the adrenal gland. Hypoglycaemia and 3-methylglucose by restricting the entry of glucose into the cell and thus producing an intracellular deficiency, and 2-deoxyglucose by inhibiting glycolysis, would thus all lead to a common result and as such be effective agents in causing a release of adrenaline with a consequent rise in the blood glucose concentration.

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