THE EFFECTS OF TRAUMA ON CARBOHYDRATE METABOLISM

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To appreciate the many effects of injury on carbohydrate metabolism, and to avoid confusion in interpretation of the findings, it is necessary to know something of the stages in the response to injury.

Stages in the response to injury.

Injuries differ in the time scale of their production. In burns and wounds of major vessels the main damage can be done quickly and fluid loss occurs from the beginning. Other trauma, such as crush injuries in man or limb ischaemia produced by tourniquets in animals, may be slow acting and the fluid loss only occurs when the circulation is restored to the damaged part. In this case there is a prehypovolaemic stage, and it is possible to distinguish the effects of the different afferent stimuli.

The metabolic response to an injury can be divided into a number of phases, the best known being the “ebb”, “flow” and “necrobiotic”. This division is mainly due to Cuthbertson (1942) who has recently illustrated these phases after different injuries in man and rat (Cuthbertson, 1970). The prehypovolaemic precedes the “ebb” phase in those injuries in which it is distinguishable.

In the “ebb” phase there is a diminished capacity for producing the heat required to meet the demands of the environment, shown by decreased oxygen consumption at ambient temperatures below the thermoneutral range. This phase may last up to 2 days (Stoner, 1968). If the injury is survived, the “flow” phase follows in which heat production is increased, often with fever even in the absence of infection. This phase usually lasts a few days but may continue for several weeks. In subjects who die directly from the injury the “ebb” phase will be followed by a necrobiotic phase, when oxygen transport falls progressively leading to increasing anaerobiosis and death.

These phases are not closed compartments. They can be affected by therapy, e.g., fluid replacement in the “ebb” phase. In man, studies have often been made on patients who have suffered relapse (infection, second operation) in the “flow” phase. A second “ebb” may then be superimposed on the “flow” phase from the original trauma.

The changes in the “ebb” phase have been studied mostly in laboratory animals, and those in the “flow” phase largely in man. Metabolic differences between species must therefore be kept in mind. Glucose metabolism is particularly likely to differ in man and other species because the human brain uses a much higher proportion of the available glucose (50% in man; 10% in the rat).

THE INJURY AND “EBB” PHASE

Hyperglycaemia.

It has been known since the time of Claude Bernard that haemorrhage and injury can cause hyperglycaemia. In man the size of this response can be fairly well correlated with the size of the injury be it due to burns (Taylor, Levenson and Adams, 1944), combat (Green et al., 1949) or obstetric haemorrhage (Murdoch, 1953). The correlation is less good in the postabsorptive rat (Ashby, Heath and Stoner, 1965; Heath and Corney, unpublished results), perhaps reflecting the different feeding pattern and smaller glycogen stores of the rat. The human response is not much affected by the patient’s nutritional state. Most of the excess glucose is derived from glycogen and the first problem is the mechanism for the mobilization of the stored glycogen.

Mobilization of glycogen stores.

Hyperglycaemia is part of the autonomic response to any adverse situation (Cannon, 1929) and the steps involved are shown in figure 1. Afferent stimuli from the damaged tissue and from volume and pressure receptors lead, via reflexes involving hypothalamic and mesencephalic centres, to stimulation of the sympathetic outflow with the secretion of adrenaline and noradrenaline by the adrenal medulla and postganglionic sympathetic nerve endings. The response depends on the species, since they differ in the relative amounts of adrenaline and noradrenaline in the adrenal medulla; on age, since the adrenal medulla is not fully developed at birth and the organ of Zuckerkandl contains noradrenaline.

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(Neville, 1969); and on the actual stimulus. A fall in blood volume is a particularly important stimulus for the adrenal medulla, which plays little or no part in the reflex response to changes in blood pressure (Walker et al., 1959; Vane, 1969). Catecholamine release in haemorrhage is well-established (see Chien, 1967). In man it increases, inter alia, after major surgery (Pekkarinen, 1960) and burns (Birke et al., 1958) and continues well into the recovery phase, as also happens in the rat after limb ischaemia (Stoner and Westerholm, 1969). Through the production of cyclic AMP these neurohormones will activate phosphorylase and cause glycogenolysis.

Depletion of muscle glycogen starts with the injury during the "prehypovolaemic" phase. In limb ischaemia, its concentration in the uninjured muscle falls steadily from the time of application of the tourniquets in both fed and fasted rats, and continues to fall throughout the "ebb" phase (Stoner, 1958). The lactate liberated is converted to glucose (fig. 1) in the Cori cycle (Cori and Cori, 1928). This process can be interrupted by adrenal medullectomy, which will largely prevent hyperglycaemia.

Not all glycogen stores are affected in this way. Brain glycogen is unaltered (Stoner, 1958) and the concentration of cardiac glycogen increases after various types of injury (Cordier and Dessaux, 1954; Stoner, 1958).

In isolated liver preparations adrenaline causes glycogenolysis but its effects in vivo are species dependent. In the cat (Evans, Tsai and Young, 1931) but not in the rabbit (Goldblatt, 1933) injection of adrenaline can cause depletion of liver glycogen. In the rabbit this can be produced by stimulation of the hepatic sympathetic nerves (Shimazu and Amakawa, 1968). In the dog adrenaline, noradrenaline and stimulation of the hepatic nerves can all cause hyperglycaemia and depletion of liver glycogen (Edwards and Silver, 1972). In man the position is unclear. In rats, injection of adrenaline, even into the portal vein (Sherlock, 1949), does not deplete liver glycogen but causes an increase (Cori and Cori, 1928). Accordingly, during the prehypovolaemic phase liver glycogen increases in both fed and fasted rats and the increase, which is part of the Cori cycle, is prevented by adrenal medullectomy (Stoner, 1958).

During the "ebb" phase it appears that liver glycogen falls in all species. High rates have been measured in rats and rabbits after scalding (Heath, 1973; Clark and Rossiter, 1944), and after hind-limb ischaemia (Stoner, 1958). The rate of fall in postabsorptive rats is faster than in controls. The fall is not prevented by adrenal medullectomy, and its mechanism is not known. It could be due to the secretion of glucagon, to increased activity in the sympathetic nerve supply to the liver or to both these factors. It is not known whether neurohypophyseal secretions play any part in these responses.

Glucagon depletes liver glycogen in the rat and is thought to be the hormone usually responsible in that species (Sokal, Sarcione and Henderson, 1964). Too little is known about the effects of injury on glucagon secretion because of the difficulties of assay. Two to tenfold increases in glucagon levels have been reported in sheep and dog during and after haemorrhage, but the largest increases were in the
latter stages when the blood glucose concentration had returned to normal or subnormal values (Halmagyi et al., 1969).

Course of hyperglycaemia.
With the mobilization of the stored glycogen (fig. 1), an injury soon causes hyperglycaemia. After most injuries the blood glucose concentration rises rapidly and steadily to its peak (up to four times normal) which depends on the severity of the injury, nutritional status, etc. During limb ischaemia there is a preliminary rise while the tourniquets are on, but a greater one after their removal. The high concentrations will persist for some hours and form an outstanding feature of the "ebb" phase.

Utilization of blood glucose.
Evidence in the "ebb" phase is sparse. Limited experiments have been performed on rats after limb ischaemia and scalding (Ashby, Heath and Stoner, 1965; Heath and Corney, unpublished results) using single intravenous injections of \(^{14}C\)-glucose. These tracer methods estimate the disposal rate, R, without disturbing the metabolic state. The rates have only been determined when conditions were most stable, around the period of maximal hyperglycaemia, using single injection techniques for which a simple procedure has been described (Corney and Heath, 1970). In the injured, postabsorptive rats R was reduced roughly in proportion to the fall in oxygen consumption which occurs in the "ebb" phase. The change in oxygen consumption is confined to the thermoregulatory fraction of the total oxygen consumption and is due to the impairment of thermoregulation by trauma (Stoner, 1969, 1971, 1972; Stoner and Marshall, 1971). This change in R is of interest, as in postabsorptive controls R is close to the total carbohydrate oxidation rate determined by indirect calorimetry. In experimental haemorrhagic shock in the dog it also seems likely (Shoemaker et al., 1973) that glucose utilization is reduced in what corresponds to the "ebb" phase. However, during the prehypovolaemic phase there is some evidence (Stoner, Threlfall and Green, 1952; Threlfall and Stoner, 1954) that injury increases the rate of disappearance of the total body carbohydrate (glucose + glucose liberated from polymers such as glycogen and glucose phosphates by acid hydrolysis).

The association of a reduced rate of plasma glucose disposal with a high plasma glucose concentration requires either that the normal hyperglycaemic release of insulin is inhibited or that there is resistance to insulin action.

Effect of trauma on insulin secretion.
The effect of several types of trauma on the circulating levels of immunoreactive insulin has been studied in a number of species including man (e.g. Ross et al., 1966; Halmagyi et al., 1966; Allison, Hinton and Chamberlain, 1968; Bauer et al., 1969; Carey, Lowery and Cloutier, 1970; Cryer et al., 1972; Cerchio et al., 1971; Drucker et al., 1973, Vigas et al., 1973). The results have been variable. In general, although the plasma concentrations have been raised they have not been raised to the levels expected for the plasma glucose concentrations. This can probably be attributed to inhibition of insulin release by the concurrent increase in that of adrenaline (Porte et al., 1966). It is perhaps not surprising, therefore, that surgical trauma performed under anaesthesia seems to have less inhibitory effect than accidental trauma. However, it is unlikely that the relative lack of insulin is the whole explanation for the persistence of the hyperglycaemia. Further information on insulin secretion after trauma has been obtained from glucose tolerance tests.

Glucose tolerance and insulin resistance.
Unlike the isotopic measurement of R, the glucose tolerance test depends upon inducing a disturbance in the metabolic state. Sufficient glucose is given to raise the plasma glucose concentration by about 200 mg/100 ml and the rate of fall of the plasma glucose concentration is then determined. Only intravenous tests will be considered here. Of several possible indices for the test, the K-value (Hamilton and Stein, 1942; Marks and Marracks, 1962), the percentage fall in blood concentration per min, seems preferable (Butterfield, Abrams and Whichelow, 1971):

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K = \frac{100(R - I)}{CV}
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where R and I are the rates of disposal and input respectively, C is the plasma concentration and V is roughly equal to the glucose space. K is only a rough summary of a complicated kinetic situation (Atkins, 1971). Normal values of K depend on the near-maximal stimulation of insulin secretion (Lerner and Porte, 1971) and the nearly complete inhibition of hepatic glucogenesis (I) (Soskin et al., 1938; Bondy, James and Farrar, 1949; Myers, 1950; Felig and Wahren, 1971b; Long et al., 1971a) produced by
the usual dose of glucose—25g/subject. Glucose disappearance (K) is slowed by injury (e.g. Thomsen, 1938; Haist and Hamilton, 1944; Haist, 1946; Mason, 1941; Seligman et al., 1947; Stoner, Threlfall and Green, 1952; Ross et al., 1966; Allison, Hinton and Chamberlain, 1968; Vigas et al., 1973) but this cannot be entirely attributed to insulin resistance or failure to secrete sufficient insulin, although the latter has been observed (Allison, Hinton and Chamberlain, 1968). Two other factors decrease values of K. After injury the body glucose pool, CV, is increased and the high plasma glucose concentration fails to inhibit hepatic glucogenesis (Ashby, Heath and Stoner, 1965; Heath and Threlfall, 1968; Shoemaker et al., 1973; Heath and Phillips, unpublished results). Nevertheless, very low K values have been reported after injury (Allison, Hinton and Chamberlain, 1968) and it must be supposed that R increased less than proportionally to the increase in glucose concentration, i.e., that there was insulin resistance. Certainly large doses of insulin have been given to injured patients with less than the expected effect on the blood glucose concentration. Insulin resistance can continue into the “flow” phase. The mechanism is not clear but could be related to increased secretion of pituitary growth hormone (Johnston et al., 1968; Nahas, 1970; McCann et al., 1973) or of glucocorticoids.

An additional effect contrary to those already discussed is the reduction in insulinase action. After haemorrhage the half-life of insulin in plasma is increased (McCormick et al., 1969).

Adrenal cortex.

The increase in adrenal cortical secretion following injury is well-known (Symington, 1969) but its precise role in the changes in carbohydrate metabolism is still obscure. As in the “flow” phase these hormones will be required in a “permissive” role but whether they play a more active part, in the insulin resistance for example, is not known. Adrenalectomy does not help in this problem although it has a dramatic effect on the response to injury. Not only is the sensitivity to injury greatly increased and the survival time shortened but the hyperglycaemia is replaced by a progressive hypoglycaemia (Stoner, 1961). It is doubtful if this implies a primary effect on carbohydrate metabolism. The changes of the injured, adrenalectomized rat (Stoner, 1958) are characteristic of the terminal, necrobiotic phase. Adrenalectomy precipitates the circulatory failure of trauma, the “ebb” phase is largely eliminated and the changes in blood glucose concentration, etc., are most probably secondary to the more rapid failure of oxygen transport (Moore, 1959).

“Flow” phase

In the “flow” phase the resting metabolism is raised (Cuthbertson, 1932, 1960; Cairnie et al., 1957; Caldwell, Hammel and Dolan, 1966; Kinney, Long and Duke, 1970; Tilstone and Cuthbertson, 1970). The excess metabolism is not simply related to the severity of the injury; it depends upon the type of injury and on age, sex and previous nutrition (Kinney, 1960; Kinney, Long and Duke, 1970). While not much affected by nutrition after the event, protein deprivation before the injury can prevent the rise in metabolism afterwards (Munro and Chalmers, 1945; Cairnie et al., 1957). Another influencing factor is the environmental temperature, for the increase is reduced or absent in the thermoneutral zone (see Stoner, 1970).

Carbohydrate metabolism.

Study of carbohydrate metabolism in the “flow” phase is complicated by nutrition. After injury food intake may be abnormal and the oral intake may be largely replaced by various forms of intravenous alimentation. It is, however, obvious that little of the excess metabolism can be supplied by endogenous glucose or glycogen stores, as these are too small. The energy sources have been discussed by Kinney, Long and Duke (1970) who concluded that protein was being broken down to provide substrate for gluconeogenesis and that up to 80% of the excess energy expenditure was derived from fat. Long et al. (1971b) determined RQ values in postoperative and seriously ill patients receiving intravenous glucose at a rate equal to that of metabolism of glucose in normal subjects. In these circumstances the total rates of carbohydrate oxidation were very similar in all three groups: normal, postoperative and severely ill.

Glucose utilization.

The rate of disposal of glucose, measured by the rate of disappearance of 14C-glucose, was up to four times faster in the seriously ill patients of Long et al. (1971b) than in normal subjects, probably due to isotopic exchange in reaction sequences such as glucose (heavily labelled)→glycogen (label diluted)→lactate (lightly labelled)→glucose (lightly labelled) which cause loss of label from glucose without net
oxidation. Rate of loss of label is, however, a measure of uptake rate and a conspicuous feature of these results was the great variability of this rate in seriously ill patients. Similar variability has been seen in glucose tolerance tests.

After severe burns the K-value and secretion of insulin in response to the glucose load may not return to normal for several weeks (Allison, Hinton and Chamberlain, 1968) whereas after uncomplicated surgery they are substantially normal after a few days (Ross et al., 1966).

**Traumatic diabetes (pseudodiabetes).**

The persistence of low K-values for some time after an injury has given rise to the idea of a traumatic form of diabetes. It is doubtful if this is a disease *sui generis* (Thomsen, 1938). The condition is not permanent and these patients probably represent severe examples of the changes described above. They would certainly be worthy of study by isotopic methods. Some of the patients may have temporary exacerbations of a pre-existing diabetic state and, rarely, diabetes can be produced by severe, direct trauma to the pancreas.

**Necrobiosis**

Necrobiosis is the final stage in fatal cases and is associated with all the haemodynamic features of classical, untreated shock. The most important change is progressive deterioration in oxygen transport to the tissues. In the presence of hypoxia the cellular uptake and phosphorylation of glucose is increased (Morgan, Randle and Regen, 1959). This, together with decreased gluconeogenesis from the same cause, leads to a terminal fall in the blood glucose concentration. These changes can occur rapidly at the end and in the rat the terminal values can be very low (Stoner, 1958). Although glucose uptake is increased, its metabolism under these conditions is incomplete and lactate, the product of anaerobic metabolism, accumulates in both cells and blood (McShan et al., 1945; Stoner et al., 1952; Threlfall, 1970 and unpublished results). The lactate/pyruvate ratio can be used as a measure of cytoplasmic oxygenation. In the necrobiotic phase it rises steadily to very high values.

The terminal accumulation of lactate must be distinguished from an earlier increase in the blood lactate concentration. In burns (Clark and Rossiter, 1944) and limb ischaemia (McShan et al., 1945; Stoner, Threlfall and Green, 1952) there is a sharp rise in the blood concentration shortly after the burning or release of the tourniquets, the extra lactate being derived from the damaged tissues. This initial rise is accompanied by an increase in the lactate/pyruvate ratio which, however, soon drops to control levels although the concentrations of lactate and pyruvate in the blood may persist above normal.

Arterial lactate concentrations are inversely related to the prognosis of the patient (Broder and Weil, 1964; Peretz et al., 1965). One can see that shortly after injury a high value could indicate severe tissue damage while at a later stage it could indicate generalized failure of oxygen transport. More information might be obtained if plasma pyruvate concentrations were measured at the same time.

**Intermediate carbohydrate metabolism**

Space does not allow a detailed discussion of the effect of injury on the intermediate metabolism of carbohydrates. The changes depend on the stage of the response. Excluding what is strictly mitochondrial metabolism some discussion is needed on the effects of injury on those reactions which lead to the production of glucose in the liver.

**Gluconeogenesis.**

Gluconeogenesis will be taken to cover the synthesis of glucose from all precursors except liver glycogen (fig. 2). The main sources are lactate, amino acids, glycerol and fructose. Gluconeogenesis maintains a sufficiency of glucose for central nervous function in two ways: by minimizing oxidation of glucose by recycling precursors such as lactate and, via exchange reactions, alanine and other amino acids (Felig and Wahren, 1971a) and by *de novo* synthesis. As the endogenous supply of glycerol is inadequate (Cahill et al., 1966), in the absence of an external supply of glucose or fructose amino-acids must be used and protein metabolized. Excretion of urea N is a measure of the rate of gluconeogenesis from protein.

Injury sets up a remarkably stable pattern of gluconeogenesis. It seems to proceed at a rather high rate in both "ebb" and "flow" phases whether estimated by N excretion (Cuthbertson, 1942), by labelling of glucose from injected precursors (Ashby, Heath and Stoner, 1965) or by splanchnic production of glucose (Shoemaker et al., 1973; Long et al., 1971b). It is not inhibited by hyperglycaemia, feeding (Cuthbertson, 1942) or by infusion of glucose at rates which normally inhibit gluconeogenesis almost completely (Long et al., 1971a,b; Felig and
A recent review (Annotation, 1972) has suggested a possible explanation, namely that catecholamine release and/or sympathetic nervous stimulation increases glucagon secretion, thereby increasing gluconeogenesis while inhibiting insulin release. Normally the sequence: glucagon→high blood glucose→insulin release→inhibition of glucagon release, causes a negative feedback which stabilizes the system but after injury this is nullified by sympathetic activity which can continue for a long time. In accordance with this explanation Hinton et al. (1971) find that nitrogen is spared when glucose is infused with high doses of insulin.

Fructose has been suggested as an intravenous fuel (Hers, 1957) on the grounds that since its entry into cells is not controlled by insulin it can be utilized better. In fact, much of a dose of fructose is converted to glucose (Wynn, 1956; Drucker et al., 1961); in normal and injured rats this is about 70% (Ashby, Heath and Stoner, 1965). Nevertheless, a case could still be made for the use of fructose (or sorbitol) on the grounds that some is not converted to glucose and part of this is oxidized (Ashby, Heath and Stoner 1965); also, since fructose enters the gluconeogenic chain at the triose phosphate stage (fig. 2) it may tend to suppress gluconeogenesis by a mass action effect, so sparing nitrogen. Some nitrogen sparing effect has been claimed (Drucker et al., 1961) but is likely to be small as the conversion of trioses to glucose is not usually rate-controlling (Exton and Park, 1967). The administration of glucose itself in the acute phase has often not been found of therapeutic value (e.g. Rosenthal, 1943) although the greater the stores of carbohydrate at the time of ischaemic limb injury the longer the survival time (Threlfall and Stoner, 1954).

**CONCLUSIONS**

Some aspects of carbohydrate metabolism after injury are now fairly well understood but there are still many gaps in our knowledge. The time would seem particularly opportune for investigating the role of insulin, glucagon and the adrenal cortical and pituitary hormones in the fate of the glucose which is produced in such abundance at the beginning of the response. Without a better understanding of these interactions, it is difficult to see how the therapeutic needs of the injured patient can be assessed or a rational therapy developed.

**REFERENCES**


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