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MALIGNANT HYPERTHERMIA: BIOCHEMICAL ASPECTS OF THE ACUTE EPISODE

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Early studies indicated that the pharmacogenetic disorder, malignant hyperthermia (MH), was inherited as an autosomally dominant trait in humans [3]. More recent interpretations indicate that MH may be inherited through more than a single gene [9, 10] and that the pattern of inheritance may vary from recessive to dominant. This uncertainty about the mode of inheritance of human MH has contributed to the confusion which abounds in biochemical studies of the molecular aetiology of the syndrome. It now seems unlikely that MH is caused by a single enzyme or protein lesion such as is seen, for instance, in McArdle's disease or phenylketonuria. While the nature of the genetic abnormality remains unclear, there is good evidence that the fundamental defect is located in the fibres of the skeletal musculature. For example: tubocurarine will not block induction of MH by halothane; muscular rigidity is one of the first signs of onset of an MH episode; the neuromuscular blocker dantrolene blocks development of the syndrome and halothane-induced contractures of biopsy strips of muscle from MH susceptible individuals; the resting intracellular free calcium ion concentration of MH muscle fibres is increased; and up to 70% of subjects show increased muscle-specific serum creatine phosphokinase activity [6, 16, 17]. Indeed, the so-called MH syndrome is now recognized as a metabolic disorder of skeletal muscle in the two major treatises on muscle disease [7, 21].

The clinical signs and symptoms of acute malignant hyperthermia have been described by numerous authors in case reports; briefly, the typical symptoms are rigidity, metabolic and respiratory acidosis, tachycardia, hyperkalaemia, hyperthermia and myoglobinuria. The severity and onset time of MH varies with the chemical nature of the volatile anaesthetic used and is usually more pronounced when used in combination with suxamethonium. The most marked, macroscopic symptoms are the skeletal muscular rigidity and rapid rate of increase of body temperature. The rigidity developed during MH onset appears not to be a regular form of contractile activity, but rather a pronounced contracture—that is, caused by a depolarization other than that initiated by a propagated action potential. The increased body temperature, which may reach 43–44 °C in the fulminant syndrome, is a consequence of an accelerated rate of energy metabolism. In the acute MH episode, it may be difficult to distinguish the exact sequence of events, and this is particularly true of the early biochemical changes. Fortunately, an excellent model of human MH was discovered in certain breeds of pig in 1966 [15]; since then it has been shown that the human and porcine MH syndromes are nearly identical with respect to changes in vital signs, muscular activity and metabolism [20]. Thus, our knowledge of the biochemical changes occurring in the acute MH episode are largely derived from controlled experiments on MH susceptible pigs and only to a lesser extent from case reports of acute episodes in humans. In the following paragraphs, I will attempt to explain in biochemical terms the nature of the features of the acute human MH episode, largely by liberal extrapolation of data derived from porcine MH studies by numerous researchers throughout the world. More detailed analyses of the early and recent literature on MH have been published in the reviews by Gronert [9, 10], Denborough [5], Ellis and Heffron [6] and Mitchell and Heffron [18]. Explicit analysis and discussion of published work attempting to identify the molecular aetiology of MH will be avoided in this review, but can be found in the paper by Ellis and Heffron [6].

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BIOCHEMICAL CHANGES AT TISSUE LEVEL

Skeletal muscle

The earliest detectable changes in the acute MH episode have been observed in the venous effluent from skeletal muscle; pH and Po_2 are decreased, while Pco_2 and lactate concentration are increased [8, 12]. These changes in the venous blood reflect earlier changes in the metabolic rate of skeletal muscle initiated by the triggering agent(s). No other tissue can produce such large amounts of lactate which can increase by up to 20 times the resting concentrations. Increase in blood lactate concentration has been shown to occur before any clear signs of tissue hypoxia are manifest. This finding remains an enigma. The presumed non-hypoxic lactate production by skeletal muscle might be caused by either or both of the following: (i) a block in the transport of pyruvate from the sarcoplasm into the mitochondria, thus preventing its oxidation via the tricarboxylic acid cycle; (ii) loss of inorganic phosphate from ATP breakdown in the muscle into the extracellular fluid.

The former explanation has not been examined experimentally, but the latter is the more probable, since it is already known that the plasma membrane of the muscle fibre becomes extremely permeable at the time of onset of acute MH [2]. The relevant changes noted by Berman's group were movement of Mg^{2+}, Ca^{2+} and inorganic phosphate into the extracellular space and plasma. The initial increase in membrane permeability may itself be caused by the massive depletion of creatine phosphate and ATP which occurs very early in the onset of MH, rather than to the decrease in pH, which has a slightly later time course [1, 13, 19]. Since MH is triggered in skeletal muscle by some as yet unknown process which increases the sarcoplasmic ionized calcium concentration, it appears likely that this calcium would activate membrane-associated phospholipases in addition to the contractile process. Such phospholipase activity would result in increased membrane permeability as fatty acid liberation progresses in the early minutes of onset of MH.

In the MH crisis, both aerobic and anaerobic metabolism increase dramatically before any detectable increases in temperature, heart rate and catecholamines are noted. The increase in whole-body aerobic metabolism has been shown to be a specific increase in the aerobic metabolic pathways of skeletal muscle, which accounts for some 40% of the body mass. This increase in metabolism represents an attempt by the muscle fibre to produce ATP at a rate sufficient to counteract the rate of ATP hydrolysis by actomyosin ATPase of the contractile apparatus, the process responsible for the rigidity which is so much an early feature of the MH crisis. At the peak of the crisis, there occurs a three-fold increase in oxygen consumption; this represents only a fraction of the maximal aerobic capacity of skeletal muscle, about one-sixth, in fact. Gronert [10] has pointed out the paradoxical nature of this small increase in relation to the large disturbance of acid–base balance and temperature alteration which occur. It would appear that there is a link between this phenomenon and the accumulation of lactate under non-hypoxic conditions; the explanation for the latter, already given above, would also account for the limited increase in oxygen consumption noted in the acute episode. At this time, it is reasonably certain that the functional deficiencies which have been observed in mitochondria from untriggered MH muscle [11] or the muscle fibre type cannot account for the attenuated aerobic metabolic rate in MH.

It is well known that, if the MH crisis is not actively treated as soon as it is diagnosed (and that is the real difficulty), the syndrome becomes irreversible. The point of irreversibility, which is difficult to determine even in the experimental situation, is probably the time at which the concentration of ATP in the muscle decreases to one-half of the resting concentration, for it is known from biochemical studies of normal muscle that rigor sets in when the energy status of the cell decreases to this value. From this stage of the acute episode, many other irreversible reactions occur, most notably increased breakdown of the mitochondrial membrane as the ATP concentration decreases to zero, and a further massive increase in plasma membrane permeability, leading to loss of larger molecules and proteins such as myoglobin. It must be emphasized that such a general increase in membrane permeability occurs because there is insufficient ATP and other nucleoside triphosphates (e.g. CTP) in the muscle fibre which are essential for the activity of the enzymes normally involved in the repair and maintenance of cell membranes. The concomitant acidotic conditions and high temperature will also cause membrane damage and a degree of denaturation of enzymes and other functional proteins. The high temperature itself will fluidize muscle

cell membranes, an effect which will increase electrolyte and small molecule permeability. Unlike the situation in muscular dystrophy, calcium-activated proteinase activity does not appear to have a role in the aetiology of MH. This general increase in permeability of the skeletal musculature and the fact that it accounts for almost half of the total body mass indicates that the products of its extreme metabolic activity during the acute episode will initiate secondary MH responses in several other tissues.

Heart

Cardiac function is undoubtedly altered in the early stages of development of MH, as indicated by the occurrence of tachycardia and arrhythmias. Later on, hypotension develops and cardiac output continues to decline and eventually ceases. During porcine MH, a five-fold increase in myocardial oxygen consumption has been measured; this change can be blocked by infusion of propranolol indicating that it is a response to increased concentrations of circulating catecholamine, which in turn are most probably elicited by the metabolic acidosis generated by the skeletal muscle. Neither lactate production nor efflux of potassium ions is altered in the heart during an MH episode. It may be concluded, therefore, that the myocardial reponse is secondary to metabolic changes originating in the skeletal muscle. The continuing decline and ultimate cessation of cardiac contractility is most probably mediated by the hyperkalaemia caused by the progressive efflux of potassium ions from the critically metabolizing skeletal musculature. It appears unlikely that there exists any primary change in the myocardium of MH-susceptible individuals which predisposes an individual to MH. Nevertheless, it must be mentioned that the occurrence of non-specific cardiomyopathic changes has been reported.

Liver

In studies of hepatic metabolism in porcine MH [14], no major abnormality of liver function was detected. Although the rate of hepatic blood flow decreased during MH, there occurred a compensatory increase in oxygen extraction which enabled splanchnic oxygen consumption to be maintained. The liver released significant potassium ions and glucose and thus contributed to the hyperkalaemia and hyperglycaemia. The hepatic lactate pool did not contribute to the characteristic metabolic acidosis in MH; rather, lactate uptake by the liver was increased during the crisis. It would also be expected that the increased secretion of catecholamines, already referred to, would stimulate hepatic glycogenolysis and would therefore explain the hyperglycaemia observed by Hall and colleagues [14].

Nervous system

For obvious reasons, no direct experimental evidence of primary biochemical changes in the central nervous in MH have been made. In contrast to whole body oxygen consumption, cerebral oxygen consumption is not altered in the porcine MH crisis; similarly, the cerebral venous concentrations of lactate and potassium ions were not altered in MH. It is unlikely, therefore, that the central nervous system is involved in the primary pathogenesis of MH. A secondary involvement is indicated, but this is caused by the acidosis, hypoxia, high temperature and hyperkalaemia. In particular, the acidosis, hypoxia and hyperthermia would inhibit cerebral mitochondrial ATP synthesis and glucose oxidation by the glycolytic pathway and the tricarboxylic acid cycle, the metabolic processes upon which the brain so critically depends for the chemical energy which sustains neuronal electrical activity. The neurological changes in humans, such as coma, are readily explicable in terms of these projected biochemical changes.

In the case of the sympathetic nervous system, considerable controversy exists in the literature on the time-scale of the involvement of the catecholamines, adrenaline and noradrenaline, in the development of the MH crisis. Catecholamine concentrations in the blood are increased 30-fold during MH, but the increases appear to follow the stimulation of skeletal muscle metabolism. Such hormonal increases would further stimulate muscle glycogenolysis and cardiac and hepatic metabolism. Disagreement also exists on whether the resting metabolic rate in MH susceptible swine is altered; fortunately, the observations on MH-susceptible humans are clear-cut. Campbell, Ellis and Evans [4], in a comprehensive study of biochemical and physiological parameters in MH susceptible and normal individuals, found that there was no difference between the resting metabolic rate of the two groups. This observation indirectly supports the view that the catecholamines exacerbate, but do not initiate, the MH reaction. Theoretical biochemical analysis of meta-

bolic control mechanisms also predicts that sympathetic activation on its own would not initiate the fulminant MH crisis; simultaneous, massive activation of ATP-degrading processes in skeletal muscle would also be required.

Blood

Unexplained acidosis, together with increased carbon dioxide pressure and decreased oxygen pressure, as measured by arterial gas analysis, are diagnostic indicators of an impending MH crisis. Metabolic acidosis caused by increased lactate production and respiratory acidosis caused by increased carbon dioxide production (cf. skeletal muscle section), both by-products of the escalating metabolism of the skeletal musculature, coexist. Total serum and ionized calcium concentrations increase during the porcine MH crisis; the increase in the latter is predictable when account is taken of the profound acidosis. The situation in the human MH crisis is unclear, because calcium-free i.v. therapy of human patients interferes with the measurement of actual total and ionized serum calcium during the acute episode. Serum potassium increases two- to three-fold during the MH crisis; it arises principally from the sarcoplasm, being released when the muscle cell membranes are damaged by both the acidity, high temperature and loss of ATP. The hyperkalaemia may cause heart block, which may progress to cardiac arrest and, ultimately, death. Sarcoplasmic proteins also leak from muscle fibres during the acute episode, but the time course of such leakage is somewhat later than that of electrolyte loss, presumably because of the greater molecular weights of the proteins. For instance it is well-known that myoglobin (molecular weight ca. 16000), the intracellular oxygen-carrying protein of red skeletal muscle, leaks into the circulation, resulting in myoglobinaemia. So too, does the enzyme creatine phosphokinase, the serum concentration of which may plateau only 24 h after the acute episode. Erythrocyte haemolysis can also occur during the acute episode; it is likely that it is caused by the acidosis, rather than by halothane or high temperature.

Kidney

Progressive loss of myoglobin from muscle and increasing myoglobinaemia is followed by myoglobinuria. This can lead to oliguria and eventually anuria, as the comparatively large protein molecules accumulate and ultimately block the pores of the basement membrane of the glomerular filtration barrier. This phenomenon can become more prominent when the patient has suffered an episode of hypotension. No biochemical data, direct or indirect, on the metabolic state of the kidney in the MH crisis are available. It is therefore not possible to say how renal tubular reabsorption would be affected in MH.

HEAT PRODUCTION

Much has been written of the metabolic origin of the heat which manifests itself as the characteristic temperature increase of the MH crisis. Contrary to early reports and suggestions, it now appears unlikely that the heat arises from uncoupling of the process of oxidative phosphorylation in the mitochondria of skeletal muscle. More recent studies indicate that most of the heat is generated by the rapid hydrolysis of high-energy phosphate compounds by actomyosin ATPase during contraction, by sarcoplasmic reticulum ATPase during relaxation, by the sodium pump enzyme system during membrane repolarization, by neturalization of hydrogen ions produced under the metabolic and respiratory acidotic conditions, by that proportion of the free energy released but not captured as ATP during the accelerated aerobic and anaerobic metabolism which occurs during the acute episode and, perhaps, by futile cycling of fructose-1, 6-bisphosphate to fructose-6-phosphate. Precise identification of the reactions producing the heat has not been possible, primarily because of the unsteady metabolic and circulatory states which prevail during the acute episode and because of uncontrolled heat losses [10].

RECOVERY FROM THE ACUTE EPISODE

The duration of postanaesthetic myalgia, myoglobinaemia and increased serum creatine phosphokinase activity indicates that complete recovery can take from a few days to a few weeks and that it is a function of the severity of the acute malignant hyperthermic episode. In biochemical terms, the enzyme systems which synthesize new membrane proteins and phospholipids and assemble them correctly in the membrane structure must be activated and provided with sufficient substrates so that the repair process can proceed at a maximum rate. Progress of repair will depend on the nutritional strategy adopted in the im-

mediate postepisodic period. Clearly, if cells have been severely damaged, necrosis will set in; this applies particularly to neurones of the central nervous system, which are irreversibly damaged by anoxia lasting longer than about 4 min. Such anoxia causes neuronal ATP depletion and ionic equilibration and, consequently, permanent neurological damage. By contrast, skeletal muscle fibres can withstand sustained anoxic periods of 20–30 min by virtue of their anaerobic glycolytic capacity and the activity of the enzyme adenylate kinase.

GENERAL CONCLUSIONS

The acute MH episode is initiated by an abrupt increase in the intracellular ionized calcium concentration of skeletal muscle. This singular event sets in train a cascade of metabolic events which depletes the high-energy phosphate reserves of the muscles. If the cascade is not interrupted and arrested very early in the onset phase (for instance, by i.v. dantrolene therapy), an irreversible phase of very rapid metabolism, rigor development and destruction of muscle cell membranes is entered and the episode becomes fatal. Thus, MH may best be regarded as a myopathy in which the skeletal muscle has an impaired ability to regulate the intracellular ionized calcium concentration when clinical concentrations of potent volatile anaesthetics or certain neuromuscular blocking agents, or both, are present. The precise intracellular defect responsible for the loss of intracellular calcium homeostasis has not been identified; it still remains the elusive target of many biomedical researchers.

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