The Biochemistry of Heat Illness

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SUMMARY: The two common forms of heat illness in the Services are heatstroke and heat exhaustion. Biochemical predisposing factors are considered for each. Susceptibility to malignant hyperthermia should be tested for in cases of heat stroke. The heterozygote status for cystic fibrosis should be established in cases of heat exhaustion.

Introduction

Lt Col Dickinson's admirable review of heat illness in the Services did not consider biochemistry (1). In the past some fatalities could be attributed to faulty arrangements, as when four officer cadets at Aldershot died in the summer of 1948 during an endurance run wearing full denim gear with heavy packs (2). However in recent times, probably due to increased awareness, cases have tended to be sporadic. As Lt Col Dickinson noted himself (3), 'Some people seem to be unduly susceptible to hyperthermia on exercise even in moderate conditions – and, sadly, the first episode may be the fatal one.' This paper reviews biochemical predisposing factors which might explain this observation.

Heat stroke and heat exhaustion are the two commonest forms of heat illness, having different aetiology, biochemistry, and predisposing factors.

Heat stroke

Heat stroke occurs in 13% cases of heat illness (1) and is caused by the body core overheating to over 41 deg.C. It is usually due to physical exertion in a climate with ambient temperature close to or above body temperature. Normally the sweat mechanism maintains a normal body temperature but heat stroke victims may cease to sweat. An RAMC medical officer working near Basra in 1943 where the noon shade temperature could reach 60 deg.C noted cessation of sweating in twelve survivors of heat stroke (4).

Clinically there is confusion, headache and a hot dry skin. Initially there is a respiratory alkalosis (low PaCO₂) due to hyperventilation, followed by a metabolic acidosis (low blood pH, high H⁺ ion conc.) and hyperlactataemia (5). The serum creatine kinase (CK) may be greatly elevated. Serum calcium may fall due to calcium binding to damaged cells. Later changes are organ failure (heart, kidney, liver), with disseminated intravascular coagulation and myoglobinuria due to rhabdomyolysis. These pathological changes were formerly thought to be due to intestinal endotoxins absorbed into the portal circulation causing release of vasoactive mediators from target cells, such as macrophages (6).

Heat stroke and Malignant Hyperthermia

It was postulated in 1978 that malignant hyperthermia is a human stress syndrome of which heat stroke is a variety (7). Two soldiers successfully treated for heat stroke were later shown to be susceptible to malignant hyperthermia by pharmacological tests on muscle biopsy (8). Malignant hyperthermia is a pharmacogenetic disorder associated with disordered intracellular ionic calcium regulation. The skeletal muscle suffers severe damage after a general anaesthetic using suxamethonium or a volatile agent such as halothane or enflurane. It occurs in about 1:50 000 adults, usually male, and is inherited as an autosomal dominant. The anaesthetic drugs cause the calcium conc. to rise in muscle myofibrils leading to muscle rigidity, hypermetabolism and sarcolemmal disruption, with hyperkalaemia and myoglobinaemia. Although serum CK may be raised in persons susceptible to malignant hyperthermia, CK testing is thought to be unreliable for screening, and malignant hyperthermia is diagnosed by *in vitro* contracture tests on skeletal muscle samples (8). It is not known what proportion of cases of heat stroke occur in persons susceptible to malignant hyperthermia.

Heat stroke and Nitric Oxide

The discovery that nitric oxide is the endothelium-derived relaxing factor (9) has led to major advances in understanding the role of nitric oxide as an important intercellular messenger. Nitric oxide has both beneficial and deleterious roles (10) and is 'bad' in heat stroke. Clark *et al* (11) observed that the changes in mental status during cerebral malaria, heat stroke, and recovery from major surgery are clinically similar. A War Office publication from 1942 (12) noted that the neurological symptoms of heat stroke are easily mistaken for those of cerebral malaria. Equally ethanol-induced coma and opioid narcosis can be clinically very similar to cerebral malaria suggesting that a common biochemical mechanism is involved in causing what are usually reversible neurological changes.

In heat stroke there are high circulating levels of the cytokines tumour necrosis factor (TNF) and interleukin-1 (IL-1) which strongly induce nitric oxide formation *in vivo* (13). These cytokines can induce nitric oxide

formation in vascular walls which can then diffuse across the blood-brain barrier causing functional changes including inhibition of calcium entry, reduced activity of the calcium-dependent nitric oxide synthase, and thus reduced nitric oxide formation in post-synaptic neurones.

Thus the current hypothesis for the biochemical mechanisms for the neurological changes in heat stroke is that cytokine-induced nitric oxide release interferes with the normal excitatory function of neuronal nitric oxide. The biochemical pathway involves intracellular ionised calcium which links heat stroke with malignant hyperthermia. It is suggested that Service personnel recovering from heat stroke should be investigated for susceptibility to malignant hyperthermia.

Heat Exhaustion

Heat exhaustion accounts for 74% cases of heat illness in service personnel (1). It is usually caused by loss of extra-cellular fluid (ECF) through a salty-sweat whilst working in a hot environment. Patients may collapse, or be greatly fatigued, with nausea, vomiting, and painful muscle cramps. Since salt and water are lost the serum sodium and chloride concentrations are normal, but the haematocrit and serum urea and osmolality are raised. The clinical picture is thus similar to loss of ECF from the gut, as in a dysentery. If ECF volume becomes critically low peripheral circulatory failure and prerenal uraemia can ensue.

A less common variant is when water loss exceeds salt loss, as when persons are deprived of water in a hot environment. Water deprivation may be voluntary as in pilgrims to the Hadj in Mecca and as described below. Water is then lost from the whole body, cell fluid and ECF. Death occurs when 15-25% body weight is lost.

Heat Exhaustion and Cystic Fibrosis

Children with cystic fibrosis have a high salt content to their sweat and have a reduced tolerance to climatic heat stress. It has been suggested that this high sweat salt content reduces the normal thirst stimulus which is a rise in body fluid osmolality (14). Children with cystic fibrosis when not forced to drink in hot environmental conditions can greatly underestimate their fluid needs (voluntary dehydration).

The relevance of this to heat exhaustion is that 1:20 to 1:25 of the general population is heterozygous for cystic fibrosis. It is not yet known whether heterozygotes for cystic fibrosis have a marginally saltier sweat than non-heterozygotes, but it is a logical hypothesis. This has been a theoretical possibility for many years, but the situation has now changed because cystic fibrosis heterozygote status can now be determined by DNA analysis of

mouthwash samples collected in 4% sucrose (15). It suggests that service personnel recovering from heat exhaustion should have their cystic fibrosis heterozygote status ascertained.

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