Hypothesis

Thiamine and High Dose Insulin Treatment for Sepsis

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Abstract: epsis is a major health problem and accounts for 20 per cent of deaths worldwide. It is the most expensive condition treated in United States hospitals at $27 billion per year or about $20,000 per patient. Treatment consisting largely of fluid resuscitation and antibiotics has only marginal impact. Mortality is about 27 per cent for hospitalized patients and about 42 per cent for patients in intensive care. There are two phases of sepsis – a hyper inflammatory phase and a subsequent hypo inflammatory phase. During the hyper inflammatory phase the metabolic rate increases associated with an increase in body temperature and a rapid escalation of immune system functioning including increased numbers of leucocytes and migration of those leucocytes to infected and damaged tissues and an increased supply and consumption of glucose to fuel this immune system. During the subsequent hypo inflammatory phase the metabolic rate declines and this is associated with a decrease in body temperature and a generalized decrease in the physiological activity of many organs including the immune system akin to hibernation. The activated immune system has priority for the available glucose over most other organs and physiological functions during such potentially life threatening circumstances. Thus adenosine triphosphate (ATP) production by mitochondria (the source of energy at the cellular level for the organism as a whole) also has a lower priority for the available glucose relative to the activated immune system. If glucose availability is threatened then mitochondrial production of ATP is partially or substantially suppressed in favor of glycolysis because glycolysis can rapidly produce large quantities of ATP that are necessary for immune cell function in infected, anaerobic, ischemic, or damaged tissues. However, glycolysis is only a temporary fix as it cannot produce the quantities of ATP necessary on an ongoing basis for the normal functioning of the healthy animal. Mitochondrial production of ATP must be recommenced for full recovery. It appears that the partial or substantial suppression of mitochondrial production of ATP by activation of the immune response becomes relatively fixated in some patients leading to a substantial ATP deficit. This is the fundamental issue of sepsis. This paper reviews the metabolism of glucose and insulin during sepsis and concludes that high dose insulin with mild hyper glycaemia in conjunction with the intravenous administration of thiamine, an inhibitor of the pyruvate dehydrogenase kinase enzymes, to re-establish physiological ATP production by mitochondria, administered early in the hypo metabolic (hypo inflammatory) phase of sepsis should significantly improve survival.

Keywords: Sepsis Treatment; mitochondria; Adenosine Triphosphate (ATP); Pyruvate dehydrogenase complex and thiamine; glycolysis; glucose and insulin

INTRODUCTION

The incidence of sepsis is highest in infants under the age of 12 months and in the elderly and the elderly also have the highest mortality rate from sepsis [1].

One definition of sepsis is that it is a syndrome of severe organ dysfunction caused by a dysregulated host response to infection. Studies have examined the balance of inflammatory and anti-inflammatory pathways and the release of pro-and anti-inflammatory cytokines, mediators, and pathogen related molecules to name a few of the avenues of investigation. Yet despite decades of preclinical and clinical research there has been disappointing progress towards a better clinical outcome [2].

Eliminating the microorganisms that initiated this process doesn't extinguish sepsis. Although antibiotic treatment improves survival of hospitalised patients it is not the only factor determining

survival. In a murine model of fulminant cecum ligation and puncture (CLP) different antibiotic dosing strategies resulted in no significant differences in survival between different antibiotic doses and no treatment [3].

THE HYPER INFLAMMATORY PHASE OF SEPSIS

Activation of the immune response (equivalent to the hyper inflammatory state of sepsis) in healthy adults results in a metabolic rate increase of 37-55% [4] which is equivalent to about 175-261 g of glucose because the immune system substantially uses glucose [5].   Core temperature also increases. Leucocyte numbers increase and migrate to sites of infection and tissue damage. Insulin resistance (IR) occurs that reduces uptake of glucose by less essential organs, the liver increases the output of glucose, the kidneys increase reabsorption of glucose, adipose tissue increases the release of free fatty acids (FFA) and glycerol that can be utilised as alternative fuels or as substrates for glucose production and skeletal muscle is catabolised to provide amino acids for gluconeogenesis. All this is to provide for the voracious appetite for glucose of the activated immune response.

In mice with a seven-fold higher metabolic rate than humans, this ravenous demand for glucose leads to the contradictory presence of both IR and increased glucose tolerance because of the increased consumption of glucose by leucocytes [6].

The amount of intravenous (IV) glucose needed is a proxy for the glucose requirements of the activated immune system. Growing pigs with an average weight of 30 kg needed 116 g of glucose over 480 minutes to maintain euglycemia when challenged with a large dose of endotoxin [7]. Lactating Holstein cows weighing an average of 718 kg needed 1000 g of glucose over 720 minutes to maintain euglycemia when challenged with a large dose of endotoxin [8].

In adult humans with severe infections such as malaria, glucose output from the liver is doubled from about 200 to 400 g/day. In children with such severe infections whose glycogen stores are diminished relative to adults severe hypoglycaemia is a common result of this high-glucose usage and this results in a four to six times higher mortality compared to children without hypoglycaemia (9,10).

The diversion of glucose to the immune system away from less essential organs and tissues was illustrated using radio labelled glucose and Positron Emission Tomography (PET) to measure glucose uptake in various organs after administration of lipopolysaccharide (LPS) to animals (Dutch dwarf rabbits). This resulted in the "almost total absence of glucose uptake shown by most organs" but increased kidney glucose reuptake thus also providing increased glucose for the activated immune system. This was associated with initial hyperglycaemia because of the reduced ability of glucose to enter cells. The animals also became hypothermic also because of the decrease in availability of glucose for most cells and thereby fuel for mitochondria [11].

Glycolysis replaces mitochondrial oxidative phosphorylation (OXPHOS) to varying degrees as the preferred ATP-producing pathway. The advantage of glycolysis for immune cells is that glycolysis is 100 times faster than OXPHOS in the acute production of ATP and can provide   these increased   quantities   of ATP in the anaerobic or ischaemic tissues characteristic of infected or damaged   tissues.   Other   organs including   tubular   epithelial   cells   and   cardiomyocytes   also substantially switch to glycolysis for their ATP production [12].

Normally 95% of the ATP consumed by cells in the healthy organism is produced by OXPHOS in mitochondria (100 -150 moles or 25-40 kg per day)[13].

Fever is an important aspect of activation of the immune response as phagocytic activity and capacity increase with increasing temperature [14] and elevated temperature is strongly associated with increased survival [15].

THE HYPO INFLAMMATORY PHASE OF SEPSIS

A negative of glycolysis is that it is unable to produce sufficient ATP on an ongoing basis for all the cells of the normal healthy organism. It is only a temporary measure for the urgent need to produce large amounts of ATP for immune cells to destroy pathogens quickly in relatively anaerobic or ischaemic tissues [5,12].

However, this situation, if prolonged, leads to a deficiency of ATP because only mitochondria can produce ATP in sufficient quantities for the recovery of all cellular functions [12,13].

This is particularly true of sepsis-induced cardiac dysfunction because the heart is dependent on a continuous supply of ATP and mitochondrial dysfunction is a key factor in septic cardiomyopathy [2] Consistent with its high metabolic rate the heart has the highest density of mitochondria of any organ constituting 30% of its total mass.

The relative suppression of mitochondrial ATP production that occurred with activation of the immune response commonly becomes relatively entrenched. This may be because insulin resistance has become entrenched or mitochondrial restart up is inhibited by the high levels of lactate produced by glycolysis or the senility of mitochondria or by high levels of some cytokines or antioxidants or some other factors.

Consistent with this, respiratory capacity is elevated in non-surviving patients relative to survivors and mitochondrial respiration associated with ATP synthesis is lowest among non-surviving septic patients [4].

Also consistent with this is the linear correlation between body temperature on emergency department admission and mortality. The crude 30-day mortality was 48% for those with a temperature <35° C and 11% for those with a temperature >41° C [15]. Functioning mitochondria prioritising uncoupled respiration over ATP production are necessary to produce fever [16] and inhibition of mitochondrial function by inhibition of the mitochondrial pyruvate carrier (MPC) prevents fever [17].

Thus, the hypo inflammatory phase of sepsis is associated with a decrease in oxygen consumption (VO_2) and the basal metabolic rate despite an elevated respiratory capacity and a lack of response to increased systemic oxygen.

A phenomenon of this hypo inflammatory phase of sepsis is multi-organ dysfunction syndrome (MODS). This is characterised by minimal cell death, reduced cellular oxygen and substrate consumption, and normal/elevated tissue oxygen levels. MODS may represent an adaptive shutdown aimed at minimizing cellular energy requirements or a defensive strategy like hibernation. [11,12].

Even sepsis-induced cardiac dysfunction may be consistent with a state of hibernation as the changes are often functional rather than structural. They can be seen as adaptive to tissue hypoxia and hypo-perfusion with downregulation of nonessential functions involving a reduced consumption of oxygen and ATP [18].

During the recovery phase of sepsis hospital survivors systemic VO_2 and resting metabolic rate are increased by 50-60% consistent with reactivation of mitochondrial production of ATP [18].

Thus, the critical issue in severe sepsis is the failure of mitochondrial reactivation necessary to produce the amounts of ATP required for full recovery [19].

GLUCOSE

There is evidence that glucose availability is associated with both the risk of sepsis and the risk of death from sepsis.

Glucose availability is important for the neonate, particularly preterm neonates, because they have limited glycogen and fat stores, a low expression of enzymes for gluconeogenesis and high glucose needs for their comparatively large brain and they are unable to respond to hypoglycaemia in a timely and adequate manner. Thus, these infants are at high risk of hypoglycaemia and 30-60% require immediate supplementary glucose to prevent morbidity and long-term complications [20]. They also have a higher risk of sepsis and mortality from sepsis [21,22].

Glucose metabolism in childhood is also illustrative of the probable key role of glucose in sepsis. Children aged 5 to 14 years have a significantly lower mortality rate from sepsis compared to adults even when having similar rates of infection. For example, in the 1918 flu pandemic the mortality rate for children was about 25% that of adults and the same phenomenon has been found in numerous other infectious conditions [23]. This apparent protective effect of childhood is associated with the highest availability of glucose than at any other age. Normalised for weight glucose production in

children aged 6 – 9 years is three times that of adults [24] and glucose demand for somatic growth is at its lowest level [25]. IR is also at its lowest level (consistent with a surfeit of available glucose) [26,27].

Consistent with the relative immunity from sepsis in children, pre-pubertal mice show greater survival than post-pubertal mice despite showing a similar degree of inflammation after 2 hours. Prevention of puberty by hormonal blockade or acceleration of puberty by oestrogen treatment led to increased or decreased survival from endotoxemia. Along with increased survival pre-pubertal mice exhibited higher per cent weight loss compared to post-pubertal mice. Greater weight loss towards the beginning of the disease course is a common finding associated with survival in mouse models of sepsis and may be because of accelerated protein catabolism to enhance liver gluconeogenesis. Pre-pubertal animals also exhibited greater dampening of cytokine expression as time passed. However, in the clinical setting there are conflicting reports as to whether female sex is protective factor during sepsis [28]. For example, the use of estrogen in postmenopausal women increased the risk of deterioration in glucose tolerance [29].

In mice mortality from sepsis is reduced by the infusion of glucose in a dose dependent manner but only early in the hypo inflammatory phase of sepsis [30,31].

Patients with comorbid diabetes and sepsis admitted to ICU units had significantly elevated plasma glucose levels compared to non-diabetic patients, and this was associated with significantly reduced 28-day mortality particularly when associated with hyperglycaemia [32].

Glucose requirements following injury are less than those following sepsis consistent with its higher glucose consumption and accordingly the increase in hepatic glucose output following injury (12.8%) is less than that following sepsis (76.6%) [33].

Evidence that death from sepsis is increased by a relative unavailability of glucose is also supported by the fact that patients who are hyperthermic are more likely to survive than those who are hypothermic [15]. Glucose is the dominant fuel of the activated immune system, and this system has priority for this fuel over other metabolic uses including thermoregulation [5]. Patients who can elevate body temperature during an infection have a relative excess of glucose above that needed for immune system needs. Patients whose glucose resources are marginal have insufficient glucose left over to fuel the less urgent requirements of thermoregulation and thus become hypothermic. Mechanically ventilated septic patients who were subjected to forced-air warming blanket for 48 hours had a 25% reduction in 28-day mortality [34].

This interpretation is supported by the finding that mice, whose metabolic rate is 7 times that of humans, housed at 30 ° C had higher survival from sepsis compared to mice housed at 20 ° C. The mice housed in thermoneutral conditions had mean energy expenditures 1.8 times basal whereas in cooler temperatures their mean energy expenditures were 3.1 times basal [35].

INSULIN

There is also evidence that insulin availability is also associated with the risk of sepsis and the risk of death from sepsis.

The heart has the highest consumption of ATP of all organs and is a sensitive barometer of ATP availability. Patients with chronic heart failure have elevated   IR and a low insulin level is associated increased mortality [36]. Consistent with this a study compared two groups of pigs after LPS administration. One group received Insulin at a dose of 1.5units/kg/h and the other group was the control. Insulin improved cardiac output, SVO_2 oxygen delivery, systemic vascular resistance, and pulmonary vascular resistance [37].

Mitochondrial protein synthesis (MiPS) is important for the maintenance of cellular function and this was measured under low and high insulin conditions with and without an infusion of essential amino acids (EAAs). Mitochondrial protein synthesis, cytochrome c oxidase (COXIV) activity and whole body Vo2 only increased with EAAs with high insulin concentrations [38].

Glucose is a major fuel for the myocardium particularly in hypo aerobic and ischaemic conditions and insulin orchestrates glucose uptake, glycolysis, and mitochondrial oxidation and thus indirectly and directly increases production of ATP [39].

Another study involved 58 Horses presenting to a Large Teaching Hospital with systemic inflammatory response (SIRS) from infection. Reduced pancreatic insulin secretion was the major factor associated with non-survival [40].

Acute kidney injury (AKI) is present in over 40% of septic patients. Many aspects of mitochondrial dysfunction contribute to AKI such as overproduction of reactive oxygen species (ROS), depletion of ATP, dissipation of mitochondrial membrane potential (MMP) and exacerbation of apoptosis. Insulin therapy prevents mitochondrial damage by excessive ROS production. It reverses the depletion of ATP and changes in MMP in mitochondria, reduces the production of oxidants, attenuates histological tissue damage, increases antioxidant levels in mitochondria and suppresses renal mitophagy [41].

Finally, in glucose infused mice LPS administration caused a large increase in circulating insulin with no change in blood glucose. However, blockade of insulin secretion in response to LPS in the presence of exogenous glucose precipitated marked hyperglycaemia and 90% mortality. In a sub-analysis of animals matched for degree of hyperglycaemia non-survivors had a markedly lower insulin level than survivors (3.5 ng/dL vs. 9.3 ng/dL) [42].

GLUCOSE PLUS INSULIN

While it may seem contradictory that increased glucose availability and increased insulin availability are both individually associated with increased survival from sepsis there is evidence that combined there is an added effect.

Cardiomyocytes in culture were subjected to simulated ischemia. Various combinations of glucose and insulin increased ATP production by up to 75% and reduced lactate production by up to 40% and reduced ischaemic cellular injury [43] and septic rats were infused with insulin and glucose to achieve an average blood glucose either in the range of 6-8 mmol/L or 8-10 mmol/L. The optimal range was 8-10 mmol/L. At this level glucose utilization was superior and the expression of GLUT mRNA and the glucose transporter across cell membranes, GLUT4 was higher [44].

Much of the mortality and morbidity associated with septic shock is due to refractory hypotension and cardiovascular collapse so counteracting this should improve survival. Glucose-insulin-potassium (GIK) was administered to 45 patients with severe sepsis/septic shock. They were divided into those who were hypodynamic and those who were non-hypodynamic. 12 Patients with hypodynamic septic shock with myocardial depression displayed improved mean arterial pressure and reduced heart rate during the first 72 hours of GIK treatment. Total insulin dose correlated with improvement [45].

The fact that plasma insulin and glucose levels are both elevated in obesity and type 2 diabetes and these conditions are both associated with lower sepsis mortality is consistent with the protective effect of the enhanced availability of insulin and glucose [32,46].

HIGH DOSE INSULIN

The amount of insulin produced by a healthy lean adult is 18-40 U/day or 0.2-0.5 U/kg/day. The basal insulin secretion is 0.5-1 U/hr. After a meal ingestion it increases up to 6 times baseline secretion and reaches a peak within 60 minutes [47].

However, much higher doses of insulin have been used in therapeutic situations and have a positive impact on IR, glucose uptake and ATP production consistent with their positive impact on cardiac function.

Two obese women with Type 2 diabetes who developed severe COVID-19 and severe insulin resistance (blood glucose > 600mg/dL) required total daily insulin of 600 units per day (>5 units/kg/day – approximately 20 times physiological production) [48].

A man weighing 65 kg with diabetic ketoacidosis (DKA) and myocardial infarction (MI) had a blood glucose on first day of 847 mg/dl and received 657 units of insulin over the first 24 hours. On subsequent days his insulin requirements varied dramatically because of fluctuating glucose levels. For example, on day 5 his insulin requirements varied from 120 units per hour to 1 unit per hour and totalled 1200 units for the day and on day 7 totalled 2200 units for the day (approximately 70 times

physiological production). No reason for these fluctuating insulin requirements was identified. After he had his coronary artery bypass graft (CABG) his insulin resistance resolved. This may have been a consequence of the increased glucose availability to cardiomyocytes following the improved vascular perfusion [49].

A Japanese man weighing 44 kg with DKA, and cardiogenic shock required 90,000 units of insulin over the first 24 hours or an average of 85 U/kg/hour (approximately 3000 times physiological production) [50].

High dose insulin (HDI) is used in burns patients to reduce muscle loss. In one study maximal insulin doses (7.7 mU/kg/min or 32 units/hour for a 70 kg patient or about 35 times physiological insulin production) combined with amino acid infusions in severe burns caused an amelioration of muscle catabolism because of a fourfold increase in protein synthesis that counteracted the increase in protein catabolism. This resulted in a plasma insulin concentration of about 900 µU/ml. However, because of this hyperinsulinemia large amounts of additional exogenous glucose (about 1300 g/day or 5600 kcal) was required to avoid hypoglycaemia (51). In a subsequent modified study insulin was administered at 2.6mU/kg/min (about 12 times the physiological production of insulin) resulting in a plasma insulin concentration of 242 µU/ml. In control subjects the plasma insulin concentration was 27.5 µU/ml. However, half of these patients also required exogenous glucose (about 400g/day or 1350 kcal) to prevent hypoglycaemia [52]. As protein synthesis has a high ATP consumption this study is consistent with the premise that high dose insulin in combination high glucose availability and amino acid supplements stimulates mitochondrial ATP production.

In another study an increase in insulinaemia from 250 mIU/L (8 times basal level) to 1250 mIU/L (40 times basal level) in a mixed selection of septic patients significantly increased glucose uptake and oxidation [53].

An animal study examined the impact of HDI on the myocardial depression associated with severe septic shock. Ten pigs were randomized to receive either HDI or normal saline while LPS was administered over 5 hours. IV Dextrose was administered to maintain plasma glucose in the range 60-150mg/dL. The insulin was administered at 2-10 units/kg/hr. Survival was 100% in the HDI arm and 60% in the saline arm. The HDI pigs had significantly better cardiovascular and metabolic variables [54].

HDI has proven superior to glucagon and catecholamines in the treatment of poison-induced cardiogenic shock in animal experiments. A study using 4 groups of pigs induced cardiogenic shock with IV propranolol and then different doses of insulin were infused – placebo, 1 U/kg/hr, 5 U/kg/hr and 10 U/kg/hr. In this study cardiac output increased with increasing doses of HDI with a 57% difference between 1 U/kg/hr and 10 U/kg/hr. The authors were unable to establish what the ceiling for HDI was. No pigs died in the 10U/kg/hr group contrasting with deaths in the other groups with most deaths in the placebo arm [55].

A review of 22 patients found that HDI treatment (up to 1000 times physiological production) for toxin induced cardiac toxicity resulted in no major disruption of glucose and electrolyte homeostasis. Despite glucose and potassium infusions hypoglycaemia and hypokalaemia were common. There was no association between these disturbances and the amount of insulin administered suggesting that the degree of insulin resistance varied between patients and even within individual patients. There was no evidence that higher doses of insulin (up to 10U/kg/h) were associated with more adverse effects that low doses [56]

A rapid and marked increase in mitochondrial function and ATP production also resulted from another example of increased fuel availability in the form of 2 hours of hyperbaric oxygen in type 2 diabetic subjects [57].

THE PYRUVATE DEHYDROGENASE COMPLEX

To increase mitochondrial ATP production during sepsis two barriers must be overcome. Firstly there is the barrier of severe IR during sepsis that inhibits glucose from crossing through cellular membranes into the cellular cytoplasm. Evidence has been presented indicating that insulin,

particularly high dose insulin, overcomes this first barrier and increases intracellular cytoplasmic glucose.

The second barrier is the suppression of the pyruvate dehydrogenase complex (PDHC). This inhibits the transfer of pyruvate from the glycolytic cytoplasmic metabolism of glucose crossing into the mitochondria from the cellular cytoplasm.

Glycolysis is the metabolic process in the cytoplasm of cells that produces ATP by breaking down glucose into pyruvate and lactate yielding 2 units of ATP. It does not require oxygen, so it is optimal for cells operating in relatively anaerobic or relatively ischaemic tissues. Under aerobic conditions, pyruvate translocates to the mitochondria, where it is oxidized to acetyl-CoA through activation of the pyruvate dehydrogenase complex (PDHC) yielding 36 units of ATP. The hypermetabolic phase of sepsis is followed by a hypometabolic phase and PDHC activity is reduced. The enzyme that is involved in suppressing PDHC activity is pyruvate dehydrogenase kinase (PDK). However, PDK is inhibited by drugs such as dichloroacetate (DCA), thiamine, amrinone, TNF-binding protein and ciprofloxacin. Administration of these chemicals enhances mitochondrial uptake of pyruvate [58].

These changes in PDHC activity are not confined to immune cells. Sepsis-induced cardiomyopathy is a major cause of death. Proteome analysis demonstrated that this was associated with increased levels of PDK4 and inhibition of PDHC activity [59]. PDK Inhibitors also rebalance transcriptional and metabolic manifestations of sepsis in liver cells during this low-energy, anti-inflammatory, immunoparalytic phase of sepsis [60].

However, stimulation of the mitochondrial PDHC during the hyperinflammatory stage of sepsis increases mortality possibly because by stimulating metabolic activity it increases glucose consumption and therefor the risk of hypoglycaemia that is a cause of death during this phase.

The vitamin, thiamine, that is also an inhibitor of the pyruvate dehydrogenase kinase enzymes, has been associated with improved clinical outcomes from sepsis. A review of 11,553 patients with a diagnosis of Sepsis-3 from the Medical Information Mart for Intensive Care IV were divided into those who received thiamine and those who did not receive thiamine while in the ICU. Those who received thiamine intravenously had reduced 28-day mortality from sepsis (HR=0.8) and reduced mortality from MI (HR=0.61) [61]. However, trials of thiamine supplementation have produced mixed results probably because of differences in design, including dosage, oral or intravenous administration, time thiamine was administered, presence of absence of thiamine deficiency, duration of administration, small sample sizes, different septic phenotypes and different combinations of additional medications. For example, one small trial of patients with severe pneumonia reported a positive impact [62] while another small trial of patients in septic shock reported no benefit [63].

CONCLUSION

High dose insulin with mild hyperglycaemia and PDK inhibitors, such as intravenous thiamine, act on different enzyme structures and have an additive stimulative effect on the PDHC production of ATP [64]. This combination administered early in the hypometabolic (hypoinflammatory) phase of sepsis should improve survival.

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