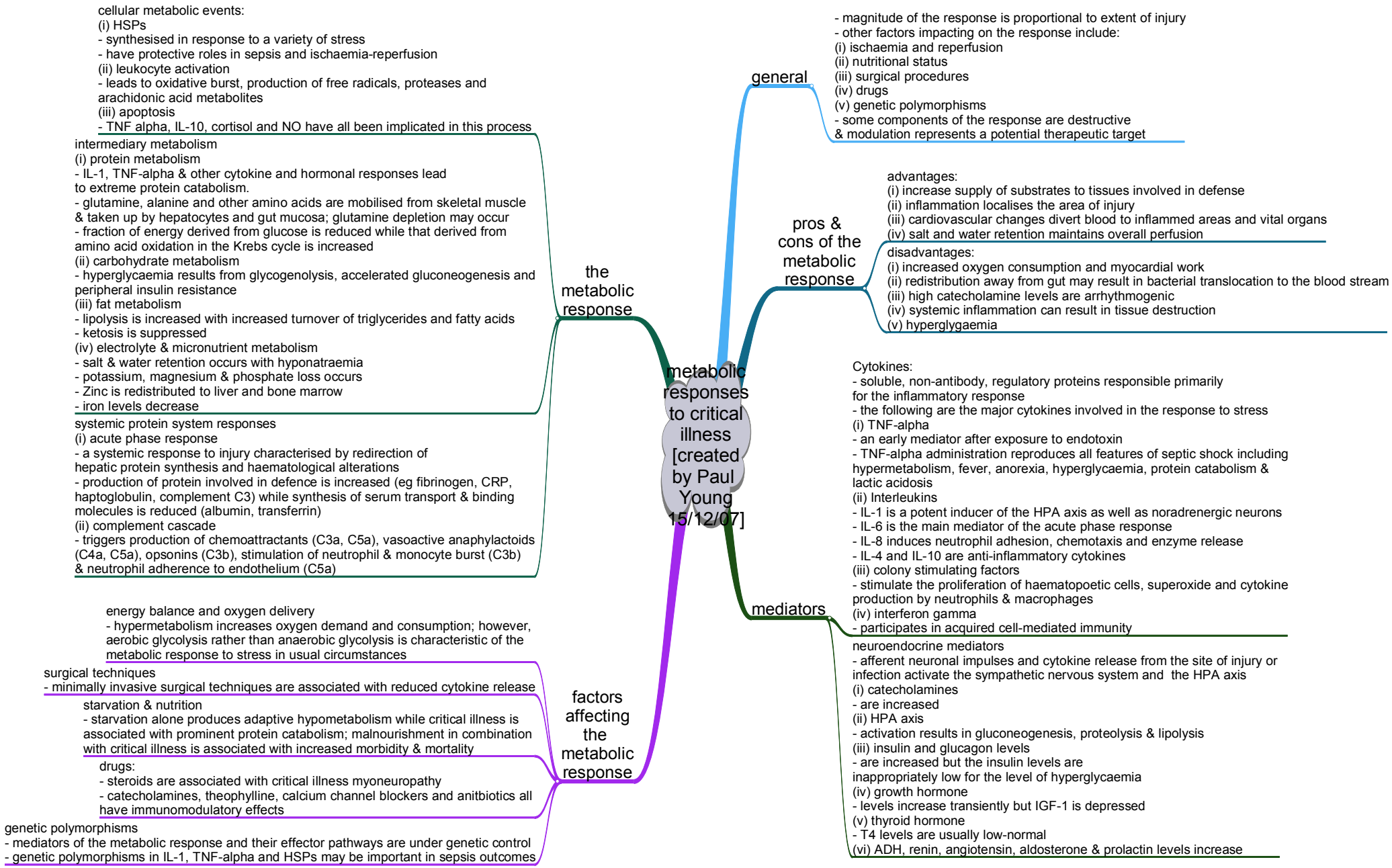
metabolic responses to critical illness [created by Paul Young 15/12/07]
general
- magnitude of the response is proportional to extent of injury
- other factors impacting on the response include:
(i) ischaemia and reperfusion
(ii) nutritional status
(iii) surgical procedures
(iv) drugs
(v) genetic polymorphisms
- some components of the response are destructive
& modulation represents a potential therapeutic target
pros & cons of the metabolic response
advantages:
(i) increase supply of substrates to tissues involved in defense
(ii) inflammation localises the area of injury
(iii) cardiovascular changes divert blood to inflammed areas and vital organs
(iv) salt and water retention maintains overall perfusion
disadvantages:
(i) increased oxygen consumption and myocardial work
(ii) redistribution away from gut may result in bacterial translocation to the blood stream
(iii) high catecholamine levels are arrhythmogenic
(iv) systemic inflammation can result in tissue destruction
(v) hyperglygaemia
mediators
Cytokines:
- soluble, non-antibody, regulatory proteins responsible primarily for the inflammatory response
- the following are the major cytokines involved in the response to stress
(i) TNF-alpha
- an early mediator after exposure to endotoxin
- TNF-alpha administration reproduces all features of septic shock including hypermetabolism, fever, anorexia, hyperglycaemia, protein catabolism & lactic acidosis
(ii) Interleukins
- IL-1 is a potent inducer of the HPA axis as well as noradrenergic neurons
- IL-6 is the main mediator of the acute phase response
- IL-8 induces neutrophil adhesion, chemotaxis and enzyme release
- IL-4 and IL-10 are anti-inflammatory cytokines
(iii) colony stimulating factors
- stimulate the proliferation of haematopoetic cells, superoxide and cytokine production by neutrophils & macrophages
(iv) interferon gamma
- participates in acquired cell-mediated immunity
neuroendocrine mediators
- afferent neuronal impulses and cytokine release from the site of injury or infection activate the sympathetic nervous system and the HPA axis
(i) catecholamines
- are increased
(ii) HPA axis
- activation results in gluconeogenesis, proteolysis & lipolysis
(iii) insulin and glucagon levels
- are increased but the insulin levels are inappropriately low for the level of hyperglycaemia
(iv) growth hormone
- levels increase transiently but IGF-1 is depressed
(v) thyroid hormone
- T4 levels are usually low-normal
(vi) ADH, renin, angiotensin, aldosterone & prolactin levels increase
the metabolic response
cellular metabolic events:
(i) HSPs
- synthesised in response to a variety of stress
- have protective roles in sepsis and ischaemia-reperfusion
(ii) leukocyte activation
- leads to oxidative burst, production of free radicals, proteases and arachidonic acid metabolites
(iii) apoptosis
- TNF alpha, IL-10, cortisol and NO have all been implicated in this process
intermediary metabolism
(i) protein metabolism
- IL-1, TNF-alpha & other cytokine and hormonal responses lead to extreme protein catabolism.
- glutamine, alanine and other amino acids are mobilised from skeletal muscle & taken up by hepatocytes and gut mucosa; glutamine depletion may occur
- fraction of energy derived from glucose is reduced while that derived from amino acid oxidation in the Krebs cycle is increased
(ii) carbohydrate metabolism
- hyperglycaemia results from glycogenolysis, accelerated gluconeogenesis and peripheral insulin resistance
(iii) fat metabolism
- lipolysis is increased with increased turnover of triglycerides and fatty acids
- ketosis is suppressed
(iv) electrolyte & micronutrient metabolism
- salt & water retention occurs with hyponatraemia
- potassium, magnesium & phosphate loss occurs
- Zinc is redistributed to liver and bone marrow
- iron levels decrease
systemic protein system responses
(i) acute phase response
- a systemic response to injury characterised by redirection of hepatic protein synthesis and haematological alterations
- production of protein involved in defence is increased (eg fibrinogen, CRP, haptoglobulin, complement C3) while synthesis of serum transport & binding molecules is reduced (albumin, transferrin)
(ii) complement cascade
- triggers production of chemoattractants (C3a, C5a), vasoactive anaphylactoids (C4a, C5a), opsonins (C3b), stimulation of neutrophil & monocyte burst (C3b) & neutrophil adherence to endothelium (C5a)
factors affecting the metabolic response
energy balance and oxygen delivery
- hypermetabolism increases oxygen demand and consumption; however, aerobic glycolysis rather than anaerobic glycolysis is characteristic of the metabolic response to stress in usual circumstances
surgical techniques
- minimally invasive surgical techniques are associated with reduced cytokine release
starvation & nutrition
- starvation alone produces adaptive hypometabolism while critical illness is associated with prominent protein catabolism; malnourishment in combination with critical illness is associated with increased morbidity & mortality
drugs:
- steroids are associated with critical illness myoneuropathy
- catecholamines, theophylline, calcium channel blockers and anitbiotics all have immunomodulatory effects
genetic polymorphisms
- mediators of the metabolic response and their effector pathways are under genetic control
- genetic polymorphisms in IL-1, TNF-alpha and HSPs may be important in sepsis outcomes