Attenuation of stress response in critically ill patients

Essay

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Abbreviations

ACTH	Adreno-cortico-trophin hormone
BEE	Basal energy expenditure
CRP	C – reactive protein
CRH	Corticotrophin releasing hormone
COX	Cyclo-oxygenase
CPAP	Continuous positive airway pressure
CO	Cardiac output
CVP	Central venous pressure
DHA	Docosahexaeonic acid
EPA	Eicopentaenoic acid
EN	Entral nutrition
FSH	Follicle stimulating hormone
GH	Growth hormone
GABA	Gamma aminobutyric acid
HMB	Hydroxy-methyl-butyrate
HPA	Hypothalamic pituitary adrenal axis
IL	Interleukin
IGF	Insulin like growth factor
IGFBP	Insulin growth factor binding protein
JNK	c-jun-NH2-terminal kinase

LIF	leukemia inhibitory factor
LH	Leuteinizing hormone
MIP	Macrophage inflammatory protein
MAPK	P38-mitogen activated protein kinase
MAAS	Motor activity assessment scale
NSAID	Non steroidal anti-inflammatory drug
PGE-2	Prostaglandin E-2
PEEP	Positive end expiratory pressure
PS	Pressure support
POMC	Pro-opiomelanocortin
RhGH	Recombinant human growth hormone
RMR	Resting metabolic rate
REE	Resting energy expenditure
RQ	Respiratory quotient
RBP	Retinol binding protein
RSS	Ramsay sedation scale
rT3	Reverse T3 hormone
SNS	Systemic nervous system
SCCM	Society for critical care medicine
SVR	Systemic vascular resistance

ScvO2	Central venous oxygen saturation
SAS	Sedation agitation scale
TNF	Tumor necrosis factor
TGF	Transforming growth factor
TSH	Thyroid stimulating hormone
TBG	Thyroid binding globulin
TPN	Total parentral nutrition
TENS	Trans-coetaneous electrical nerve stimulation
TBSA	Total body surface area
VT	Tidal volume
VMA	Vanilmandelic acid

Chapter 1:

The stress response definition & effects

History and definition

The stress response is the name given to the hormonal and metabolic changes which follow injury or trauma. It is the activation of the genetically preprogrammed "fright-flight" response as a result of some bodily insult. The response is essentially an activation of the pituitary-adrenal axis to release catecholamines and cortisol (and other stress hormones). This is part of the systemic reaction to injury which encompasses a wide range of endocrinological, immunological and haematological effects **(Wilmore et al, 1980)**.

After the early work on the stress response attention turned to the ability of anaesthetic agents to modify the endocrine and metabolic responses has been studied enthusiastically.

The endocrine response is activated by afferent neuronal impulses from the site of injury. These travel along sensory nerve roots through the dorsal root of the spinal cord, up the spinal cord to the medulla to activate the hypothalamus **(little & Girolami , 1999)** .

Effects of the stress response:

1) Mediators:

Cytokines

They are inflammatory mediators increased in the hypermetabolic state.

Cytokines are a group of low-molecular-weight proteins which include the interleukins and interferons. They are produced from activated leucocytes, fibroblasts and endothelial cells as an early

response to tissue injury and have a major role in mediating immunity and inflammation **(Sheeran & Hall, 1997)** The cytokines act on surface receptors on many different target cells and their effects are produced ultimately by influencing protein synthesis within these cells **(Helmy et al, 1999).**

Cytokines are proteins secreted by activated monocytes and phagocytes and are either produced locally at the sites of injury or systemically in response to injury or shock. One of the main factors is the tumor necrosis factor (TNF) which accelerates protein catabolism. A wide variety of actions characteristic of the acute inflammatory responses can be triggered by IL-l and TNF. Many of these actions involve arachidonate intermediates. These include myelopoiesis, release of neutrophils, augmentation of some neutrophil functions, vasodilation and induction of cell adhesion proteins, and thrombomodulin expression by endothelial cells, proteolysis and glycogenolysis in muscles; mobilization of lipids from adipocytcs, induction of acute phase protein synthesis and glycogenolysis in the liver, induction of fibroblast proliferation. osteoclast activation, and release of collagenase from chondrocytes, induction of slow-wave sleep activity in the brain, a variety of endocrine responses including release of ACTH, endorphins, growth hormone, vasopressin from the pituitary; release of insulin from pancreatic cells, catecholamine, and cortisol from the adrenals. TNF and, to a lesser extent, IL-I may contribute to the wasting (cachexia) characteristic of chronic infections and other inflammatory or neoplastic diseases by these mechanisms as well as by inhibiting appetite. In all of these actions, as well as in the production of fever, IL-I and TNF can act synergistically **(Harrison et al, 2005).**

The cytokines have a major role in the inflammatory response to physical stress and trauma. They have local effects of mediating and maintaining the inflammatory response to tissue injury, and also initiate some of the systemic changes which occur. The main cytokines released are interleukin-1 (IL-1), tumor necrosis factor-α (TNF-α) and IL-6. The initial reaction is the release of IL-1 and TNF-α from activated macrophages and monocytes in the damaged tissues. This stimulates the production and release of more cytokines, in particular, IL-6, the main cytokine responsible for inducing the systemic changes known as the acute phase response **(Sheeran, 1997).**

Concentrations of circulating cytokines are normally low and may be undetectable. Within 30–60 min after the start of injury, IL-6 concentration increases; the change in concentration becomes significant after 2–4 h. Cytokine production reflects the degree of tissue trauma, so cytokine release is lowest with the least invasive and traumatic procedures, for example, bed side procedures. The largest increases in IL-6 occur after major procedures such as joint replacement, major vascular and colorectal surgery. After these operations, cytokine concentrations are maximal at about 24 h and remain elevated for 48–72 h postoperatively after ICU admission.

The acute phase proteins

The acute-phase proteins are a group of circulating proteins synthesized by hepatocytes. Circulating levels of these proteins are increased or decreased during injury. Among these proteins are also protease inhibitors such as alpha-1, antitrypsin and alpha-2

macroglobulin, which may be important in protecting the host against tissue damage. Other acute phase proteins are C-reactive protein and alpha1-acid glycoprptein, which may have important effects on immune cell bactericidal activity **(Wilmore et al, 2000).** Cortisol and glucagon are known to facilitate hepatic uptake of nitrogenous substrates. lnterleukin-1, TNF and lnterleukin-6 are able to enhance production of certain acute-phase proteins in vitro. In vivo TNF administration also enhances preservation of liver mass and increases levels of acute-phase proteins. The net result is mobilization of peripheral nitrogenous substrates that are transported to and utilized in the splanchnic bed and wounds for protein synthesis **(Monk et al, 1996).**

A number of changes occur following tissue injury which are stimulated by cytokines, particularly IL-6. This is known as the 'acute phase response'; one of its features is the production in the liver of acute phase proteins. These proteins act as inflammatory mediators, anti-proteinases and scavengers and in tissue repair. They include C-reactive protein (CRP), fibrinogen, α_2-macroglobulin and other anti-proteinases. The increase in serum concentrations of CRP follows the changes in IL-6. Production of other proteins in the liver, for example, albumin and transferrin, decreases during the acute phase response. Concentrations of circulating cations such as zinc and iron decrease, partly as a consequence of the changes in the production of the transport proteins **(Hall, 1997).**

Interaction between the immune system and the neuro-endocrine system:

The cytokines IL-1and IL-6 can stimulate secretion of ACTH from isolated pituitary cells *in vitro*. In patients after ICU admission, cytokines may augment pituitary ACTH secretion and subsequently increase the release of cortisol. A negative feedback system exists, so that glucocorticoids inhibit cytokine production. The cortisol response to stress is sufficient to depress IL-6 concentrations **(Jamson et al, 1997).**

2) The hormonal response

Sympathoadrenal response

Hypothalamic activation of the sympathetic autonomic nervous system results in increased secretion of catecholamines from the adrenal medulla and release of norepinephrine from presynaptic nerve terminals. Norepinephrine is primarily a neurotransmitter, but there is some spillover of norepinephrine released from nerve terminals into the circulation. The increased sympathetic activity results in the well recognized cardiovascular effects of tachycardia and hypertension. In addition, the function of certain visceral organs, including the liver, pancreas and kidney, is modified directly by efferent sympathetic stimulation and/or circulating catecholamines (**Baarms et al, 1998).**

The hypothalamic–pituitary–adrenal axis

Anterior pituitary

Anterior pituitary hormone secretion is stimulated by hypothalamic releasing factors. The pituitary synthesizes corticotrophin or adrenocorticotrophic hormone (ACTH) as part of a larger precursor molecule, pro-opiomelanocortin. The precursor is metabolized within the pituitary into ACTH, ß-endorphin and an N-terminal precursor. Growth hormone and prolactin are also secreted in increased amounts from the pituitary in response to stressful stimuli. Concentrations of the other anterior pituitary hormones, thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH) and luteinizing hormone (LH) do not change markedly during early ICU admission **(Lyons & Meeran, 1997).**

Corticotrophin

Corticotrophin (ACTH) is a 39 amino acid peptide, produced in the pituitary from the larger molecule, pro-opiomelanocortin. ACTH stimulates the adrenal cortical secretion of glucocorticoids so that circulating concentrations of cortisol are increased. Surgery is one of the most potent activators of ACTH and cortisol secretion, and increased plasma concentrations of both hormones can be measured within minutes of the start of surgery **(Donald et al, 1993).**