

Clinical Nutrition and Metabolism Group Symposium on 'Nutrition in the severely-injured patient'

Part 1

Substrate metabolism in the metabolic response to injury

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In healthy subjects the metabolic response to starvation invokes regulatory mechanisms aimed at conservation of protein mass. This response is characterized by a decrease in energy expenditure and a progressive decrease in urinary N excretion. Many non-endocrine diseases induce anorexia and a decrease in food intake. However, in contrast to the metabolic reaction to starvation in healthy subjects, anorectic patients with serious diseases have increased energy expenditure and protein catabolism, associated with profound neuroendocrine alterations. These neuroendocrine changes are induced by two mechanisms. First, afferent nerves inform the central nervous system of tissue injury which results in neuroendocrine activation. Second, tissue injury stimulates the production of inflammatory mediators, which in turn results in neuroendocrine and metabolic effects. Although these metabolic changes enable the organism to survive short-lasting diseases by using endogenous substrates, in protracted serious diseases these changes will result in loss of functioning protein mass and may endanger survival. Moreover, tissue injury alters the metabolic responses to nutrition, reflected in the persistence of catabolism as long as serious tissue injury remains.

Metabolism: Disease: Neuroendocrine changes: Cytokines

Tissue injury in general induces more or less characteristic metabolic changes. The present paper focuses on the regulatory mechanisms involved in these metabolic changes. Since disease is frequently associated with anorexia, first, the metabolic effects of starvation will be discussed. The metabolic effects of disease will be discussed in relation to those of starvation. The main part of the present paper will focus on the major principles of metabolic regulation. From these regulatory mechanisms the inappropriate utilization of nutrients in disease can be understood.

Starvation

Evolution has provided the organism with a complex system that enables it to survive starvation for almost 2 months in

the presence of water. During the initial phase of starvation the rate of protein breakdown decreases, reflected in diminishing amounts of N in the urine (Gardner *et al.* 1979). If this adaptation of protein metabolism did not occur, it could be hypothesized that the ability to withstand starvation would be greatly decreased. Resting energy expenditure also decreases by 10–15 % during starvation. These metabolic changes during starvation indicate increased metabolic efficiency, an appropriate response to the absence of nutrition.

Metabolic effects of disease

Anorexia is a frequent symptom of disease. Although the causes of anorexia are complex, there are indications that

factors like leptin may be involved. For instance, administration of endotoxin to rodents induces a dose-dependent induction of leptin RNA in adipose tissue, associated with a dose-dependent reduction in food intake (Grunfeld *et al.* 1996). Although food intake is frequently reduced in disease, the adaptation to starvation described earlier does not occur. In contrast, disease induces metabolic alterations that can be summarized as catabolism. For instance, resting energy expenditure, urinary N excretion (reflecting protein breakdown), lipolysis etc. increase (Sauerwein & Romijn, 1991). The magnitude of this catabolic reaction is related to the extent of tissue injury rather than to the type of disease.

Metabolic regulation in disease

The metabolic effects of disease are associated with endocrine changes, characterized by increased plasma concentrations of glucagon, cortisol and catecholamines. Consequently, there is an altered balance between insulin, the major anabolic hormone, and these catabolic hormones in favour of catabolism (Moeniralam *et al.* 1998). An example of these changes is illustrated by a study of Wolfe *et al.* (1987) in burn patients. Glucagon, cortisol and catecholamines increased two-, four- and eight to ten fold respectively compared with healthy controls. Wolfe *et al.* (1987) reported that these endocrine changes were causally related to the metabolic effects of disease. For instance, lipolysis was increased by more than 100 %; the effect in these burn patients being greatly reduced by propranolol. The increase in glucose production was to a large extent reduced by administration of somatostatin, which decreases glucagon secretion.

The causal relationship between endocrine changes induced by disease and metabolic changes is also illustrated by studies in volunteers (Bessey *et al.* 1984). Prolonged infusion of cortisol, glucagon and adrenaline was shown to increase resting energy expenditure and protein catabolism.

The next question is how these neuroendocrine changes are induced. In this respect the brain, together with afferent and efferent nerve stimulation, is very important. Stimulation of afferent nerves by tissue injury is a major factor involved in neuroendocrine stimulation (for example, see George *et al.* 1974). For instance, severing of afferent nerves blunts the increase in cortisol in experimental burn injury. Activation of the brain is also important. For instance, after trauma there is an increase in resting energy expenditure, which decreases with pentobarbital therapy which reduces brain activity (Dempsey *et al.* 1985). Stimulation of afferent nerves from injured tissue results in neuroendocrine changes by two mechanisms. First, this stimulation results, through complicated neural pathways, in alterations in hypothalamo-pituitary regulation, and consequently in altered function of peripheral endocrine organs. Second, stimulation of the brain by tissue injury invokes responses of the autonomous nervous system, which also effects the function of peripheral endocrine glands. For instance, stimulation of the peripheral end of the splanchnic nerve stimulates glucagon release, resulting in hyperglycaemia (Bloom & Edwards, 1975). Finally, it should be recognized that peripheral nerves have more extensive nerve endings than is generally accepted. There

are indications that adipocytes have direct contact with nerve endings (Youngstrom & Bartness, 1995). Stimulation of these nerves results in increased lipolysis. Thus, stimulation of efferent nerves does not alter metabolism only by modulation of endocrine function, but also by direct effects on peripheral tissues.

Tissue injury does not alter metabolism only through the nervous system, but also by the induction of inflammatory mediators such as interleukins 1 and 6, tumour necrosis factor etc. These mediators have pleiotropic effects and act in a complex network. The endocrine and metabolic effects of these mediators are illustrated by the effects in human subjects (Sauerwein & Romijn, 1991). Administration of cytokines such as interleukin 6 and tumour necrosis factor induce profound neuroendocrine changes, with stimulation of secretion of corticotropin, cortisol, (nor) adrenaline and glucagon (van der Poll *et al.* 1991; Stouthard *et al.* 1995). This process is associated with metabolic effects manifested by increased resting energy expenditure and lipolysis. It is likely that these mediators act at multiple levels: hypothalamus; pituitary; peripheral; endocrine glands; peripheral tissues (Warren *et al.* 1987). Thus, the metabolic changes induced by disease are the result of a complex interaction between the central nervous system, hormones, stimulation of autonomous nerves, inflammatory mediators and peripheral hormones. These complex changes do not result only in changes in whole-body metabolism, but probably also in differentiation in metabolism at the tissue level, depending on the condition (e.g. injured *v.* healthy tissue).

Inappropriate utilization of nutrition in disease

Nutrition reverses the catabolic state of starvation. However, in general, nutrition does not completely reverse the catabolic reaction to tissue injury. The changes in regulatory pathways described earlier are maintained as long as tissue injury persists, and are not completely reversed by nutrition.

This process is illustrated by the effects of nutrition on protein, glucose and lipid metabolism in disease (Sauerwein & Romijn, 1995). In critically-ill patients protein catabolism persists irrespective of the amount of protein in the diet. Glucose oxidation is decreased irrespective of the amount of carbohydrates in the diet. There is an increase in lipolysis which is not decreased by nutrition. The increase in lipolysis results in increased delivery of fatty acids to the liver. In the liver these fatty acids are re-esterified to form triacylglycerols. However, there is a problem with secretion of VLDL-triacylglycerols, manifested by liver steatosis, which is a common reaction to disease. This altered utilization of nutrients in tissue injury will improve after recovery from the disease.

Summary

The metabolic response to disease is characterized by catabolism. This process is a favourable reaction to disease because it enables the organism to survive in the presence of anorexia. However, the alterations in metabolic regulation will also result in cachexia if the duration of the disease is

prolonged. Moreover, these alterations result in appropriate utilization of nutrients as long as serious tissue injury persists.

References

- Bessey PQ, Watters JM, Aoki TT & Wilmore DW (1984) Combined hormonal infusion simulates the metabolic response to injury. *Annals of Surgery* **200**, 264–281.
- Bloom SR & Edwards AV (1975) The release of pancreatic glucagon and inhibition of insulin in response to stimulation of sympathetic innervation. *Journal of Physiology* **253**, 157–173.
- Dempsey DT, Guenter P & Mullen JL (1985) Energy expenditure in acute trauma to the head with and without barbiturate therapy. *Surgery, Gynecology and Obstetrics* **160**, 128–134.
- Gardner DF, Kaplan MM, Stanley CA & Utiger RD (1979) Effect of tri-iodothyronine replacement on the metabolic and pituitary responses to starvation. *New England Journal of Medicine* **300**, 579–584.
- George JM, Reier CE, Ianese RR & Rower JM (1974) Morphine anesthesia blocks cortisol and growth hormone response to surgical stress in humans. *Journal of Clinical Endocrinology and Metabolism* **38**, 736–741.
- Grunfeld C, Zhao C, Fuller J, Pollock A, Moser A, Friedman J & Feingold K (1996) Endotoxin and cytokines induce expression of leptin, the ob gene product in hamsters. *Journal of Clinical Investigation* **97**, 2152–2157.
- Moeniralam HS, Endert E, Ackermans MT, van Lanschot JJB, Sauerwein HP & Romijn JA (1998) Sufentanil alters the inflammatory, endocrine and metabolic responses to endotoxin in dogs. *American Journal of Physiology* **275**, E440–E447.
- Sauerwein HP & Romijn JA (1991) Cytokines: role in human metabolism. In *Update in Intensive Care and Emergency Medicine 1991*, pp. 254–261 [JL Vincent, editor]. Berlin: Springer Verlag.
- Sauerwein HP & Romijn JA (1995) Adult macronutrient requirements. In *Artificial Nutritional Support in Clinical Practice*, pp. 137–149 [J Payne-James, G Grimble and D Silk, editors]. London: Edward Arnold.
- Stouthard JML, Romijn JA, van der Poll T, Endert E, Klein S, Bakker PJM, Veenhof CHN & Sauerwein HP (1995) Endocrine and metabolic effects of interleukin-6 in humans. *American Journal of Physiology* **268**, E813–E819.
- van der Poll T, Romijn JA, Endert E, Borm JJ, Buller HR & Sauerwein HP (1991) Tumor necrosis factor mimics the metabolic response to acute infection in healthy humans. *American Journal of Physiology* **261**, E457–E465.
- Warren RS, Donner DB, Starnes HF & Brennan M (1987) Modulation of endogenous hormone action by recombinant human tumor necrosis factor. *Proceedings of the National Academy of Sciences USA* **84**, 8619–8622.
- Wolfe RR, Herndon D, Jahoor F, Miyoshi H & Wolfe M (1987) Effect of severe burn injury on substrate cycling by glucose and fatty acids. *New England Journal of Medicine* **317**, 403–408.
- Youngstrom TG & Bartness TJ (1995) Catecholaminergic innervation of white adipose tissue in Siberian hamsters. *American Journal of Physiology* **265**, R744–R751.