Leading article

Insulin resistance in sepsis

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Hyperglycaemia and glycosuria in surgical patients with severe infection have been recognized for over 200 years as indicative of a poor clinical outcome. Although the concept of 'insulin resistance' was first formulated in relation to diabetes mellitus in 1924, it was not until the 1950s that it was postulated that many metabolic abnormalities associated with stress, injury or infection related to a loss of tissue sensitivity to insulin. Insulin resistance is defined as unresponsiveness of anabolic processes to the normal effects of insulin and is said to exist when the metabolic features of insulin deficiency (notably hyperglycaemia, increased lipolysis and protein catabolism) are observed in the presence of normal or raised concentrations of plasma insulin[1]. Effective nutritional support may be compromised by insulin resistance in the critically ill patient because of the associated hyperglycaemia and the failure of feeding regimens to restore lean body mass. While a therapeutic intervention to restore the 'anabolic signal' might conceivably speed recovery, progress in this field has been hampered by an inability to determine the precise underlying mechanism of loss of insulin sensitivity.

The induction of insulin resistance in sepsis is almost impossible to study in the clinical setting because of the practical difficulty of determining the exact time of onset of infection. However, experimental studies of infection in human volunteers[2] suggest that insulin resistance develops within a few hours and may last for several weeks after recovery[3]. *In vivo* techniques combining euglycaemic hyperinsulinaemic clamping (producing controlled conditions of glycaemia and hyperinsulinaemia) and stable isotope infusion (enabling measurement of hepatic glucose output and, predominantly, skeletal muscle glucose uptake) have produced valuable human data. These studies show that the main effect of loss of insulin sensitivity is loss of insulin-mediated skeletal muscle glucose storage[4]. Nevertheless, the cellular and molecular events underlying these abnormalities remain unclear.

Although sepsis, trauma and other critical illness states are characterized by a counterregulatory hormone response, and counterregulatory hormones may induce insulin resistance *in vivo*, clinical studies have failed to demonstrate either temporal or quantitative correlations between the counterregulatory hormone response and defective insulin-mediated glucose disposal[5]. Similarly, while infection and trauma are associated with increasing circulating concentrations of proinflammatory cytokines, including interleukin 6 and tumour necrosis factor (TNF) α, and TNF-α is linked to insulin resistance in diabetes and malignancy, it remains unclear whether change in insulin-mediated glucose uptake in skeletal muscle in sepsis could be accounted for by the direct effects of these cytokines. Although studies using muscle cell lines strongly suggest that TNF-α can directly inhibit insulin signalling, they are not supported by observations in intact muscle.

While recent animal studies of sepsis suggest impairment of insulin receptor substrate 1 signalling[6] (a key early step in insulin signal transduction), insulin-resistant septic animals retain normal glucose metabolic responses to insulin-like growth factor I[7], despite the two metabolic stimuli sharing many signalling components. In addition, the muscle content of glucose transporter (GLUT) 4 protein, the principal insulin-sensitive glucose transporter, and its messenger RNA are unchanged in sepsis; it is unclear whether translocation of GLUT-4 to the plasma membrane of the muscle cell, an essential step for glucose transport, is preserved. These observations are difficult to reconcile with the apparently selective impairment of glucose storage, which implies a defective signalling step at a more distal locus in the insulin signalling pathway in relation to glycogen synthesis.

The cellular and molecular mechanisms underlying insulin resistance and their relationship to the observed metabolic abnormalities remain unclear. Nevertheless, an understanding of the consequences of insulin resistance may be of practical importance in the management of the critically ill patient. The time-honoured view of insulin resistance in such a clinical situation is that the resistance may confer benefit by preserving glucose for the tissues that need it most. In tissues such as the brain, healing wounds and immune cells, fuel substrate uptake is not believed to be mediated by insulin. This view may no longer be sustainable as insulin therapy has been shown to promote protein anabolism and wound healing[8] in burned patients. Furthermore, in a recent randomized controlled trial aggressive insulin therapy in critically ill patients significantly reduced infection-related morbidity and mortality rates[9].

The mechanisms underlying these dramatic therapeutic effects and their relationships to alterations in fuel substrate metabolism are as yet uncertain. However, these important

observations suggest, in addition to its role in intermediary metabolism, that insulin also plays a role in regulating the immune response, at least in the critically ill patient. The beneficial effect of exogenous insulin therapy is most marked in patients who have been critically ill for at least 5 days, a stage of illness that is associated with immunological dissonance, characterized by a predominance of anti-inflammatory cytokine actions and relative immunosuppression. As the proinflammatory cytokine response, and particularly TNF-α, is known to be of importance in defending the organism from bacterial infection, this suggests that insulin therapy under these circumstances may act, at least in part, by reversing immunological dissonance. This concept is supported by the recent demonstration in humans that the *in vivo* proinflammatory cytokine response to endotoxin is augmented by exogenous insulin infusion[10].

In the light of the above, it seems reasonable to state that a greater understanding of the mechanisms underlying the development of the insulin resistance that accompanies sepsis, and the metabolic and immunological consequences of the insulin-resistant state, holds promise. Such knowledge can be expected to offer new therapeutic strategies for the management of severe sepsis, a condition of largely unaltered prognosis over several decades.

References

1 Carlson GL, Little RA. Insulin resistance and tissue fuels. In *Organ Metabolism and Nutrition: Ideas for Future Critical Care*, Kinney JM, Tucker HN (eds). Raven Press: New York, 1994; 49–69.
2 Agwunobi AO, Reid C, Maycock P, Little RA, Carlson GL. Insulin resistance and substrate utilization in human endotoxemia. *J Clin Endocrinol Metab* 2000; **85**: 3770–3778.
3 Virkamaki A, Yki-Jarvinen H. Mechanisms of insulin resistance during acute endotoxaemia. *Endocrinology* 1994; **134**: 2072–2078.
4 Saeed M, Carlson GL, Little RA, Irving MH. Selective impairment of glucose storage in human sepsis. *Br J Surg* 1999; **86**: 813–821.
5 Thorell A, Nygren J, Ljungqvist O. Insulin resistance: a marker of surgical stress. *Curr Opin Nutr Metab Care* 1999; **2**: 69–78.
6 Nunes AL, Carvalheira JB, Carvalho CR, Brenelli SL, Saad MJ. Tissue-specific regulation of early steps in insulin action in septic rats. *Life Sci* 2001; **69**: 2103–2112.
7 Lang CH. IGF-I stimulates muscle glucose uptake during sepsis. *Shock* 1996; **5**: 22–27.
8 Pierre EJ, Barrow RE, Hawkins HK, Nguyen TT, Sakurai Y, Desai M *et al*. Effects of insulin on wound healing. *J Trauma* 1998; **44**: 342–345.
9 van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M *et al*. Intensive insulin therapy in the surgical intensive care unit. *N Engl J Med* 2001; **345**: 1359–1367.
10 Soop M, Duxbury H, Agwunobi AO, Gibson JM, Hopkins SJ, Childs C *et al*. Euglycemic hyperinsulinemia augments the cytokine and endocrine responses to endotoxin in humans. *Am J Physiol Endocrinol Metab* 2002; **282**: E1276–E1285.