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Pain and Postoperative Recovery

SURGERY initiates an abnormal metabolic state characterized by a perioperative general fuel mobilization, increased energy expenditure, and breakdown of body tissues, partly explained by a loss or reduction of insulin sensitivity. It is presumed that perioperative variables, such as anesthesia, pain, fasting, hypoxemia, immobilization, and hemorrhage, might contribute to the establishment of a catabolic phase. However, few studies have attempted to dissect the various components of the metabolic stress response and to quantify their contributions. Greisen *et al.*[1] have explored the hypothesis that pain itself is at least partly responsible for the metabolic upset. The question is difficult to answer because postsurgical pain is normally associated with the products of tissue injury, the inflammatory response, and activation of the sympathetic nervous system and the hypothalamic–pituitary axis. All these factors are known to influence endocrine and metabolic responses.

Insulin affects many functions, from intermediary metabolism to tissue growth and differentiation. Its anabolic action favors synthetic pathways by directing substrates into glycogen, protein, and lipid synthesis, whereas its anticatabolic function is to inhibit glycogenolysis, proteolysis, and lipolysis. Although insulin acts on all of intermediary metabolism, its chief control is exerted on the glucose system, a critical homeostatic variable that is regulated within a narrow range. Insulin stimulates the uptake of glucose in insulin-sensitive tissues and suppresses liver endogenous glucose production. A decrease in insulin sensitivity has been shown to continue for at least 5 days after upper abdominal surgery, with normalization after approximately 3 weeks.[2] There seems to be a dose–response relation in postoperative insulin sensitivity in patients exposed to surgical procedures of different intensity, and this is independent of predisposing factors.

To reduce the influence of variables other than pain, Greisen *et al.*[1] used painful electrical stimulation of the skin in healthy, conscious male volunteers, with each subject serving as his own control. The subjects were told to maintain the stimulation for 30 min at a level of 8 on a 10-point visual analog scale, where 10 equaled unendurable pain. Therefore, one would assume that the stimulation was quite painful. It is important to know that the subjects had constant control of the stimulus and were able to adjust its intensity at all times. This element of control would be expected to minimize fear and stress. Insulin sensitivity was assessed with the hyperinsulinemic euglycemic glucose clamp technique, a useful method to study the actions of insulin in stressful conditions.[3] Within the physiologic range of hyperinsulinemia, the rate of glucose infused at steady state glucose concentrations gives a measure of whole-body glucose uptake.

These authors were able to demonstrate a direct effect of the painful stimulation on insulin sensitivity. The rate of disappearance of isotopically-labeled glucose decreased by 16%, and the rate of glucose infusion necessary to maintain the target glucose plasma concentration (5 mM) decreased by 22%. The effect was statistically significant and of a magnitude comparable to that seen after minor surgical procedures. Three questions arise from this experiment.

First, is it possible to completely dissociate pain from all other variables? To their credit, Greisen *et al.*[1] did not merely assume that their protocol minimized sympathetic nervous system arousal and hypothalamic–pituitary axis activation—they checked it *via* measurement of blood levels of s-cortisol, epinephrine, norepinephrine, and free fatty acids. All of these except norepinephrine increased during the painful stimulation and remained increased for up to 1 h. Therefore, it seems that although stress was minimized, it was not eliminated. It may be impossible to eliminate hypothalamic–pituitary axis and sympathetic nervous system activation completely when using very painful stimulation in a conscious subject. Although conceptually interesting, the distinction between pain itself and the reactions to it is not particularly critical in the surgical case because controlling the pain is obviously easier than controlling its consequences.

Second, there is the question of the duration of experimentally-evoked reduction in insulin sensitivity and its relation to the duration of the effect initiated by surgery. As Greisen *et al.*[1] are careful to note, in the experimental subjects, the change in insulin sensitivity was shown to last for at least 3 h after termination of the painful stimulation. In the surgical patient, the phenomenon lasts for days to weeks.

Third, there is a question that relates to the use of cutaneous stimulation to evoke pain. Not all pain is the same. Pain-responsive primary afferent neurons (nociceptors) that innervate different tissues have different anatomic projections and different effects on central nervous system function. For example, cutaneous noci-

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ceptors and deep tissue nociceptors terminate in different regions of the spinal gray matter.[4] Nociceptors that innervate the pelvic viscera synapse on a special population of spinal neurons that have a unique projection to the brain *via* the midline of the posterior column white matter.[5] Activation of C-fiber cutaneous and muscle nociceptors has clearly different effects on pain transmission. Activation of C-fiber nociceptors evokes an *N*-methyl-D-aspartate receptor–mediated state of central hyperexcitability in spinal cord neurons. This has been shown to be of great importance to postinjury states, in which it accounts for much postinjury pain and hyperalgesia.[6] Nociceptors that innervate muscle are far more potent in evoking central hyperexcitability than are nociceptors that innervate the skin.[7] In addition, we now know that tissue injury and inflammation activate a class of nociceptors that is otherwise unresponsive to noxious stimuli.[8] The function of these "silent" nociceptors is unclear, but they are certain to be activated in the postoperative stage.

The importance of a perioperative abnormal metabolic state is unclear, but it is reasonable to suspect that it might have a deleterious effect on recovery. Recent data suggest that the degree of postoperative insulin resistance is significantly correlated with the length of postoperative hospital stay.[9] This reinforces our belief that aggressive perioperative pain relief should be a major goal in that it might influence the degree of postoperative reduction of insulin sensitivity and consequently recovery. Unfortunately, opioid administration, whether systemic or intrathecal, is less effective than neural blockade techniques with local anesthetics in suppressing the surgical stress response.[10] This is in accordance with the lack of effect of intrathecal morphine on sympathetic nerve activity, assessed by direct intraneural recordings, compared with the pronounced sympathetic blockade that is achieved during spinal anesthesia with local anesthetics.[11]

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References

1. Greisen J, Juhl CB, Grofte T, Vilstrup H, Jensen TS, Schmitz O: Acute pain induces insulin resistance in humans. ANESTHESIOLOGY 2001; 95:578–84
2. Thorell A, Efendic S, Gutniak M, Haggmark T, Ljungqvist: Insulin resistance after abdominal surgery. Br J Surg 1994; 81:59–63
3. DeFronzo RA, Topbin JD, Andres R: Glucose clamp technique: A method for quantifying insulin secretion and resistance. Am J Physiol 1979; 237:E214–23
4. Cervero F, Connell LA: Distribution of somatic and visceral primary afferent fibers within the thoracic spinal cord of the cat. J Comp Neurol 1984; 230:88–98
5. Nauta HJ, Soukop VM, Fabian RH, Lin JT, Grady JJ, Williams CG, Campbell GA, Westlund KN, Willis WD: Punctate midline myelotomy for the relief of visceral cancer pain. J Neurosurg 2000; 92(suppl 2):125–30
6. Woolf CJ, Salter MW: Neuronal plasticity: Increasing the gain of pain. Science 2000; 2881:1765–1769
7. Woolf CJ, Wall PD: Relative effectiveness of C-primary afferent fibers of different origins in evoking a prolonged facilitation of the flexor reflex in the rat. J Neurosci 1989; 6:1433–42
8. Schmidt R, Schmelz M, Torebjork HE, Handwerker HO: Mechano-insensitive nociceptors encode pain evoked by tonic pressure to human skin. Neuroscience 2000; 98:793–800
9. Thorell A, Nygren J, Ljunqvist: Insulin resistance: A marker of surgical stress. Current Opin Clin Nutr Metab Care 1999; 2:69–78
10. Christensen P, Brandt MR, Rem J, Kehlet H: Influence of extradural morphine on the adrenocortical and hyperglycaemic response to surgery. Br J Anaesth 1982; 54:24–8
11. Kirno K, Lundin S, Elam M: Effects of intrathecal morphine and spinal anaesthesia on sympathetic nerve activity in humans. Acta Anaesthesiol Scand 1993; 37:54–7