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Acute Pain Induces Insulin Resistance in Humans

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Background: **Painful trauma results in a disturbed metabolic state with impaired insulin sensitivity, which is related to the magnitude of the trauma. The authors explored whether pain *per se* influences hepatic and extrahepatic actions of insulin.**

Methods: **Ten healthy male volunteers underwent two randomly sequenced hyperinsulinemic–euglycemic (insulin infusion rate, 0.6 mU · kg^{-1} · min^{-1} for 180 min) clamp studies 4 weeks apart. Self-controlled painful electrical stimulation was applied to the abdominal skin for 30 min, to a pain intensity of 8 on a visual analog scale of 0–10, just before the clamp procedure (study P). In the other study, no pain was inflicted (study C).**

Results: **Pain reduced whole-body insulin-stimulated glucose uptake from 6.37 ± 1.87 mg · kg^{-1} · min^{-1} (mean ± SD) in study C to 4.97 ± 1.38 mg · kg^{-1} · min^{-1} in study P ($P < 0.01$) because of a decrease in nonoxidative glucose disposal, as determined by indirect calorimetry (2.47 ± 0.88 mg · kg^{-1} · min^{-1} in study P *vs.* 3.41 ± 1.03 mg · kg^{-1} · min^{-1} in study C; $P < 0.05$). Differences in glucose oxidation rates were not statistically significant. The suppression of isotopically determined endogenous glucose output during hyperinsulinemia tended to be decreased after pain (1.67 ± 0.48 mg · kg^{-1} · min^{-1} in study P *vs.* 2.04 ± 0.45 mg · kg^{-1} · min^{-1} in study C; $P = 0.06$). Pain elicited a twofold to threefold increase in serum cortisol ($P < 0.01$), plasma epinephrine ($P < 0.05$), and serum free fatty acids ($P < 0.05$). Similarly, circulating concentrations of glucagon and growth hormone tended to increase during pain.**

Conclusions: **Acute severe pain decreases insulin sensitivity, primarily by affecting nonoxidative glucose metabolism. It is conceivable that the counterregulatory hormonal response plays an important role. This may indicate that pain relief in stress states is important for maintenance of normal glucose metabolism.**

INSULIN resistance has been noted to accompany various stressful occurrences such as burns,[1] trauma,[2] sepsis,[3] and surgery.[4] Such conditions are characterized by tissue injury and increased afferent input to the central nervous system, including activity in nociceptive pathways. The mentioned conditions all have an inflammatory component, of which pain is one of the cardinal symptoms. However, it is unknown to what extent pain *per se* contributes to the development of impaired insulin sensitivity.

Earlier observations may indirectly suggest that pain itself leads to insulin resistance. The decrease in insulin sensitivity after surgery is proportional to the magnitude of operation,[5] and since major surgery is considered more painful than minor surgery, this dose–response relation is in accordance with the proposal of pain being a mediator of the response. The onset of insulin resistance during surgery[6] and the finding that postoperative insulin resistance is partially prevented by epidural anesthesia[7] also favor a neural element as mediator. Pain can be defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage,[8] and an unpleasant emotional experience in itself has been shown to cause insulin resistance.[9] We hypothesize that pain *per se* is a sufficient stimulus to induce insulin resistance; consequently, we examined the effect of nontraumatic painful transcutaneous electrical stimulation on *in vivo* insulin actions and the concomitant dynamics in concentrations of the counterregulatory hormones.

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Materials and Methods

Subjects

Ten healthy male volunteers participated. Mean age was 27 yr (range, 20–36 yr), mean body weight was 82 kg (range, 63–106 kg), and mean height was 184 cm (range, 179–196 cm). No subjects were taking any medications, including nonprescription analgesics. Before participation, the nature, purpose, and potential risks of the study were explained to the subjects, and their written informed consent was obtained. The study was approved by the Ethical Committee, Aarhus, Aarhus County, Denmark.

Study Design and Procedures

Each subject participated in two randomly sequenced hyperinsulinemic–euglycemic clamp studies,[10] performed at least 2 weeks apart (fig. 1): the pain experiment (study P), with electrical stimulation, and the control experiment (study C), in which the volunteers underwent the same procedures as in the pain experi-

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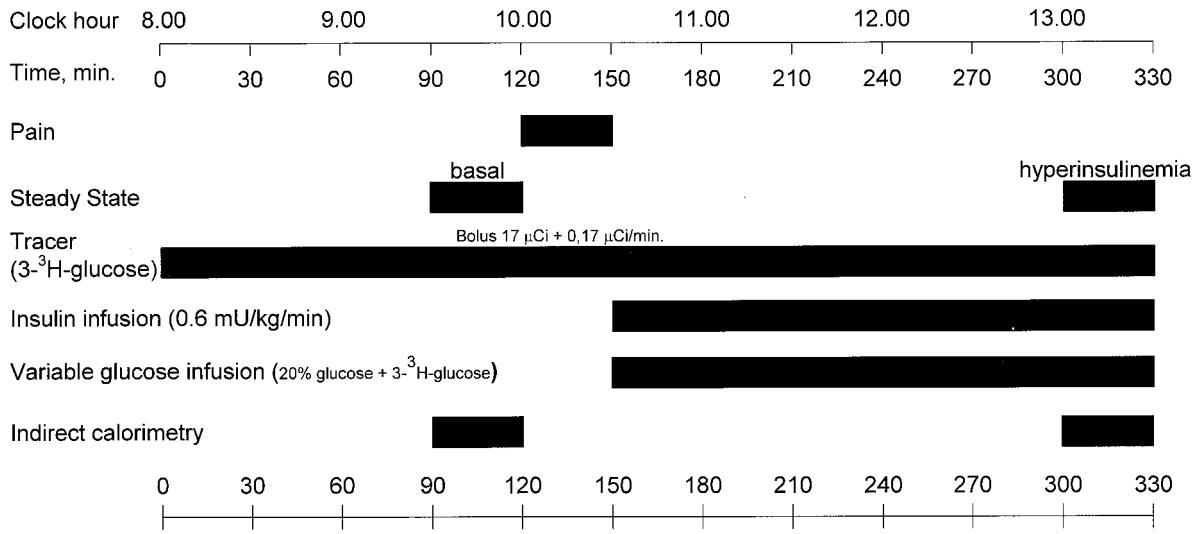

Fig. 1. Schematic representation of the study protocol.

ment except for the painful electrical stimulation. Before the experiments the volunteers were informed about which study they were participating in on the given day.

For each experiment the subjects came to the laboratory after a 10-h fast. All consumed a weight-maintaining diet consisting of at least 300 g of carbohydrate, and physical activity was comparable for the 3 days before the experiments. Catheters (Venflon; Vigo, Helsingborg, Sweden) were inserted at 7:30 AM. One catheter was placed in an arterialized hand vein (oxygen saturation > 90%) for blood sampling, and another catheter was placed in the contralateral antecubital vein for infusions. The experiments were started at 8:00 AM and ended at 1:30 PM. The subjects remained in the supine position. References to elapsed time are relative to the start of the experiment (*i.e.*, 0–330 min).

After 150 min, insulin (Insulin Actrapid; Novo-Nordisk, Copenhagen, Denmark) was infused intravenously at a constant rate of 0.6 mU · kg^{-1} · min^{-1} for 180 min (time, 150–330 min). At 8:00 AM (time, 0 min) a bolus dose (17 μCi) of [3-^{3}H]glucose (DuPont–New England Nuclear, Boston, MA) was injected, followed by a constant-rate infusion (0.17 μCi/min) throughout the experiment. Plasma glucose was clamped at 5 mmol/l, as described in principle by DeFronzo *et al.*[10] Eight of the 10 volunteers underwent the described protocol for tritiated glucose. To minimize rapid dilution of the labelled glucose pool with unlabelled glucose, [3-^{3}H] glucose was added to the glucose infused during the clamp.[11,12] Blood for determination of glucose-specific activity and concentrations of serum free fatty acids and hormones (serum insulin, growth hormone, cortisol and plasma glucagon, epinephrine, and norepinephrine) was drawn at the following times: 90, 105, 120, 135, 150, 165, 180, 210, 240, 270, 300, 315, and 330 min. The intervals between 90 and 120 min and 300 and 330 min were defined as the basal state and the hyperinsulinemic "steady state" period, respectively (fig. 1). Indirect calorimetry[13] (Deltatrac Metabolic Monitor; Datex, Helsinki, Finland) was performed during these two periods.

Electrical Stimulation

In the pain experiment, electrical stimuli (square wave, 0.3 ms in duration, 2 Hz, and an intensity range of 0–100 mA) were applied *via* a wet felt electrode held onto the abdominal skin. Four stimulation sites were marked on the abdominal skin (5 and 15 cm lateral to the umbilicus, bilateral). To prevent skin damage, the sites were stimulated in turn for 1 min each for a total period of 30 min. The volunteers were in manual control of the stimulus intensity and were instructed to constantly adjust the intensity during the 30-min stimulation period so that the perceived stimulus intensity was 8 on a visual analog scale of 0 (no pain) to 10 (unendurable pain). The electrical stimuli were given for 30 min from time 120–150 min (fig. 1).

Analyses and Calculations

Plasma glucose concentrations were determined in duplicate immediately after sampling (Beckman Instruments, Palo Alto, CA). Serum insulin concentrations were measured in duplicate by a two-site immunospecific insulin enzyme-linked immunosorbent assay.[14] Plasma glucagon concentrations were determined by radioimmunoassay, as described by Orskov *et al.*[15] Serum free fatty acid concentrations were determined by a colorimetric method using a commercial kit (Wako Chemicals, Neuss, Germany). Serum growth hormone and cortisol were measured with radioimmunoassays (DELFIA; Wallac Oy, Turku, Finland). Plasma epinephrine and norepinephrine concentrations were determined by electrochemical detection after high-pressure liquid chromatography.[16]

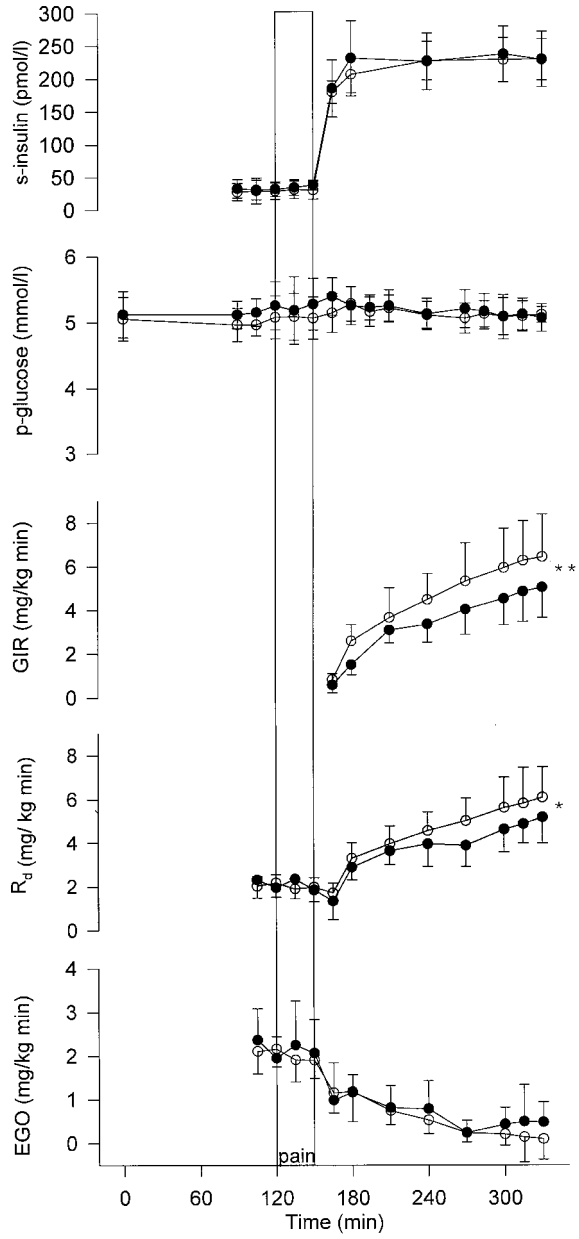

Fig. 2. Mean serum insulin concentration, plasma glucose concentration, glucose infusion rate (GIR), rate of isotopically determined disappearance of glucose (R_d), and endogenous glucose output (EGO) (± SD) in basal state (minutes 90–120) and during subsequent 180-min hyperinsulinemic–euglycemic clamp (insulin infusion rate, 0.6 mU · kg^{-1} · min^{-1}) in 10 healthy volunteers (n = 8 for R_d and EGO data) during control conditions (open circles) and after painful electric stimulation of the abdominal skin for 30 min (filled circles). The pain was stimulated at 120–150 min. *P < 0.05, **P < 0.01 between the two studies.

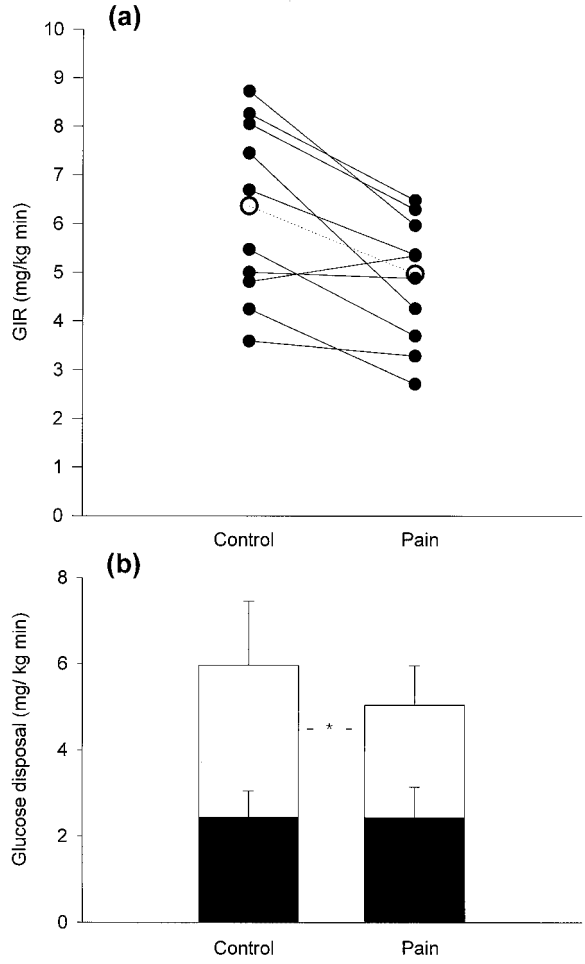

Fig. 3. (*A*) Individual glucose infusion rates (GIR) after 150–180 min of clamping with control conditions and with painful electric stimulation of the abdominal skin for 30 min. White dots represents the mean value in both studies. (*B*) Rate of disappearance of glucose in healthy subjects (n = 8) during the control study and after painful electric stimulation of the abdominal skin for 30 min. All values are given as mean ± SD. Open bars = nonoxidative glucose disposal; filled bars = glucose oxidation. *P < 0.05 between the two studies.

After determination of plasma-specific activity of glucose, the non–steady state equation described by Finegood *et al.*[11] was used for calculation of glucose appearance/disposal rates. A pool fraction of 0.65 and a distribution volume of 220 ml/kg were assumed. Respiratory-exchange ratios were determined by indirect calorimetry. Protein oxidation rates were estimated from urinary excretion of urea. Net lipid oxidation and glucose oxidation rates were computed from the above measurements, and nonoxidative glucose disposal was calculated by subtraction of the glucose oxidation rates from the total isotopically determined glucose disposal.

Statistical Analyses

The two-tailed Student *t* test for paired data and two-way analyses of variance (ANOVA) for repeated measurements and post hoc comparisons were used for statistical analyses. If data were not parametrically distributed (such as concentrations of serum growth hormone), a natural logarithm transformation was performed, and normal distribution of the transformed data was achieved. *P* values less than 0.05 were considered significant. All values are given as mean ± SD except for serum growth hormone data, which are given as medians (25th, 75th percentiles).

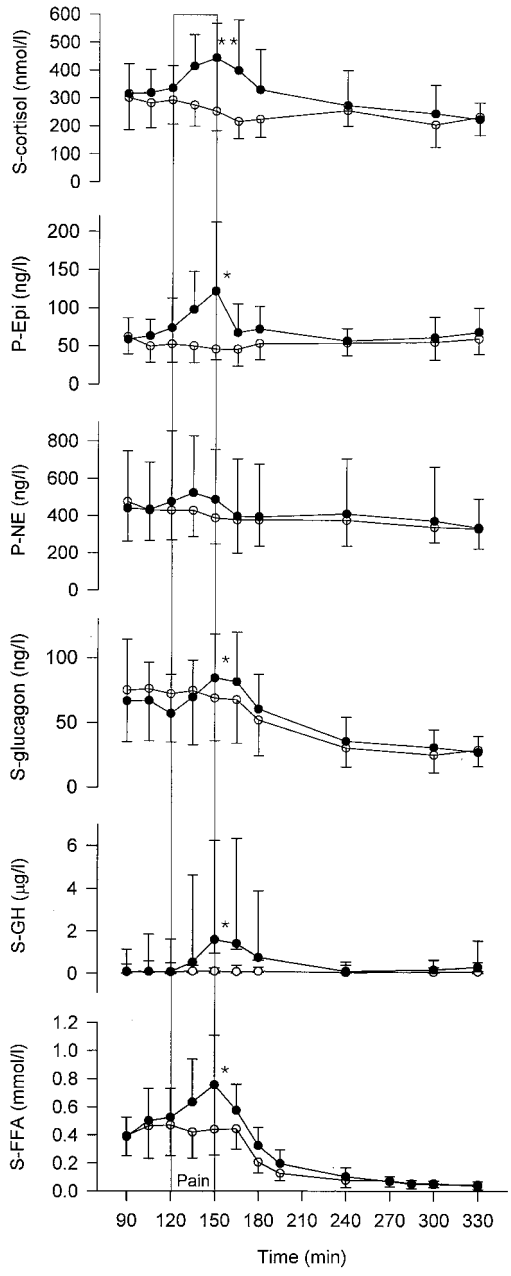

Fig. 4. Mean concentrations of serum cortisol (S-cortisol), plasma epinephrine (P-Epi), plasma norepinephrine (P-NE), serum glucagon (S-glucagon), and serum free fatty acids (S-FFA) (± SD) during the control study (open circles) and after painful electric stimulation of the abdominal skin for 30 min (filled circles). Serum growth hormone (S-GH) data are medians (25th, 75th percentiles). The pain was stimulated at 120–150 min. *$P < 0.05$, **$P < 0.01$ between the two studies.

Results

The electrical stimulation of the skin elicited local hyperemia lasting for about 1 h after the end of stimulation. The pain ceased at the same moment the electric stimulation ended, and the visual analog scale score was 0 for the rest of the experiment. Hyperesthesia to von Frey filament (touch) and brush was present for a few hours after stimulation, even after the hyperemia disappeared. No other symptom or sign of tissue damage was observed.

Glucose Metabolism (Figs. 2 and 3)

Serum insulin concentrations at baseline (33 ± 13 *vs.* 30 ± 13 pmol/l) and during the clamp (231 ± 41 *vs.* 223 ± 32 pmol/l) were comparable in the two experiments (study P *vs.* study C). Arterialized plasma glucose concentrations at baseline were slightly higher in the pain study than in the control study (5.23 ± 0.35 *vs.* 5.06 ± 0.25 mmol/l; $P < 0.05$), but during the clamp condition they were similar (5.14 ± 0.16 in study P *vs.* 5.17 ± 0.16 in study C).

Basal rates of glucose disposal (2.14 ± 0.31 *vs.* 2.13 ± 0.34 mg · kg^{-1} · min^{-1}) and glucose oxidation (1.58 ± 0.37 *vs.* 1.51 ± 0.34 mg · kg^{-1} · min^{-1}) did not differ between study P and study C. After cessation of pain, the glucose infusion rates necessary to maintain plasma concentrations of glucose at approximately 5.0 mmol/l decreased (4.97 ± 1.38 in study P *vs.* 6.37 ± 1.87 mg · kg^{-1} · min^{-1} in study C; $P < 0.01$). Likewise, pain diminished the isotopically determined rate of glucose disposal (5.04 ± 0.91 in study P *vs.* 5.97 ± 1.49 mg · kg^{-1} · min^{-1} in study C; $P < 0.05$; n = 8). Pain lead to impairment of nonoxidative glucose disposal during hyperinsulinemia, in comparison with the control data (2.47 ± 0.88 *vs.* 3.41 ± 1.03 mg · kg^{-1} · min^{-1}; $P < 0.05$), whereas glucose oxidation rates (2.43 ± 0.71 in study P *vs.* 2.44 ± 0.62 mg · kg^{-1} · min^{-1} in study C) and lipid oxidation rates did not change. Endogenous glucose output during hyperinsulinemia tended to be higher after pain (0.49 ± 0.51 in study P *vs.* 0.12 ± 0.40 mg · kg^{-1} · min^{-1} in study C; $P = 0.13$). The decline from basal state (1.67 ± 0.48 in study P *vs.* 2.04 ± 0.45 mg · kg^{-1} · min^{-1} in study C) likewise tended to be smaller ($P = 0.06$).

Counterregulatory Hormones and Free Fatty Acids (Fig. 4)

Concentrations of the hormones were comparable in the basal state between the control and the pain study. Pain increased the s-cortisol value from 331 ± 92 to a peak of 445 ± 123 nmol/l, whereas the cortisol value decreased slightly during the control study, from 297 ± 85 to 251 ± 70 nmol/l ($P < 0.01$ for comparison of values between studies at 150 min). Plasma epinephrine concentrations increased during pain, from 64 ± 25 to 122 ± 92 ng/l at 150 min, whereas it was unaltered in the control study (46 ± 13 ng/l; $P < 0.05$). Neither plasma norepinephrine nor plasma glucagon concentrations differed between the studies (ANOVA). However, the increment in plasma glucagon from baseline to cessation of pain was augmented after pain (21.0 ± 22.8 *vs.* 5.6 ± 11.5 pg/ml; $P < 0.05$), as was the incremental area under the curve (895 ± 758 *vs.* 108 ± 113 pg · ml^{-1} · min; $P < 0.05$). Finally, pain increased serum growth hormone values (median [25th, 75th percentiles]) from 0.09

(0.06, 1.90) to 1.60 (0.60, 4.90) μg/l at the end of pain, *versus* an increase to 0.12 (0.07, 0.15) μg/l in the control study ($P = 0.05$). Likewise, the incremental area under the curve was increased in the pain study (99.2 [27.3, 336.4] *vs.* 0.9 [0, 77.5] $\mu g \cdot l^{-1} \cdot min$; $P < 0.05$).

Serum concentrations of free fatty acids were comparable in the two experiments in the basal state (0.48 ± 0.19 in study P *vs.* 0.44 ± 0.19 mmol/l in study C). During pain, the concentrations increased to 0.76 ± 0.35 mmol/l, *versus* 0.44 ± 0.19 in the control study (time = 150 min; $P < 0.05$). The subsequent suppression of serum free fatty acids during insulin infusion was comparable in the two studies.

Discussion

This study demonstrates that acute severe nontraumatic pain decreases insulin sensitivity, as assessed by the hyperinsulinemic–euglycemic clamp. Only rates of nonoxidative glucose disposal were found to be decreased (average, 28%), whereas glucose oxidation rates were unaltered. The ability of insulin to suppress endogenous glucose output tended to be reduced after pain. Pain elicited increases in circulating concentrations of epinephrine, cortisol, growth hormone, and free fatty acids; thus, these substances may contribute to the altered glucose homeostasis after pain.

When comparing the results of this investigation with previous studies on glucose metabolism performed in painful stress conditions, it is important to bear in mind the methodological differences among studies. Type and severity of tissue injury, intensity of pain, anaesthetic techniques used, clinical characteristics of subjects studied (*e.g.*, age, body composition, and preexisting glucose intolerance), time of evaluation, matching of control group, degree of fasting, clinical course (complicated or uneventful), and amount and quality of nutritional support are all potentially important factors.

In a study of healthy volunteers demonstrating increased capability of hepatic urea synthesis after a pain stimulus identical to the one used here, we found an increase in plasma glucose during pain and a hormonal response comparable to that observed in the current study, suggesting an impaired insulin sensitivity.[17]

Studies of human stress injury have shown that elective surgery is probably the most common cause and represents the purest model in the uneventful case. Postsurgical insulin resistance apparently develops in a dose–reponse-like manner. Thus, it has been demonstrated that a muscle needle biopsy decreases insulin sensitivity acutely by 13%,[18] laparoscopic cholecystectomy decreases insulin sensitivity by 18% the day after surgery,[19] total hip replacement results in a 30–40% reduction,[20,21] and major abdominal surgery decreases insulin sensitivity by 50–60% the day after surgery.[22–24] In cases that are uneventful, the state of insulin resistance is fully reversible within 2–3 weeks from the surgery.[4] In these studies, no systematic evaluation of the intraoperative or postoperative pain intensity was performed. In addition, information on administrated analgesics is incomplete, and the studies offer only indirect information on the possible effect of pain on glucose metabolism.

In our study, pain diminished insulin sensitivity by 22%, which is comparable to the reduction observed after minor surgery. Thus acute pain itself can induce insulin resistance without tissue injury. The explanation may be that pain elicited acute release of several counterregulatory hormones and, consequently, free fatty acids. Even though all these concentrations normalized before the end of the study, they may together have contributed to insulin resistance, from which recovery is rather slow.

Of course, we cannot exclude the possibility that electrical stimulation, in addition to the production of pain, is responsible for some of the reported findings. In a similar study, using the same pain stimulus, we found that stimulation (mean pain score of 0.5 on a visual analog scale of 0–10) during blockade with local anesthesia abolished the endocrine[17] and immunologic[25] response to stimulation. Furthermore, local blockade completely abolished the increase in energy expenditure seen during stimulation.[26] On the basis of these observations, we find it very unlikely that the electrical stimulation *per se* induces the endocrine and metabolic changes described in this paper.

Cortisol has powerful anti-insulin effects on glucose metabolism,[27] and about 120 min of physiological hypercortisolemia appears sufficient to induce insulin resistance.[28] Epinephrine mediates insulin resistance acutely within minutes,[29] and in this study epinephrine may be responsible for the acute increase in free fatty acids seen during pain. The increase in free fatty acids may be involved in the pain-elicited insulin resistance, *via* the glucose–fatty acid cycle,[30] inhibition of the glycogen synthesis,[31] and inhibition of glucose transport.[32] The increment in glucagon during pain is not supposed to have any effects on muscle insulin–stimulated glucose uptake.[33] However it may have contributed to the tendency toward a decrease in suppression of endogenous glucose output seen after pain. Growth hormone infusion and a single bolus administration induce insulin resistance in muscle[34] within in a few hours.

It is important, however, to underscore that this study proves no causality between the elevation of concentrations of the classic stress hormones and the reduction in insulin sensitivity. One way to address this could be to perform infusions of counteracting hormones mimicking the concentration profiles observed in the current study. In many of the cited studies of postoperative glucose metabolism, the concentrations of stress hormones were not or only slightly increased, suggesting that elevation

of hormones may not be mandatory to induce insulin resistance. In a previous study showing that a needle biopsy of the muscle decreases insulin sensitivity,[18] marked elevations occurred only in concentrations of cortisol, whereas growth hormone and epinephrine concentrations did not increase.

The impaired insulin action after pain probably resides in skeletal muscle. Regarding intracellular mechanisms of the impairment of insulin action immediately after surgery, a recent study by Thorell *et al.*[20] demonstrated defects in both skeletal muscle GLUT-4 translocation and glycogen synthase activity. The impaired function of glycogen synthase is well in agreement with our finding of reduced nonoxidative glucose disposal. However, it is clearly of pathophysiologic interest whether other insulin-sensitive tissues (*e.g.*, the heart) also exhibit a modified insulin-stimulated glucose uptake in response to pain. It should be noted that the heart tissue does not become insulin-resistant after short-term exposure to growth hormone.[35]

Insulin has many nonglucose actions. It acts anabolically on protein and fat metabolism and has many other actions, such as on water and salt, the autonomic and central nervous systems, and vascular and thermogenesis homeostasis.[36] It is tempting to suggest that pain may induce alterations in sensitivity to many of these insulin actions as well as to the insulin-stimulated glucose disposal.

The release of hormones and free fatty acids may in part explain the decrease in insulin sensitivity, suggested also by the notion of the hormones working in an additive manner on glucose metabolism.[37] To delineate the specific role of the various hormones and the enhanced release of free fatty acids, studies with blocking of individual hormones and free fatty acids should be performed. Another possible mediator of the response to pain is neural signaling with nociceptive afferent impulses to the central nervous system and sympathetic efferent impulses to the muscles and the liver. Sympathetic nerve activity in the liver causes increased glucose release from the hepatocytes,[38] but in this case one would expect an increase in plasma noradrenaline, which was absent in the current study. Cytokines could also be candidates for such mediation, as they have been shown to increase after surgery[39] and to induce insulin resistance.[40] However, we have previously shown that no proinflammatory cytokines (interleukin $1\alpha/\beta$, interleukin 6, and tumor necrosis factor α) could be detected in plasma during or after a pain stimulus equivalent to the one used in this study (unpublished data).

Normally, the development of insulin resistance is taken to be an unfavorable sign. It invariably coexists with stressful situations, as mentioned. The pathologic conditions are all reversible or potentially reversible and so is the associated insulin resistance. The question is, then, does it matter if an individual becomes transiently insulin resistant? This issue still needs to be clarified. The degree of postoperative insulin resistance, however, is related to the length of hospital stay and perioperative blood loss.[41]

In conclusion, the current study shows that acute severe pain decreases insulin sensitivity by affecting nonoxidative glucose metabolism. The insulin resistance seems to be due at least in part to release of counterregulatory hormones. Our study suggests the importance of administering pain relief in trauma and stress states, if possible even before pain is sensed, to improve glucose metabolism.

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