Effect of fentanyl on morphine levels in the brain in rats receiving intracerebroventricular injection of TNF-α

YUICHIRO SHIROUZU, KAZUO SHIROUZU, AND SHOGO YOSHIDA
Department of Surgery, Kurume University, School of Medicine, Kurume 830, Japan

Shirouzu, Yuichiro, Kazuo Shirouzu, and Shogo Yoshida. Effect of fentanyl on morphine levels in the brain in rats receiving intracerebroventricular injection of TNF-α. Am. J. Physiol. 275 (Endocrinol. Metab. 38): E635–E640, 1998.—Fentanyl citrate analgesia attenuates the excess nitrogen excretion in the urine and glucose production induced by trauma. On the other hand, intracerebroventricular injection of morphine stimulates excretion of stress hormones, such as catecholamines and corticosterone. Furthermore, morphine levels in the brain are increased during fasting and sepsis. The aims of this study were to determine whether intracerebroventricular injection of tumor necrosis factor-α (TNF-α) elevates morphine levels in the rat brain and whether prophylactic administration of fentanyl blocks metabolic responses induced by intracerebroventricular injection of TNF-α because of a reduction of morphine levels in the brain. Morphine levels in the brain were increased from 648 to 1,134 fmol/g at 30 min after intracerebroventricular injection of TNF-α (P < 0.05 vs. control). This increase was associated with an increase in stress hormones (corticosterone: 416.1 ± 69.1 ng/ml, P < 0.05 vs. control; epinephrine: 3.7783 ± 681.3 pg/ml, P < 0.01 vs. control) and an enhancement of proteolysis (254.2 ± 45.7 μmol Leu·kg⁻¹·h⁻¹, P < 0.01 vs. control) and glucose production (7.5 ± 0.7 mg·kg⁻¹·min⁻¹, P < 0.05 vs. control). Fentanyl reduced morphine levels in the brain to 624 fmol/g (not significant vs. control), resulting in a reduction of stress hormone levels in the plasma and blunted metabolic responses. In conclusion, prophylactic administration of fentanyl prevented an increase in morphine levels in the brain induced by intracerebroventricular injection of TNF-α, leading to a reduction in stress hormone levels and subsequent metabolic responses.

protein turnover; glucose turnover; cytokine

CHANGES IN THE HORMONAL MILIEU after a surgical insult cause a loss of protein (9) and an enhancement of glucose production (5). An important factor in the activation of the hypothalamic-pituitary-adrenal axis is pain at the wound site (19). Indeed, morphine analgesia can block releases of adrenocorticotrophic and growth hormones in humans at the hypothalamic level (12), and epidural analgesia improved nitrogen balance after abdominal surgery (38).

Fentanyl is a phenylpiperidine derivative, a synthetic narcotic. Fentanyl-oxygen analgesia produces greater cardiovascular stability and no venousodilation compared with morphine (34). We have previously reported that systemic fentanyl analgesia reduced postoperative interleukin (IL)-6 levels and cortisol excretion, resulting in greater nitrogen balance than conventional anesthesia alone (43). Furthermore, And et al. (2) reported that high doses of sufentanil analgesia during surgery reduced the hyperactivity of the hypothalamic functions, leading to a decrease in surgical complications and morbidity rate in neonates undergoing cardiac surgery. In addition to decreasing the protein loss and improving clinical outcome, we showed that fentanyl analgesia reduced glucose production and was associated with a lower level of stress hormones after trauma than pentobarbital anesthesia in rats (40).

In contrast to analgesia with morphine and fentanyl during surgery, Molina et al. (23) demonstrated that 1 μg/kg of morphine injection into the cerebroventricular space of unstressed rats led to the excretion of stress hormones and an increase in glucose production compared with rats receiving an intracerebroventricular injection of saline. In addition to these observations, they found that fasting and sepsis increased morphine levels in the brain (24, 26).

Cytokines such as tumor necrosis factor (TNF), IL-1, and IL-6 have been shown to initiate cachexia found in sepsis, surgical trauma, and the presence of tumor (13, 17, 35). The central neuroendocrine response initiated by cytokines is partially involved in protein-losing processes, because intracerebroventricular injection of either TNF or IL-1 induces excretion of stress hormones, such as cortisol, catecholamine, and glucagon in a similar manner to morphine, resulting in a loss of body weight and an associated increase in glucose production (4, 30).

The aims of this study were to determine whether morphine in the brain was involved in the metabolic changes induced by intracerebroventricular injection of TNF-α and whether prophylactic fentanyl citrate administration prevented an increase in morphine levels in the brain, resulting in prevention of a loss of protein and a subsequent increase in glucose production induced by intracerebroventricular administration of TNF-α.

METHODS

Animal preparation and experimental protocol. Male Sprague-Dawley rats (n = 163, body weight: 225–250 g) were purchased from the Kuroda Animal Facility Center (Kumamoto, Japan) and housed in the animal facility of Kurume University under the condition of a 12:12-h light-dark cycle. The animals were fed standard rat chow (Clea, Tokyo, Japan) and water ad libitum for 7 days before the insertion of catheters into the lateral ventricular space and jugular vein. The experimental protocol was approved by the Kurume University Ethical Committee.

On day 0, the rats were anesthetized with an intramuscular injection of pentobarbital sodium (50 mg/kg, Dainippon Pharmaceutical, Tokyo, Japan) and positioned in a stereo-
taxic apparatus (Neuro Science, Tokyo, J apan). The skin and connective tissues were removed from the skull, a hole was drilled, and a 24-gauge cannula (Terumo, Tokyo, J apan) was placed into the unilaterial ventricle by use of stereotaxic coordination: 0.3 mm posterior to bregma, 1.3 mm lateral from the midline, and 4.25 mm below the surface of the skull. The cannula was secured with dental cement (Hy-bond Glasionomer CX, Shofu, Kyoto, J apan) and anchored to the skull with two stainless steel screws. After the cannulation into the lateral ventricular space, the catheter was inserted into the jugular vein for administration of fentanyl citrate and total parenteral nutrition (TPN) solutions as described previously (41, 44).

The rats were placed in the individual metabolic cages and maintained on standard rat chow and water ad libitum for 5 days. On day 4, food was removed from the metabolic cages to eliminate gut absorption of glucose and amino acids as sources of glucose and leucine appearance from the gut. TPN was begun with a half-strength solution for the next 12 h to allow the animals to adapt to TPN, and a full-strength diet (10.4 kcal·kg⁻¹·h⁻¹, 0.06 g N·kg⁻¹·h⁻¹) was given overnight to avoid a loss of body weight induced by starvation. The TPN solution consisted of glucose (Hi-Calic NCH, Terumo), standard amino acid solution (Moriprone F, Morishita, Osaka, J apan), lipid (Intralipid, Otsuka Pharmaceutical, Tokushima, J apan), and adequate minerals and vitamins as described previously (41, 44).

On day 5 at 9:00 AM, the rats were randomly assigned into five groups according to the following treatments: 1) 5 µl saline injection into an intracerebroventricular space (control); 2) saline (icv) plus intravenous injection of fentanyl citrate (50 µg/kg, Sanko Pharmaceutical, Tokyo, J apan); 3) TNF-α (iv) plus injection of fentanyl citrate (iv); 4) saline (icv) plus injection of human recombinant TNF-α (0.6 µg/rat iv; Amgen, Boulder, CO); 5) saline (iv) plus injection of TNF-α (0.6 µg icv). Fentanyl citrate was given intravenously before intracerebroventricular injection of either saline or TNF-α, because fentanyl given before the surgery inhibited any trauma-induced elevation of glucose production (40).

Immediately after each treatment, isotopically labeled glucose and leucine were given to the 65 rats, as previously described, to determine glucose and leucine specific activities and leucine kinetic (44, 44); the rats were primed with 6 µCi of [6-3H]glucose (Du Pont-NEN, Boston, MA), and both [6-3H]glucose and [1-14C]leucine (Du Pont-NEN) mixed in TPN solution were given constantly via TPN catheter (2 µCi·h⁻¹·rat⁻¹) each for 4 h (40, 44). To confirm that leucine and glucose specific activities had attained plateau in the plasma and muscle free amino acids within 4 h, another 48 rats receiving either saline or TNF-α into the brain were killed at 60, 120, 180, 210, 225, or 240 min after initiation of the each treatment, and blood and gastrocnemius muscle were collected. At the end of the 4-h isotope infusion period, the 65 animals were decapitated, and mixed blood and gastrocnemius muscle were collected. The muscle and blood were immediately frozen in liquid nitrogen and stored at −80°C for later analysis of protein and glucose turnover. Another 50 rats receiving TPN solution without the infusion of isotopes were killed at 30 or 240 min after the each treatment to determine levels of corticosterone and catecholamines in the plasma, seromucoid protein levels in the serum, and morphine levels in the brain.

Analytic procedures and measurements. The specific activity of plasma glucose was measured as described previously (40). The specific activity of [1-14C]leucine in supernatant and protein of muscle and plasma was measured as described previously (42, 44). Briefly, sulfosalicylic acid (4%, 3 ml, Wako Pure Chemical, Osaka, J apan) was added to plasma and skeletal muscle, sonicated on ice, and centrifuged. The supernatant was lyophilized overnight and reconstituted. Because the aliquot consisted of doubly labeled (3H, 14C) quenched nitrogen and stored at 80°C for later analysis of protein and glucose turnover, the supernatant was lyophilized overnight and reconstituted. The amount of protein in the aliquot was measured by a modified Lowry method (Sigma Chemical, St. Louis, MO), and 14C was counted in a liquid scintillation counter (Aloka).

Corticosterone, glucagon, and insulin levels in the plasma were analyzed by RIA as described previously (40). Epinephrine and norepinephrine levels in the plasma were measured by HPLC with fluorescence detection (Special Reference Laboratory, Tokyo, J apan). Seromucoid fraction was obtained by sequential precipitation of serum in 0.6 M perchlorate and 2% phosphotungstic acid, as described by Hellerstein et al. (16), and the concentration of this fraction was measured colorimetrically using the Bradford reagent (Sigma Chemical). Morphine levels in the brain were measured according to the modification of the two previously published methods (21, 28) by use of an isocratic analytic system equipped with an L-7100 pump (Hitachi), an MCM column (ODS 5 µm, 4.6 × 150 mm, MC Medical, Tokyo, J apan), a recorder (Chromelon Chromatography Data Systems, Gynkotek HPLC, Munich, Germany), and an electrochemical detector (Coulomet 11500A, ESA, Bedford, MA) with a 5202 guard cell and a 5011 analytic cell (ESA).

Calculations. Because the substrate specific activity reached a plateau at 120 min in TNF-α-treated rats receiving [6-3H]glucose (775 ± 220 dpm/µmol), we used the steady-state method for calculation of glucose production. In agreement with our prior report (44) and data of others (18), free leucine specific activity reached a plateau at 180 min both in plasma (39,666 ± 1,250 dpm/µmol) and in supernatant (10,476 ± 4,200 dpm/µmol) of skeletal muscle after intracerebroventricular injection of TNF-α, as well as in control rats receiving saline via intracerebroventricular catheter (data not shown); thus a steady-state method was used in calculation of the substrate flux and protein synthesis rate in the skeletal muscle and plasma protein. The fluxes of glucose and leucine were calculated by dividing the tracer infusion rate by the substrate specific activity in the plasma obtained at the end of a 4-h isotope infusion, by use of the Steele equation. Endogenous glucose and leucine production rates were calculated by a subtraction of the exogenous glucose and leucine infusion rates from the total glucose and leucine production rates, respectively (glucose infusion rate: 34.1 ± 0.6 mg·kg⁻¹·min⁻¹; leucine infusion rate: 289.1 ± 7.2 µmol·leucine·kg⁻¹·h⁻¹). In estimation of leucine flux, the use of the plasma leucine specific activity results in a small underestimation compared with the value found when α-ketoglucosacarate (KIC) specific activity is used for the calculation. Because Castellino et al. (7) reported that differences in the response of leucine flux to insulin infusion are not large, irrespective of whether leucine or KIC specific activity is used, we (42, 44) and other authors (18) have used the plasma leucine specific activity for the calculation of leucine flux instead of KIC. Because it is unclear whether plasma leucine or KIC specific activity more closely reflects the actual precursor pool for the fractional synthesis rate, leucine specific activity was also used to calculate fractional synthesis rate of muscle and mixed protein by use of Garlick’s 1973 formula (11).

\[
\frac{S_{\text{gl}}}{S_{\text{pl}}} = \frac{\lambda_l}{(\lambda_l - K_S)} \left(1 - e^{-K_S t}\right) - \frac{K_S}{(\lambda_l - K_S)} \left(1 - e^{-K_S t}\right)
\]
where $S_B$ is the specific activity of protein-bound leucine, $S_i$ is the specific activity of leucine in the intracellular fluid in muscle and plasma protein, the constant $\lambda_i = 60$, $t$ is the duration of isotope infusion (h), and $K_s$ is the fractional synthesis rate.

Statistical analysis. All data are expressed as means ± SE. Statistical analysis was done by analysis of variance, and Fisher’s least significant test was employed to differentiate significant differences among the means, with use of Macintosh Performa 588 (Apple Computers, Cupertino, CA; Statview 412 supplied by Abacus Concepts, Berkeley, CA). Mean differences were considered statistically significant at $P < 0.05$.

RESULTS

Intracerebroventricular injection of TNF-α caused a 100% increase in glucose production compared with the control rats [control: $36.0 ± 0.9$ mg·kg$^{-1}$·min$^{-1}$ vs. TNF (icv): $75.7 ± 0.7$, $P < 0.05$, Table 1], whereas systemic injection of TNF-α did not alter glucose production rate. TNF-α-induced increase in glucose production was prevented by prophylactic administration of fentanyl (fentanyl + TNF: $4.8 ± 0.7$ mg·kg$^{-1}$·h$^{-1}$, not significant vs. control). Like glucose production, plasma glucose levels were increased with intracerebroventricular injection of TNF-α compared with the control [control: $95 ± 6$ g/dl vs. TNF (icv): $182 ± 27$, $P < 0.01$], and prophylactic administration of fentanyl reduced glucose levels from 182 to 108 g/dl.

The fractional synthesis rate (FSR) of muscle in the intracerebroventricular injection of TNF-α-treated animals was depressed by 50% compared with control rats [control: $14.1 ± 1.6$ %/day vs. TNF (icv): $7.7 ± 0.7$, $P < 0.01$]. Fentanyl prevented this reduction of the muscle FSR (Table 1). In contrast to the decrease in the muscle FSR, the plasma mixed protein FSR was increased with intracerebroventricular injection of TNF-α compared with that of control rats [control: $37.6 ± 4.9$ %/day vs. TNF (icv): $57.4 ± 7.1$, $P < 0.01$]. Giving the same dose of TNF-α via the intravenous catheter did not alter the plasma mixed protein FSR. Fentanyl prevented the increase in mixed plasma protein FSR caused by intracerebroventricular injection of TNF-α, and no differences were found between fentanyl plus TNF-α and control groups. In association with an increase in FSR of plasma mixed protein with intracerebroventricular injection of TNF-α, the seromucoid protein fraction levels in the serum were elevated with intracerebroventricular injection of TNF-α compared with control [control: $445.2 ± 22.3$ µg/ml vs. TNF (icv): $675.1 ± 28.5$, $P < 0.01$]. As with the plasma mixed protein FSR, fentanyl blocked this increase in the serum seromucoid protein fraction levels. The whole body protein breakdown rate, as evaluated from the endogenous leucine production rate, was also greater with intracerebroventricular injection of TNF-α than with the control treatment [control: $90.9 ± 18.3$ µmol Leu·kg$^{-1}$·h$^{-1}$ vs. TNF (icv): $254.2 ± 45.7$, $P < 0.01$], and fentanyl blunted this increase in whole body protein breakdown rate induced by intracerebroventricular injection of TNF-α.

Cortisol, epinephrine, norepinephrine, and glucagon levels in the plasma were all increased with intracerebroventricular injection of TNF-α at 30 min after the injection but returned to control levels at 240 min (Table 2). Fentanyl inhibited this elevation at 30 min induced by TNF-α. Neither fentanyl alone nor intravenous injection of TNF-α caused an increase in stress hormone levels at 30 min after the injection. In agreement with the stress hormone levels in the plasma, a significant increase in the brain morphine levels with intracerebroventricular injection of TNF-α compared with the control rats was found at both 30 and 240 min after the intracerebroventricular injection of TNF-α [at 30 min, control: $648 ± 102$ fmol/g vs. TNF (icv): $1,134 ± 80$ fmol/g, $P < 0.05$; at 240 min, control: $806 ± 142$ fmol/g vs. TNF (icv): $1,162 ± 92$ fmol/g, $P < 0.05$; Table 2], and fentanyl inhibited this increase. Morphine levels in the brain were not elevated either by fentanyl alone or by intravenous injection of TNF-α. The anabolic hormone insulin was not altered with intracerebroventricular injection of TNF-α, and there were no significant differences among the five groups (Table 2).

DISCUSSION

Molina et al. (25) demonstrated that 80 µg of intracerebroventricular injection of morphine enhanced proteolysis, probably due to an increase in epinephrine and corticosterone, but they were unable to eliminate the effects of hypoxia and acidosis induced by this dose of morphine on protein metabolism. In a preliminary study, we found that 1 µg of morphine bolus injection via intracerebroventricular catheter caused neither acidosis nor hypoxia but did cause an increase in whole body protein breakdown rate (32), which was associated with an elevation of glucose production due to an increase in catecholamine and corticosterone levels compared with the control rats. As with morphine, 100 µg of fentanyl by intravenous injection depressed breathing and caused acidosis in rats (41). Fifty micro-

Table 1. Changes in protein and glucose metabolism 4 h after initiation of treatment

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Fentanyl</th>
<th>Fentanyl + TNF (icv)</th>
<th>TNF (iv)</th>
<th>TNF (icv)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$n$</td>
<td>15</td>
<td>12</td>
<td>12</td>
<td>11</td>
<td>15</td>
</tr>
<tr>
<td>Muscle FSR, %/day</td>
<td>14.1 ± 1.6</td>
<td>14.4 ± 2.0</td>
<td>12.1 ± 1.9</td>
<td>12.2 ± 1.1</td>
<td>7.7 ± 0.7*</td>
</tr>
<tr>
<td>Plasma protein FSR, %/day</td>
<td>37.6 ± 4.9</td>
<td>39.8 ± 6.3</td>
<td>34.3 ± 4.4</td>
<td>31.7 ± 1.4</td>
<td>57.4 ± 7.1*</td>
</tr>
<tr>
<td>Seromucoid protein, µg/ml</td>
<td>445.2 ± 22.3</td>
<td>504.1 ± 53.2</td>
<td>549.1 ± 32.8</td>
<td>531.4 ± 32.6</td>
<td>675.1 ± 28.5*</td>
</tr>
<tr>
<td>WPBR, µmol Leu·kg$^{-1}$·h$^{-1}$</td>
<td>90.9 ± 18.3</td>
<td>123.0 ± 26.2</td>
<td>128.7 ± 34.2</td>
<td>118.7 ± 19.7</td>
<td>254.2 ± 45.7*</td>
</tr>
<tr>
<td>Glucose levels in plasma, g/dl</td>
<td>95 ± 6</td>
<td>105 ± 9</td>
<td>108 ± 12</td>
<td>92 ± 6</td>
<td>182 ± 27*</td>
</tr>
<tr>
<td>Glucose production, mg·kg$^{-1}$·h$^{-1}$</td>
<td>3.6 ± 0.9</td>
<td>3.7 ± 0.5</td>
<td>4.8 ± 0.7</td>
<td>3.8 ± 0.8</td>
<td>7.5 ± 0.7*</td>
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</tbody>
</table>

Values are means ± SE; $n$, nos. of animals/group. TNF, tumor necrosis factor; FSR, fractional synthesis rate; WPBR, whole body protein breakdown rate. Significantly different from other 4 groups (ANOVA): *$P < 0.01$, †$P < 0.05$. 

Downloaded from http://ajpendo.physiology.org/ by 10.220.33.3 on September 8, 2017
grams of intravenous fentanyl did not reduce the blood pH of rats compared with those receiving saline [pH, saline: 7.453 ± 0.003 vs. fentanyl (iv): 7.458 ± 0.009]. Although high doses of TNF-α (700 µg/kg) cause metabolic acidosis in rats (37), acidosis did not occur with an 0.6-µg injection of TNF-α into the brain (pH: 7.478 ± 0.017) in this study. The effect of acidosis on protein turnover and glucose production was, therefore, not a factor in the present study.

Bernardini et al. (4) reported that 0.2 µg of TNF-α injection via intravenous catheter did not cause any elevation of adrenocorticotropic hormone (ACTH) and corticosterone levels (130 ng/ml) in the plasma. Similarly, in the present study, 0.6 µg of TNF-α injection via intravenous catheter did not cause any increase in corticosterone levels in the plasma. Furthermore, the dose of TNF-α that causes an elevation of corticosterone levels to 350 ng/ml was 10 µg of TNF-α injection via intravenous catheter, and an increase in corticosterone levels was necessary to cause protein catabolism by TNF-α injection (22). Therefore, probably more than 10 µg of TNF-α injection via intravenous catheter are required for alteration of metabolic response in rats.

The central administration of TNF-α caused an elevation of stress hormone levels, resulting in a decrease in the muscle protein synthesis rate, an increase in whole body protein breakdown, and an enhancement of glucose production. In agreement with the present study, Plata-Salaman et al. (29) demonstrated that intracerebroventricular injection of 0.5 µg of TNF-α caused anorexia and a loss of body weight. The present study suggested that metabolic change with intracerebroventricular injection of TNF-α was independent of an impairment of food intake resulting from anorexia, because the rats received TPN solution during the measurement of protein turnover and glucose production.

The present study showed that acute-phase protein synthesis was increased with intracerebroventricular injection of TNF-α, similar to that observed in trauma and sepsis. De Simoni et al. (10) reported that 0.4 µg of TNF-α via intracerebroventricular injection did not enhance IL-6 levels in the plasma, and in this study the systemic administration of TNF-α altered neither serum levels in the plasma nor mixed plasma protein synthesis rate compared with control rats. Because corticosterone enhanced seromucoid protein synthesis (3), an increase in acute-phase protein synthesis induced by intracerebroventricular injection of TNF was probably due to an increase in corticosterone excretion (Table 1).

Both glucose levels and production rate were increased by intracerebroventricular administration of TNF-α, and fentanyl administration blocked this response. An enhancement of glucose metabolic alteration by intracerebroventricular injection of TNF occurred probably because plasma glucagon levels were increased as a result of an increase in catecholamine levels (14). Insulin levels, on the other hand, were unaltered by intracerebroventricular injection of TNF-α in the present study. Insulin is a major anabolic hormone, and secretion of insulin was depressed by α-action of catecholamines on the pancreatic β-cells after surgical stress (1). Because glucose utilization with glucose challenge was not completely impaired in catabolic patients (6) and high-glucose TPN solution was infused in the present study, insulin levels were not depressed by intracerebroventricular injection of TNF-α.

Our previous study showed that prophylactic administration of fentanyl results in lower insulin levels 24 h after the surgery than pentobarbital anesthesia alone and that this is associated with a depression of glucose production in rats receiving TPN solution (40). Thus insulin was probably involved in glucose and protein metabolism at the later period of this experimental protocol.

The release of ACTH is mediated by prostaglandins (15), and both TNF-α and IL-1 induce prostaglandin E2 production in the brain (4, 20). We found that fentanyl citrate blocked the catabolic response induced by intra-

### Table 2. Morphine levels in the brain and stress hormone levels in the plasma

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Fentanyl (iv)</th>
<th>Fentanyl (iv) + TNF (icv)</th>
<th>TNF (iv)</th>
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<tbody>
<tr>
<td>Morphine, fmol/g</td>
<td></td>
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<tr>
<td>30 min</td>
<td>648 ± 102</td>
<td>720 ± 86</td>
<td>624 ± 193</td>
<td>651 ± 93</td>
</tr>
<tr>
<td>240 min</td>
<td>805 ± 142</td>
<td>759 ± 68</td>
<td>820 ± 50</td>
<td>827 ± 77</td>
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<tr>
<td>Epinephrine, pg/ml</td>
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<tr>
<td>30 min</td>
<td>462.4 ± 108.4</td>
<td>1,271 ± 127.5</td>
<td>1,326.5 ± 597.5</td>
<td>976.0 ± 108.0</td>
</tr>
<tr>
<td>240 min</td>
<td>1,005.7 ± 478.8</td>
<td>956.5 ± 517</td>
<td>923.0 ± 311.0</td>
<td>1,300.8 ± 57.7</td>
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<tr>
<td>Norepinephrine, pg/ml</td>
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<tr>
<td>30 min</td>
<td>262.0 ± 35.0</td>
<td>276.0 ± 14.2</td>
<td>254.0 ± 34.0</td>
<td>274.3 ± 74.8</td>
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<tr>
<td>240 min</td>
<td>241.7 ± 26.0</td>
<td>366.5 ± 72.5</td>
<td>351.0 ± 122.0</td>
<td>325.3 ± 36.6</td>
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<tr>
<td>Corticosterone, ng/ml</td>
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<tr>
<td>30 min</td>
<td>252.3 ± 44.4</td>
<td>239.5 ± 46.7</td>
<td>225.6 ± 32.5</td>
<td>234.6 ± 24.5</td>
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<tr>
<td>240 min</td>
<td>234.0 ± 113.0</td>
<td>206.0 ± 26.8</td>
<td>214.6 ± 12.4</td>
<td>235.4 ± 61.4</td>
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<tr>
<td>Glucagon, pg/ml</td>
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<tr>
<td>30 min</td>
<td>54.5 ± 6.1</td>
<td>43.0 ± 7.5</td>
<td>48.5 ± 12.5</td>
<td>53.1 ± 6.5</td>
</tr>
<tr>
<td>240 min</td>
<td>58.3 ± 13.9</td>
<td>59.6 ± 10.3</td>
<td>68.0 ± 10.9</td>
<td>68.4 ± 22.4</td>
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<tr>
<td>Insulin, ng/ml</td>
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<td></td>
</tr>
<tr>
<td>30 min</td>
<td>10.3 ± 2.0</td>
<td>8.1 ± 3.6</td>
<td>10.7 ± 3.2</td>
<td>8.2 ± 5.2</td>
</tr>
<tr>
<td>240 min</td>
<td>9.1 ± 3.2</td>
<td>7.9 ± 3.1</td>
<td>8.3 ± 3.4</td>
<td>7.8 ± 1.7</td>
</tr>
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</table>

Fifty rats were killed either 30 or 240 min after treatment. Values are means ± SE of 5 rats at each time point in each group. Significantly different from other 4 groups (ANOVA): *P < 0.05, †P < 0.01.
cerebroventricular injection of TNF-α. One possible reason for this inhibition by fentanyl citrate is that opiates inhibit the biosynthesis of both prostaglandins and cAMP (8). If opiates do in fact inhibit the biosynthesis of prostaglandins and cAMP, it is not implausible that prostaglandins and morphine both mediate the catabolic response induced by intracerebroventricular injection of TNF-α.

Fentanyl and morphine are synthetic and natural narcotics, respectively. The effects of these opiates, however, are not exactly identical, because we found no enhancement of stress hormone levels with systemic administration of fentanyl, whereas a study by Radosevich et al. (31) showed that systemic morphine administration caused an increase in glucose production in dogs. Fentanyl is ultra short acting, and the narcotic potency of fentanyl citrate is 150-fold greater than that of morphine (33). In addition to these characteristic differences between these opiates on catabolic response, it is still remains unclear why, for morphine and fentanyl, which are both involved in a μ-receptor of opiate (34), there is a difference between these opiates on catabolic response in unstressed rats.

In summary, the catabolic responses initiated by an intracerebroventricular injection of TNF-α were associated with an increase in morphine levels in the brain, resulting in an elevation of stress hormone levels and subsequent changes in protein and glucose metabolism. These catabolic responses were blocked by a prophylactic administration of fentanyl. One possible mechanism for this blocking is that fentanyl reduced morphine levels in the brain. The prevention of elevated morphine levels in the central nervous system by the systemic injection of fentanyl citrate, therefore, explains how fentanyl analgesia reduces surgical stress levels after surgery.

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Address for reprint requests: S. Yoshida, Kurume Univ., Dept. of Surgery, Metabolic Unit, 67 Asahi-machi, Kurume-shi, Fukuoka 830, Japan.

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