The opiate sufentanil alters the inflammatory, endocrine, and metabolic responses to endotoxin in dogs

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Moeniralam, Hazra S., Erik Endert, Mariette T. Ackermans, J. Jan B. van Lanschot, Hans P. Sauerwein, and Johannes A. Romijn. The opiate sufentanil alters the inflammatory, endocrine, and metabolic responses to endotoxin in dogs. Am. J. Physiol. 275 (Endocrinol. Metab. 38): E440–E447, 1998.—Sufentanil is a synthetic µ-opioid receptor agonist frequently used in anesthesia and critically ill patients. To evaluate the effects of sufentanil on the inflammatory, neuroendocrine, and metabolic responses to endotoxin, we studied six dogs during saline infusion (control), during sufentanil infusion (1.5 µg·kg⁻¹·h⁻¹), after endotoxin injection (1.0 µg/kg iv), and during combined endotoxin and sufentanil administration. The rate of appearance of glucose was determined by infusion of [6,6-2H₂]glucose. Sufentanil inhibited this endotoxin-induced stimulation of glucose production by 70% (P < 0.01) and increased interleukin-6 (IL-6) response by 70% (P < 0.01). Sufentanil per se induced a transient neuroendocrine activation. Sufentanil also increased plasma concentrations of insulin and catecholamines after endotoxin (P < 0.05 vs. endotoxin alone) and increased plasma glucose levels by ~36% (from 6.1 ± 0.1 to 8.3 ± 0.6 mmol/l, P < 0.05 vs. endotoxin alone). Endotoxin stimulated glucose production transiently by 95% (24.2 ± 3.2 vs. control 12.4 ± 1.0 µmol·kg⁻¹·min⁻¹, P < 0.05). Paradoxically, sufentanil inhibited this endotoxin-induced stimulation of glucose production (P < 0.05 vs. endotoxin alone). In conclusion, sufentanil modulates the response to intravenous endotoxin by dissociating the TNF and IL-6 response, increasing insulin and catecholamine levels, and depressing the increase in glucose production. Therefore, opiates alter inflammatory, endocrine, and metabolic regulation in endotoxia.

tumor necrosis factor; interleukin-6; hormones; glucose

INFECTION INDUCES A VARIETY of acute changes in physiological regulation. A bolus of endotoxin mimics these acute changes induced by infection. The inflammatory response induced by endotoxin is characterized by increased production of cytokines such as tumor necrosis factor (TNF), interleukin-1 (IL-1), and IL-6 and is associated with neuroendocrine activation and metabolic changes (7, 17, 19, 20, 31). The neuroendocrine activation induced by endotoxin is reflected in increased plasma concentrations of glucoregulatory hormones (31). The metabolic changes associated with inflammation are characterized by increased glucose production, lipolysis, and net protein breakdown (7, 19, 31).

The response to surgery reveals many similarities with the inflammatory, endocrine, and metabolic reactions to infection. Because high doses of opiates decrease the hormonal and metabolic responses to surgery (4, 8, 9, 15, 26), we hypothesized that opiate administration also alters these responses to endotoxin. This potential alteration of the reaction to infection by exogenous opiates could be of clinical relevance because many critically ill patients receive opiates for analgesia.

To evaluate whether exogenous opiates modulate the inflammatory, endocrine, and metabolic responses to endotoxin, we studied six awake dogs on four different occasions: 1) saline infusion (control), 2) sufentanil infusion (1.5 µg·kg⁻¹·h⁻¹), 3) endotoxin administration (1.0 µg/kg), and 4) endotoxin administration during sufentanil infusion. We used sufentanil because this synthetic µ-opioid receptor agonist is frequently used during anesthesia and in critically ill patients.

MATERIALS AND METHODS

Experimental animals. Six male mongrel dogs (33 ± 1 kg) were studied on four different occasions. Before the study all dogs were observed for 2 wk. Only dogs with normal stools, absent febrile disease, normal physical examination, and normal laboratory results (liver function tests, creatinine, leukocyte counts, and hemoglobin content) were included. The dogs were fed once a day a standard diet, consisting of 64% carbohydrate, 7% fat, 26% protein, and 3% fiber, based on dry weight (D. B. Brok, Hope Farms, Woerden, The Netherlands).

The study was approved by the Ethical Committee for Animal Experiments of the Academic Medical Center, University of Amsterdam, and was performed according to the guidelines of the Dutch Law for Animal Experiments.

Study design. Each dog was studied on four different occasions with an interval of at least 3 wk between each study. Each study lasted 360 min. The order in which the studies were performed was determined by balanced assignment. Study A consisted of 360 min of saline infusion to control for changes over time (control study). Study B consisted of 360 min of sufentanil infusion (1.5 µg·kg⁻¹·h⁻¹) to study the effects of sufentanil per se. In study C, endotoxin (1.0 µg/kg) was injected intravenously after 120 min of saline infusion. Study D consisted of 360 min of sufentanil infusion, with endotoxin administration after 120 min of sufentanil infusion. We used sufentanil because this synthetic opiate acts similarly as morphine by binding to the µ-opioid receptor (23) but does not have cardiovascular side effects like morphine (22). To get acquainted to the experimental procedure, the dogs were trained daily in the experiment room to lie quiet for a few hours. Four days before each experiment a femoral arterial catheter was inserted during general anesthesia [1% isoflurane, Forene, Abbott Laboratories, Queensbough, Kent, UK, and N₂O-O₂ (1:1) ventilation]. After insertion, the catheter was filled with heparin (200 U/ml), closed, and placed in a subcutaneous pocket.

Each study period started at 8 AM after an overnight fast of 18 h. On the morning of the experiment the skin around the
pocket was anesthetized with lidocaine and opened. Subsequently, the femoral arterial catheter was obtained from the pocket and attached to a monitor for continuous intra-arterial blood pressure monitoring (Hewlett Packard) and blood sampling. A catheter was inserted into the right cephalic vein for infusion of saline or administration of endotoxin. Another catheter was inserted into the left cephalic vein for [6,6-
H2]glucose infusion and, dependent on the protocol, sufentanil infusion. These cephalic catheters were inserted without local anesthesia.

After blood samples were obtained for the determination of basal glucose concentrations and enrichments, a primed (17.6 µmol/kg), continuous infusion (0.22 µmol·kg⁻¹·h⁻¹) of [6,6-
H2]glucose was started at −120 min. In studies B and D a continuous infusion of 1.5 µg·kg⁻¹·h⁻¹ sufentanil (Janssen-Cilag, Tilburg, The Netherlands) was started simultaneously, at −120 min. Two hours were used for equilibration of stable isotope enrichment before endotoxin or saline administration. At t = 0 min, basal measurements and blood samples were obtained, followed by the administration of either saline or endotoxin (1.0 µg/kg). Endotoxin, derived from E. coli (0111:B4, lot 31H4000, phenol extracted; Sigma Chemical, St. Louis, MO) was suspended in sterile pyrogen-free saline. A solution of 100 µg/ml was made, divided into several tubes (Costar, Cambridge, MA), and stored at −20°C. Before injection the endotoxin solution was thawed at 37°C, vortexed for 3 min, diluted, and vortexed again for 10 min. Because circulatory shock itself may induce metabolic changes, a dose of endotoxin (1.0 µg/kg) was chosen that induces considerable secretion of cytokines without induction of circulatory shock (20).

At the end of the experiment, all catheters were removed, and the dogs were observed thoroughly during the next 48 h. Measurements and blood samples. Mean arterial blood pressure and heart rate were derived from intra-arterial pulse waves, monitored continuously (Hewlett-Packard, Amsterdam, The Netherlands), and recorded every 5 min. Body temperature was measured before and every 30 min after endotoxin administration using a rectal thermometer.

Arterial blood samples for the determination of plasma glucose concentrations and enrichments were obtained before (−15, −10, −5, 0 min) and after (30, 60, 90, 120, 180, and 240 min) endotoxin administration. Arterial blood samples for the determination of plasma TNF, IL-6, lactate, glucagon, insulin, catecholamines, and cortisol were obtained before and 60, 120, 180, and 240 min after endotoxin or saline administration.

Sample processing. Blood for determination of plasma glucose concentration and enrichment, TNF, IL-6, and insulin levels was collected in prechilled heparinized tubes and stored on ice. Immediately after sampling the blood samples were centrifuged (3,000 rpm, 4°C, 10 min) and plasma was stored at −20°C until further analysis. Whole blood was added to reduced glutathione-EGTA buffer or trasylol for determination of catecholamines and glucagon, respectively. Sodium fluoride blood was added to 10% perchloric acid for lactate determination.

Biochemical analysis. All measurements were performed in duplicate. All measurements of each dog were analyzed in the same run. Plasma insulin concentration was determined by RIA (Insulin RIA 100; Pharmacia Diagnostic, Uppsala, Sweden; detection limit 2 mU/l); plasma glucagon concentration by RIA (Daichi Radiosotope Laboratories, Tokyo, Japan; detection limit 15 ng/l); plasma concentrations of norepinephrine and epinephrine by HPLC and fluorescence detection, using α-methyl-norepinephrine as an internal standard (12); and plasma cortisol levels by fluorescence polarization immunoassay on technical device X (Abbott Laboratories, Chicago, IL; detection limit was 50 nmol/l).

Plasma TNF concentrations were determined by ELISA, kindly provided by W.A. Buurman (University of Maastricht, Maastricht, The Netherlands), detection limit 15 pg/ml (S). IL-6 bioactivity was measured with an IL-6-dependent B-9 hybridoma cell line kindly provided by L.A. Aarden (Central Laboratory of the Netherlands Red Cross Blood Transfusion Service, Amsterdam, The Netherlands) (10). The detection limit of the bioassay was 1 pg/ml. IL-6 standard contained human recombinant IL-6 (Costar, Badhoevedorp, The Netherlands), which was serially diluted.

Glucose concentrations and enrichments were determined by gas chromatography-mass spectrometry (Gas Chromatograph model 5890 II, Mass Spectrometer model 5899 A, Hewlett-Packard, Fullerton, CA; column HPInnowax AT-1, 30 cm × 0.25 mm × 0.2 µm; Alltech, Deerfield, IL). β-Phenyl-
-glucose was used as internal standard (36); intra-assay coefficient of variation was 1–4%, interassay coefficient of variation was 1.5–5%, and detection limit was 1.5 mM (0.5% enriched). Plasma lactate was measured by enzymatic method (Boehringer Mannheim, Almere, The Netherlands) on a Cobas Bio Centrifugal Analyzer. Plasma free fatty acid (FFA) concentrations were measured using an enzymatic method (Wako Chemicals, Neuss, Germany).

Statistical analysis and calculations. All values are expressed as means ± SE. Non-steady-state equations and, when appropriate, steady-state equations were used to calculate the rate of appearance (Ra) of glucose, as adapted for the use of stable isotopes (24). The distribution volume of glucose was assumed to be 165 ml/kg. The metabolic clearance rate (MCR) of glucose was calculated by dividing Ra of glucose by plasma glucose concentration. Changes from basal values within each group were tested by ANOVA for randomized block design, using the Newman-Keuls test when appropriate. Differences between the four protocols at each time point were tested by using the same test. P < 0.05 was considered to be statistically significant.

RESULTS

Clinical parameters. During sufentanil infusion the dogs were sleepy but could be awakened easily. Sufenta-
nil did not induce respiratory depression. This was reflected in blood gas analyses, indicating that there were no differences in pH or Pco2 between the experiments with and without sufentanil.

Endotoxin increased body temperature from 38.2 ± 0.1 to 40.6 ± 0.5°C (P < 0.01, Fig. 1). Sufentanil decreased body temperature from 38.4 ± 0.2 to 36.4 ± 0.2°C (P < 0.01) and abolished the endotoxin-induced increase in body temperature (t = 150 min, endotoxin 40.6 ± 0.5 vs. sufentanil-endotoxin 36.9 ± 0.3°C, P < 0.05). Endotoxin increased heart rate (from 75 to 99 ± 7 beats/min at t = 120 min, P < 0.05) and mean arterial blood pressure (from 103 ± 3 to 126 ± 6 mmHg at t = 30 min, P < 0.01; Fig. 1). Sufentanil per se had no influence on heart rate and blood pressure but abolished the endotoxin-induced increase in heart rate (t = 120 min, endotoxin 99 ± 7 vs. sufentanil-endotoxin 65 ± 4 beats/min, P < 0.05) and did not affect the endotoxin-induced increase in blood pressure [from 107 ± 7 to 125 ± 4 mmHg, at t = 180 min, P < 0.05, not significant (NS) vs. endotoxin].
TNF and IL-6. Endotoxin increased plasma TNF (from values below detection limits in all dogs to \(917 \pm 108\) pg/ml, \(P < 0.01\)) and IL-6 levels (from values below detection limit in all dogs to \(27 \pm 6\) ng/ml, \(P < 0.01\)). Sufentanil per se did not change plasma TNF or IL-6 levels. Sufentanil decreased the TNF response to endotoxin by \(60\%\) (at \(t = 60\) min, endotoxin \(917 \pm 108\) pg/ml vs. sufentanil-endotoxin \(383 \pm 58\) pg/ml, \(P < 0.01\)). In contrast, sufentanil increased the endotoxin-induced IL-6 response by \(70\%\) (at \(t = 180\) min, endotoxin \(27 \pm 6\) ng/ml vs. sufentanil-endotoxin \(45 \pm 5\) ng/ml, \(P < 0.01\); Fig. 2).

Glucoregulatory hormones. Endotoxin increased plasma concentrations of insulin from \(6 \pm 1\) to \(11 \pm 2\) mU/l (maximal at \(t = 120\) min, \(P < 0.05\)), glucagon from \(7 \pm 6\) to \(160 \pm 42\) ng/l (maximal at \(t = 120\) min, \(P < 0.01\)), and cortisol from \(0.06 \pm 0.02\) to \(0.71 \pm 0.07\) µmol/l (maximal at \(t = 240\) min, \(P < 0.01\)). Plasma epinephrine and norepinephrine levels were not affected by endotoxin (Fig. 3). Sufentanil infusion increased plasma levels of all measured glucoregulatory hormones (maximal at \(t = 0\), \(P < 0.01\) vs. control). Compared with endotoxin alone, sufentanil infusion increased plasma insulin levels after endotoxin administration (at \(t = 240\) min, endotoxin \(4 \pm 1\) mU/l vs. sufentanil-endotoxin \(10 \pm 2\) mU/l, \(P < 0.05\)). Plasma glucagon levels were not different between both endotoxin experiments. Plasma catecholamine levels remained higher during combined sufentanil-endotoxin administration compared with endotoxin alone (at \(t = 240\) min, epinephrine \(8.0 \pm 1.7\) vs. \(1.4 \pm 0.4\) nmol/l, \(P < 0.05\); norepinephrine \(2.1 \pm 0.3\) vs. \(0.6 \pm 0.1\) nmol/l, \(P < 0.05\)). Endotoxin altered the neuroendocrine response to sufentanil because epinephrine and norepinephrine levels were higher at \(t = 180\) and \(240\) min than during sufentanil without endotoxin (\(P < 0.05\)). Plasma cortisol levels were not different between endotoxin and combined sufentanil-endotoxin administration (at \(t = 240\) min, endotoxin \(0.71 \pm 0.06\) vs. sufentanil-endotoxin \(0.66 \pm 0.08\) µmol·kg\(^{-1}\)·min\(^{-1}\), NS).

Glucose metabolism. Plasma glucose levels did not change after endotoxin. However, 120 min of sufentanil infusion increased plasma glucose levels by \(36\%\) (from \(6.1 \pm 0.1\) to \(8.3 \pm 0.6\) mmol/l at \(t = 0\), \(P < 0.05\); Fig. 4). These plasma levels remained elevated during sufentanil infusion (\(P < 0.05\) vs. control and vs. endotoxin) and were not affected by additional endotoxin administration.

Within each study there was no difference in the tracer-to-tracee ratios of glucose between \(t = -15, -10, -5,\) and 0 min. In the combined endotoxin-sufentanil study there were no differences in tracer-to-tracee ratios before and after endotoxin administration, indicating the presence of isotopic steady state during the whole experiment (Fig. 4).

\(R_a\) of glucose at \(t = 0\) was not different between the control study (\(13.3 \pm 0.5\) µmol·kg\(^{-1}\)·min\(^{-1}\)) and the endotoxin study (\(13.8 \pm 1.2\) µmol·kg\(^{-1}\)·min\(^{-1}\)). Endotoxin increased \(R_a\) of glucose to a maximum of \(24.2 \pm 3.2\) µmol·kg\(^{-1}\)·min\(^{-1}\) (at \(t = 120\) min, \(P < 0.01\) vs.
Sufentanil alone transiently increased $R_a$ of glucose by $\sim 36\%$ (maximal at $t = 0$, sufentanil $18.1 \pm 2.5$ vs. control $13.3 \pm 0.5 \, \text{mmol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, $P < 0.05$). Sufentanil inhibited the endotoxin-induced increase in $R_a$ of glucose considerably (e.g., $t = 120$ min, endotoxin $24.2 \pm 3.2$ vs. sufentanil-endotoxin $17.6 \pm 1.5 \, \text{mmol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, $P < 0.05$). The MCR of glucose at $t = 0$ was not different among the four studies (control $2.2 \pm 0.2$, endotoxin $2.3 \pm 0.2$, sufentanil $2.2 \pm 0.1$, and sufentanil-endotoxin $2.0 \pm 0.1 \, \text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$). Endotoxin increased MCR of glucose to a maximum of $4.5 \pm 0.5 \, \text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ (at $t = 180$ min) vs. control $2.2 \pm 0.2 \, \text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ($P < 0.01$). Sufentanil infusion depressed the endotoxin-induced increase in glucose clearance (from $t = 30$–$180$ min, $P < 0.01$ between endotoxin and sufentanil-endotoxin).

Lactate and FFA. Endotoxin increased plasma lactate levels from $0.5 \pm 0.1$ to $1.8 \pm 0.2 \, \text{mmol/l}$ ($P < 0.01$). Sufentanil transiently increased plasma lactate levels (maximal at $t = 0$, sufentanil $1.2 \pm 0.1$ vs. control $0.4 \pm 0.1 \, \text{mmol/l}$, $P < 0.05$). Plasma lactate levels remained elevated after endotoxin administration during sufentanil infusion ($P < 0.01$, NS, vs. endotoxin; Fig. 5).

In the saline experiment FFA concentrations increased from $0.47 \pm 0.05$ to $0.57 \pm 0.06 \, \text{mmol/l}$ ($t = 240$ min, $P < 0.05$), explained by a prolongation of the postabsorptive state, whereas during sufentanil infusion, FFA concentrations did not change: $0.41 \pm 0.13$ ($t = 0$) vs. $0.36 \pm 0.11 \, \text{mmol/l}$ ($t = 240$ min, NS, vs. saline). Endotoxin decreased FFA concentrations from $0.55 \pm 0.11$ ($t = 0$) to $0.37 \pm 0.06 \, \text{mmol/l}$ ($t = 120$ min, $P < 0.05$), followed by an increase to $0.68 \pm 0.15 \, \text{mmol/l}$ ($t = 240$ min). Sufentanil altered the response of FFA levels to endotoxin, because FFA concentrations progressively decreased from $0.60 \pm 0.07$ ($t = 0$) to $0.32 \pm 0.03 \, \text{mmol/l}$ ($t = 240$ min, $P < 0.05$ vs. endotoxin).

**DISCUSSION**

In accordance with previous observations (8, 17, 19, 20, 31), endotoxin induced a variety of inflammatory,
neuroendocrine, and metabolic responses. Sufentanil dissociated the TNF and IL-6 responses to endotoxin by inhibiting TNF and stimulating IL-6 responses. Sufentanil per se increased the plasma levels of all measured glucoregulatory hormones. These neuroendocrine effects of sufentanil were also present after endotoxin. This neuroendocrine response during sufentanil administration was associated with a decreased stimulation of endogenous glucose production by endotoxin and with decreased FFA concentrations. Therefore, opiate

![Graphs showing plasma glucose levels, tracer-to-tracer ratios of [6,6-2H2]glucose, rate of appearance (Ra) of glucose, and metabolic clearance rate (MCR) before and after administration of saline (A) or endotoxin (B) during continuous infusion of saline (circles) vs. sufentanil (squares), n = 6. Values are means ± SE. * P < 0.05, saline vs. sufentanil. † P < 0.05, saline-endotoxin vs. sufentanil-endotoxin.](image1)

![Graphs showing plasma lactate levels before and after administration of saline (A) or endotoxin (B) during continuous infusion of saline (circles) vs. sufentanil (squares), n = 6. Values are means ± SE. * P < 0.05, saline vs. sufentanil. † P < 0.05, saline-endotoxin vs. sufentanil-endotoxin.](image2)
analgesia modulates the inflammatory, neuroendocrine, and metabolic responses to acute infection, as mimicked by endotoxin injection.

This study documents a dissociation of the IL-6 and TNF responses to endotoxin by opiates. Interestingly, in rats high doses of morphine increase plasma IL-6 levels. Moreover, morphine potentiated IL-1-induced IL-6 production in these rats, which was antagonized by naloxone (1). In our dogs a much lower dose of sufentanil did not induce IL-6 secretion, but we observed a potentiating effect of sufentanil on endotoxin-induced IL-6 production. This stimulation of IL-6 production can be due to direct effects of sufentanil, because many cell types (including macrophages) contain µ-opioid receptors (25, 30). There are no data available on the direct effects of opiates on TNF production. Alternatively, indirect effects of sufentanil on the cytokine network could be involved, because activation of the neuroendocrine system by sufentanil may modulate cytokine production. For instance, plasma epinephrine levels were much higher in the sufentanil-endotoxin study compared with endotoxin alone. Epinephrine has been shown to modulate cytokine production. For instance, in a perfused liver model in rats, epinephrine inhibited endotoxin-induced TNF production and potentiated endotoxin-induced IL-6 production (18). In vivo, epinephrine also inhibited endotoxin-induced TNF production in healthy humans (28). Cortisol is a less likely candidate for modulating the endotoxin-induced cytokine response in our study, because endotoxin-induced plasma cortisol reached the same levels with or without the presence of sufentanil. Moreover, corticosteroids decrease both the TNF and IL-6 response to endotoxin (27). In summary, the dissociation of the TNF and IL-6 responses to endotoxin by sufentanil may involve direct effects of opiates on cytokine-producing cells or indirect effects of opiates on cytokine production, e.g., through increased secretion of catecholamines.

Opiates stimulate glucose Ra indirectly via the secretion of glucoregulatory hormones (2, 6, 13, 14), in line with our observations. Endotoxin stimulated glucose Ra, at least in part, via the stimulation of the secretion of glucoregulatory hormones. Sufentanil, however, inhibited this stimulation of glucose Ra by endotoxin, despite even higher plasma epinephrine levels. An explanation for this paradoxical, attenuated response of glucose Ra in the sufentanil-endotoxin experiments might be related to higher insulin levels compared with the endotoxin experiments. Alternatively, we cannot exclude a direct inhibitory effect of sufentanil on glucose production. Opioid receptors are present within the liver (30), and stimulation of these hepatic receptors probably inhibits glucose production. For instance, endogenous glucose production is inhibited by β-endorphin in dogs during pancreatic clamp conditions (21), and β-endorphin and sufentanil act through binding to the same opioid receptor (23). Therefore, the inhibition of endotoxin-stimulated endogenous glucose production by sufentanil in our experiment may involve direct and indirect effects of opiates, e.g., stimulation of opioid receptors on hepatocytes and/or stimulation of insulin secretion.

In contrast to the inhibitory effects of opiates on the endocrine response to surgery (4, 8, 9, 15, 26), we did not find an inhibitory effect of sufentanil infusion on the endocrine response to intravenous endotoxin. The initial neuroendocrine response to surgery is induced through afferent neural impulses from the injured tissue (29). Apparently, the activation by these impulses of central endocrine regulation is blocked by exogenous opiates. The neuroendocrine reaction to endotoxemia involves stimulation of the neuroendocrine system through inflammatory mediators. These differences in the initial reaction to surgery and intravenous endotoxin may be involved to explain the discrepant effects of opiates in these conditions.

The infusion of sufentanil started simultaneously with the start of infusion of [6,6-2H2]glucose. One might argue that isotopic steady state was not obtained in the sufentanil experiments before endotoxin or saline administration. Even though we cannot exclude an effect of non-steady-state conditions in the first hours of the sufentanil experiments, there was no difference between basal tracer-to-tracee ratios within each experiment before saline or endotoxin administration. Most importantly, however, tracer-to-tracee ratios of glucose were constant throughout the sufentanil-endotoxin study as shown in Fig. 4. Therefore, even though the simultaneous start of the sufentanil and [6,6-2H2]glucose infusion is subject for debate, this does not invalidate our observation on the effects of sufentanil on glucose kinetics after endotoxin.

The question arises whether endotoxin tolerance may affect our conclusions, because each dog was studied twice with endotoxin. Endotoxin tolerance is induced by continuous endotoxin infusion or by intravenous injections of small amounts of endotoxin for several consecutive days (16). In contrast, in our study endotoxin was administered with an interval of at least 3 wk between each dose. Moreover, the order in which the studies were performed was determined by balanced assignment, and this did not influence the highly significant differences in this small number of dogs. Therefore, our study design is not influenced by effects of endotoxin tolerance.

Sufentanil decreased body temperature by almost 2°C, irrespective of endotoxin administration and the subsequent induction of pyrogenic cytokines like TNF and IL-6. This hypothermic response to opiates is believed to be mediated centrally through µ-opioid receptors (3). It is uncertain to what extent this slight decrease in body temperature may have influenced our results. Nonetheless, not all our data can be explained by this effect of sufentanil on thermoregulation. For instance, insulin secretion is decreased by hypothermia (11), whereas it increased during sufentanil infusion.

Anesthetic doses of sufentanil in dogs decrease heart rate and blood pressure (22). This decrement in heart rate is probably related to increased vagal activity. In
our study a much lower dose of sufentanil did not induce changes in heart rate or blood pressure. Nonetheless, sufentanil prevented the endotoxin-induced tachycardia, which may point to modulation of parasympathetic activity by sufentanil, at least in the presence of endotoxin. We did not measure cardiac output or organ perfusion, which are also likely regulators of metabolic fluxes. In addition to decreases in heart rate and blood pressure by anesthetic doses of sufentanil in dogs, sufentanil induces a small but significant decrease in cardiac output (22). However, sufentanil anesthesia has no clinically significant influence on mesenteric blood flow (32). Therefore, it seems unlikely that the effects of sufentanil on the endotoxin-induced changes in glucose metabolism in our study can merely be explained by a difference in splanchic perfusion.

In conclusion, sufentanil infusion induces many changes in the physiological responses to intravenous endotoxin. Sufentanil depresses endotoxin-induced tachycardia and fever. Sufentanil dissociates the effects of endotoxin on TNF and IL-6 production. Sufentanil increased the insulin and catecholamine response to endotoxin and depressed the endotoxin-induced increase in glucose production. Therefore, opiate analgesia modulates the responses to endotoxin at multiple levels.

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REFERENCES


