Modulation of Glucose Production by Indomethacin and Pentoxifylline in Healthy Humans

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Indomethacin, an inhibitor of prostaglandin synthesis that modulates cytokine production, increases hepatic glucose output (HGO) in humans. However, prostaglandins stimulate glucose production in vitro. To investigate the mechanism of HGO stimulation by indomethacin, we compared the effect of pentoxifylline, an inhibitor of cytokine production, versus saline (study 1, n = 6) and of indomethacin versus the combination of indomethacin and pentoxifylline (study 2, n = 5) on basal HGO. HGO was measured by primed, continuous infusion of 3-^{3}H-glucose. In study 1, pentoxifylline infusion resulted in an immediate, transient decrease of HGO of approximately 50% (from 12.9 ± 0.4 to 6.0 ± 1.7 μmol/kg/min after 15 minutes, $P < .03$ v control). There were no differences in concentrations of glucoregulatory hormones between the two experiments. In study 2, after indomethacin administration, HGO increased transiently by approximately 84% (from 9.7 ± 0.7 at baseline to 16.7 ± 2.4 μmol/kg/min after 135 minutes, $P < .05$). However, pentoxifylline did not affect the increase in HGO induced by indomethacin. There were no differences in concentrations of glucoregulatory hormones between the two experiments. Therefore, indomethacin stimulates HGO by mechanisms unrelated to glucoregulatory hormones, prostaglandins, or cytokines.

HEPATIC GLUCOSE OUTPUT (HGO) is regulated by the interaction of several mechanisms. Major factors involved in the regulation of HGO are glucoregulatory hormones and substrate concentrations, especially plasma glucose.[1-3] In the liver, there is intensive interaction between Kupffer cells and hepatocytes, and in vitro animal data suggest that products of Kupffer cells influence glucose production by hepatocytes (HGO). Stimulated Kupffer cells produce prostaglandins,[4] which stimulate glycogenolysis by hepatocytes.[5-7] In addition, Kupffer cells produce cytokines like interleukin-1-(IL-1), IL-6, and tumor necrosis factor (TNF),[4,8] which modulate glucose production by hepatocytes.[9-15] These in vitro data indicate that paracrine intrahepatic factors could be involved in the (patho)physiological regulation of HGO.

In vivo, indomethacin increases HGO considerably in healthy volunteers.[16] This stimulatory effect of indomethacin is not mediated by alterations in the secretion of glucoregulatory hormones, because plasma concentrations of these hormones are not altered by indomethacin.[16] This observation suggests that paracrine mechanisms are involved in the regulation of HGO in vivo. Because prostaglandins stimulate glucose production in vitro and indomethacin inhibits prostaglandin synthesis, it is unlikely that the stimulation of HGO by indomethacin is caused merely by modulation of prostaglandin synthesis. Indomethacin also modulates cytokine production by macrophages.[17-19] To evaluate whether this modulation of cytokine production is involved in the stimulation of HGO by indomethacin, we evaluated the effects of saline infusion versus pentoxifylline (an inhibitor of cytokine production by macrophages)[20-22] on HGO (n = 6) and of indomethacin alone versus the combination of indomethacin and pentoxifylline on HGO (n = 5) in healthy volunteers. HGO was measured by primed, continuous infusion of tritiated glucose. To provide support for the counteracting effects of indomethacin and pentoxifylline on cytokine production in vivo, we also measured in vitro cytokine production in blood obtained during these studies.

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Submitted August 31, 1995; accepted July 8, 1996.

Supported in part by the Netherlands Organisation for Scientific Research and the Dutch Diabetes Foundation (J.A.R.).

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0026-0495/96/4512-0003$03.00/0

SUBJECTS AND METHODS

Subjects

In study 1, six healthy men aged 34 ± 2 years (mean ± SEM) were studied. Their height was 184 ± 2 cm, weight 76 ± 3 kg, body fat 18% ± 2% (measured by body impedance analyzer BIA 109; Akern, Florence, Italy),[23] and body mass index 23 ± 1 kg · m^{-2}. In study 2, five healthy male volunteers aged 28 ± 2 years were studied. Their height was 188 ± 3 cm, weight 81 ± 4 kg, body fat 19% ± 2%, and body mass index 23 ± 1 kg/m^2. There were no differences in the above-mentioned parameters between subjects in studies 1 and 2. A medical history and physical examination were completely normal in all subjects. No subject had a family history of diabetes mellitus or used any medication. The subjects were consuming a weight-maintaining diet of at least 250 g carbohydrates for 3 days before the study. Some of the subjects in study 1 participated in a previous study of the effects of pentoxifylline on glucose production.[24] Verbal informed consent was obtained from all. The studies were approved by the Institutional Ethics and Isotope Committees.

Study Design

Each subject served as his own control and completed two study protocols separated by an interval of at least 1 month. In study 1, subjects were studied twice: once during infusion of pentoxifylline 2.1 mg · min^{-1} (1-(5-oxohexyl)-3,7-dimethylxanthine; Bufa, Uitgeest, The Netherlands) and on another occasion during infusion of saline (control study). This dose of pentoxifylline has been shown to inhibit the TNF response after a bolus injection of lipopolysaccharide (LPS) to humans.[25] In study 2, the effects of indomethacin (Indocid; Merck Sharp & Dohme, Haerlem, The Netherlands) 150 mg orally versus the effects of indomethacin 150 mg orally and pentoxifylline infusion 2.1 mg · min^{-1} were evaluated. The studies were performed in random order and separated by at least 3 weeks. Subjects were studied in the postabsorptive state after a 14-hour

fast. A 19-gauge catheter was inserted into a forearm vein for infusion of 3-^{3}H-glucose. Another 19-gauge catheter was inserted retrogradely into a wrist vein of the contralateral arm, which was maintained at 65°C in a thermoregulated Plexiglas (Rohm & Haas, Philadelphia, PA) box (for sampling of arterialized venous blood).[26] The catheters were kept patent by a slow saline drip.

After baseline samples were taken for determination of background activity, a primed (120 nCi · kg^{-1}), continuous (1.5 nCi · kg^{-1} · min^{-1}) infusion of 3-^{3}H-glucose (Amersham, Den Bosch, The Netherlands) was started ($t = -2$ hours) and continued throughout the study. After a 2-hour equilibration period, three plasma samples were collected with intervals of 5 minutes for determination of baseline 3-^{3}H-glucose specific activity.

At 0 hours, pentoxifylline or saline infusion was started (study 1). In a previous study, the inhibitory effect of pentoxifylline on HGO disappeared after 45 minutes of infusion.[24] Therefore, in study 2, indomethacin was administered after 1 hour of pentoxifylline infusion. Blood samples for measurement of glucose specific activity and concentrations of glucose, insulin, C-peptide, glucagon, epinephrine, norepinephrine, cortisol, and growth hormone were collected simultaneously at regular intervals from the beginning ($t = 0$ hours) until the end of the study ($t = 7$ hours). Concentrations of lactate and free fatty acids (FFA) were measured at the beginning ($t = 0$ hours), 1 hour, 4 hours, and 7 hours after infusion of pentoxifylline/saline. Blood samples for measurement of ex vivo LPS-stimulated production of TNF, IL-1, and IL-6 were obtained at the beginning ($t = 0$ hours) (0.5 hours for study 1 only) and 1, 1.5, 2, 2.5, 4, and 7 hours after pentoxifylline/saline administration.

Assays

All measurements were performed in duplicate, and all samples from each subject were analyzed in the same assay. Plasma glucose level was measured by the glucose oxidase method (Beckman Glucose Analyzer; Beckman Instruments, Mijdrecht, The Netherlands). Plasma glucose specific activity was measured as described elsewhere.[27,28] Plasma insulin concentration was measured by commercial radioimmunoassay (RIA) (Pharmacia Diagnostics, Uppsala, Sweden); C-peptide by commercial RIA (RIA-Matt; Malinckrodt Diagnostica, Dietzenbach, Germany); glucagon by RIA (Daiichi Radioisotope Laboratories, Tokyo, Japan; glucagon antiserum elicited in guinea pigs against pancreatic specific glucagon, cross-reactivity with glucagon-like substances of intestinal origin <1%); catecholamines by high-performance liquid chromatography and electrochemical detection, after purification on Biorex 70 and concentration by solvent extraction[29]; cortisol by fluorescence polarization immunoassay on technical device X (Abbott Laboratories, Chicago, IL); and growth hormone by immunoradiometric assay (Nichols Institute, Los Angeles, CA). The interassay variation of the insulin assay was 9.7% and 6.9% at insulin concentrations of 15 to 60 and 60 to 120 pmol/L, respectively. The intraassay variation of the insulin assay was 6.9% and 5.0%, respectively. The detection limit of the insulin assay was 15 pmol/L. Plasma lactate level was measured by enzymatic methods (Boehringer, Almere, The Netherlands) on a Cobas Bio centrifugal analyzer (Roche, Mÿdrecht, The Netherlands). Serum FFA levels were measured by an enzymatic method (NEFAC; Wako Chemicals, Neuss, Germany).

Ex vivo cytokine production. Cytokine production was measured in whole blood, to avoid extensive manipulation with cells involved with the separation of monocytes. Production of cytokines in whole blood was corrected for the number of monocytes, the main cells that produce cytokines in blood.[30] Leukocyte counts and leukocyte differentiation were determined in blood anticoagulated with EDTA (potassium salt) with the use of a flow cytometer (Technicon H1 system; Technicon Instruments, Tarrytown, NY). Blood (15 mL) for ex vivo cytokine production was obtained by direct venipuncture in sterile syringes and immediately transferred to a 50-mL tube containing 750 IU heparin (Organon Teknika, Boxtel, The Netherlands) and 45 μg aprotinin (Boehringer). After gentle mixing, the blood was divided into three tubes. Tube A (unstimulated cytokine concentration) containing 100 μL phosphate-buffered saline ([PBS] pH 7.4) was centrifuged immediately and the plasma frozen at −70°C. Tube B (control) containing 100 μL PBS was incubated at 37°C for 22 hours, and after centrifugation the plasma was stored at −70°C. Tube C containing 100 μL (50 μg) LPS (*Escherichia coli* K-235; Sigma Chemical, St Louis, MO; 10 μg 10 μg LPS · mL^{-1} whole blood) was treated identically to tube B.

Cytokine assays. TNF was determined by enzyme-linked immunosorbent assay ([ELISA][31] detection level in our laboratory, 30 pg · mL^{-1}), IL-1 by a commercial immunoradiometric assay (Medgenix, Brussels, Belgium; detection level, 50 pg · mL^{-1}), and IL-6 by a commercial ELISA (CLB, Amsterdam, The Netherlands; detection level, 50 pg · mL^{-1}).

Calculations and Statistics

Glucose output was calculated by the steady-state (baseline samples) and non–steady-state equations of Steele[32] in their derivative form. The effective volume of distribution for glucose was assumed to be 165 mL · kg^{-1}. The results are presented as the mean ± SEM. Data within experiments were analyzed by ANOVA and Fisher's least-significant difference test for multiple comparisons, as indicated. Data between experiments were analyzed by signed-rank test (data within one study) and by rank-sum analysis (data between studies). Statistical significance was set at P less than .05.

RESULTS

Glucose Metabolism and Substrate Concentrations

Study 1. Baseline values for plasma glucose and HGO were not different between the two studies. Baseline measurements of glucose specific activity indicated that isotopic steady state was reached in both studies after 2 hours of infusion of tritiated glucose. Glucose specific activity measured at 5-minute intervals was 317 ± 32 ($t = -10$ minutes), 314 ± 34 ($t = -5$ minutes), and 312 ± 31 ($t = 0$ minutes) dpm/μmol glucose in the saline experiment, and 290 ± 21, 288 ± 20, and 285 ± 20 dpm/μmol glucose before the start of pentoxifylline infusion. During the control study, plasma glucose decreased from 5.2 ± 0.1 ($t = 0$ hours) to 4.7 ± 0.1 mmol · L^{-1} ($t = 7$ hours, $P < .01$) and HGO decreased gradually from 12.2 ± 0.5 to 9.9 ± 0.7 μmol · kg^{-1} · min^{-1}, respectively ($P < .01$). During pentoxifylline infusion, the decrease in plasma glucose (from 5.3 ± 0.1 to 5.0 ± 0.1 mmol · L^{-1}, $P < .01$) was not different from the control study. During the first half-hour of pentoxifylline infusion, HGO decreased transiently by approximately 50% ($P < .05$), in contrast to a decrease of only approximately 4% in the control study within this interval ($P < .03$ *v* control study). However, subsequently, HGO returned to baseline values and was not different from the values obtained in the control study (Fig 1A).

Lactate concentrations did not change and were not different between the two experiments. FFA concentrations increased in both experiments ($P < .05$); the increase during pentoxifylline infusion tended to be greater

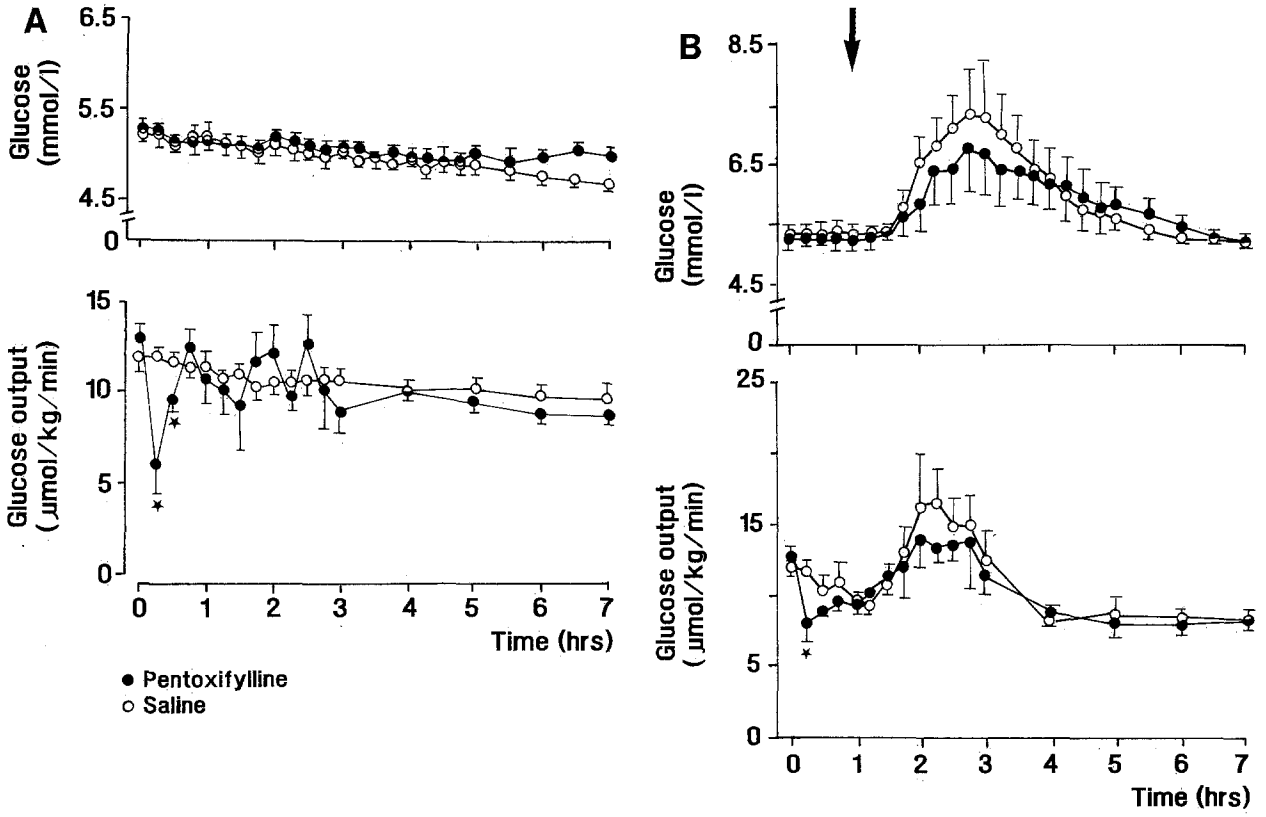

Fig 1. (A) Study 1: Effects of pentoxifylline infusion (●) versus saline infusion (○) on plasma glucose concentrations and HGO. Pentoxifylline infusion (2.1 mg · min^{-1}) was started at t = 0 hours and continued throughout the study (*P < .05, pentoxifylline v control). (B) Study 2: Effects of indomethacin alone (○) versus effects of indomethacin and pentoxifylline (●) on plasma glucose concentrations and HGO. Pentoxifylline infusion (2.1 mg · min^{-1}) was started at t = 0 hours and continued throughout the study; indomethacin (150 mg orally) was administered at t = 1 hour (arrow) (*P < .05, pentoxifylline v pentoxifylline and indomethacin).

(0.48 ± 0.06 mmol/L at t = 0 hours to 0.91 ± 0.08 mmol/L at t = 7 hours) than during the control study (0.36 ± 0.06 to 0.74 ± 0.06 mmol/L, P = .08).

Study 2. Baseline values for plasma glucose and HGO were not different among the two studies. Baseline glucose specific activity was 295 ± 11 (t = −10 minutes), 286 ± 18 (t = −5 minutes), and 286 ± 17 (t = 0 minutes) dpm/μmol glucose before indomethacin administration, and 262 ± 16, 259 ± 13, and 264 ± 22 dpm/μmol glucose, respectively, before combined pentoxifylline/indomethacin administration. Therefore, in both studies, isotopic steady state was reached before administration of the drugs. After indomethacin, plasma glucose and HGO increased (P < .05) transiently in all subjects by approximately 38% and 84%, respectively. During pentoxifylline infusion, plasma glucose concentration did not change during the hour before indomethacin was given, whereas HGO decreased transiently (P < .05) by approximately 30% (P < .05 indomethacin v indomethacin/pentoxifylline). However, after the first 0.75 hours of pentoxifylline infusion, there were no differences in plasma glucose concentration and HGO between the two studies. After administration of indomethacin at 1 hour, plasma glucose increased transiently (P < .05) by approximately 30% (NS, indomethacin v indomethacin/pentoxifylline). However, pentoxifylline did not significantly affect the increase in HGO induced by indomethacin (Fig 1B).

Lactate concentrations did not change in the indomethacin experiment (0.61 ± 0.11 mmol/L at t = 0 hours v 0.62 ± 0.09 mmol/L at t = 7 hours), but increased in the indomethacin/pentoxifylline experiment (from 0.62 ± 0.06 to 0.77 ± 0.12 mmol/L, P < .05; NS between both experiments). FFA concentrations did not change in the indomethacin experiment (0.58 ± 0.07 mmol/L at t = 0 hours v 0.64 ± 0.10 mmol/L at t = 7 hours), but increased in the indomethacin/pentoxifylline experiment (0.59 ± 0.07 v 1.00 ± 0.08 mmol/L, P < .01; P < .05 between both experiments).

Pentoxifylline Levels

Baseline levels of pentoxifylline were not detectable in studies 1 and 2. During pentoxifylline infusion, steady-state pentoxifylline levels (~2.5 μmol · L^{-1}) were reached after 2 hours in both study 1 and study 2. Pentoxifylline levels reached in study 1 during pentoxifylline infusion were not different from those in study 2 (Table 1).

Hormones

Study 1. Baseline values for insulin, C-peptide, and counterregulatory hormones were not different between

Table 1. Plasma Concentrations of Pentoxifylline (μmol/L) During Infusion of Pentoxifylline 2.1 mg · min^{-1} Versus Saline (study 1) and After Indomethacin Administration Without and With Infusion of Pentoxifylline (study 2)

Study	Time (h)					
	0	1	2	3	5	7
1						
Pentoxifylline	0 ± 0	2.1 ± 0.1*	2.6 ± 0.2*	2.4 ± 0.2*	2.5 ± 0.2*	2.8 ± 0.2*
Saline	0 ± 0	NM	NM	NM	NM	NM
2						
Indomethacin	0 ± 0	NM	NM	NM	NM	NM
Pentoxifylline + indomethacin	0 ± 0	1.9 ± 0.1*	2.7 ± 0.4*	2.2 ± 0.2*	2.3 ± 0.4*	2.1 ± 0.4*

Abbreviation: NM, not measured.
*$P < .01$ *v* basal.

the studies. Plasma concentrations of insulin, glucagon, and norepinephrine were not affected by pentoxifylline infusion. Plasma concentrations of C-peptide declined from 0.69 ± 0.14 to 0.54 ± 0.10 mmol/L ($P < .05$) in the control experiment and from 0.66 ± 0.14 to 0.54 ± 0.11 nmol/L ($P < .05$) during pentoxifylline infusion (NS, control *v* pentoxifylline study). Plasma epinephrine increased in the control study after 2 hours and did not change during pentoxifylline infusion (NS, pentoxifylline *v* control study). Plasma cortisol declined transiently in the control experiment ($P < .05$) and did not change during pentoxifylline infusion ($P < .05$ *v* control). Plasma growth hormone increased transiently ($P < .05$) in both experiments (NS, pentoxifylline *v* control study) (Fig 2A).

Study 2. Baseline values for insulin, C-peptide, and counterregulatory hormones were not different between the two studies. Plasma concentrations of insulin, glucagon, and epinephrine did not change and were not different between the two studies. Plasma C-peptide concentrations did not change after indomethacin administration (from 0.59 ± 0.08 at $t = 0$ hours to 0.55 ± 0.13 nmol/L at $t = 7$ hours) or after combined indomethacin/pentoxifylline administration (from 0.53 ± 0.08 to 0.60 ± 0.1 nmol/L, respectively, NS between groups). From 1.5 hours on, plasma norepinephrine declined gradually in the indomethacin experiment ($P < .05$ *v* $t = 1$ hour), whereas no changes occurred in the indomethacin/pentoxifylline experiment (NS, indomethacin/pentoxifylline *v* indomethacin). Plasma cortisol did not change in the indomethacin experiment and increased transiently between 2 hours and 3 hours in the indomethacin/pentoxifylline experiment ($P < .05$ *v* $t = 1$ hour; NS, indomethacin/pentoxifylline *v* indomethacin). Plasma growth hormone did not change in the indomethacin experiment and increased transiently in the indomethacin/pentoxifylline experiment ($P < .01$; $P < .05$ indomethacin/pentoxifylline *v* indomethacin experiment) (Fig 2B).

Cytokine Production

Leukocyte and monocyte counts were not different between the studies. Cytokine concentrations in supernatants of unstimulated whole blood (tubes A and B) were below detection levels in all experiments. There was no effect of pentoxifylline on in vitro cytokine production (study 1, Fig 3).

After administration of indomethacin, LPS-stimulated TNF, IL-1, and IL-6 production in whole blood increased by approximately 69%, 30%, and 17%, respectively ($P < .05$ *v* $t = 1$ hour). Pentoxifylline administration significantly inhibited this indomethacin-induced increase in cytokine production ($P < .05$).

DISCUSSION

Indomethacin administration increased HGO transiently by approximately 84% from 90 to 180 minutes after oral administration, in accordance with our previous observation.[16] This increase in HGO induced by indomethacin was not affected by pentoxifylline. This observation does not support the possibility that the increase in HGO induced by indomethacin is related to a modulation of paracrine cytokine production within the liver.

In addition to the major regulatory mechanisms of glucose production like hormones and substrate supply, there is in vitro evidence for the existence of intrahepatic paracrine mechanisms like prostaglandins and cytokines that modulate glucose production by hepatocytes. Unfortunately, the physiological relevance of paracrine factors cannot be ascertained directly in vivo, for obvious reasons. The relation between these paracrine factors and glucose production can be studied in vivo by administration of these factors or drugs that modulate the endogenous production of cytokines and prostaglandins. The effects of infusion of prostaglandins and cytokines on HGO are difficult to interpret, due to their pleiotropic effects. In previous studies, we infused TNF and IL-6 in volunteers, which resulted in a concomitant stimulation of glucose production and of glucagon, cortisol, and catecholamines.[9,33] Therefore, it remained unclear whether the effects of TNF and IL-6 on glucose production resulted from direct effects on hepatocytes or whether the increase in glucose production was merely mediated by stimulation of hormone secretion. In the present study, we evaluated the changes in glucose production induced by administration of indomethacin and of pentoxifylline, neither of which affect the secretion of glucoregulatory hormones. Indomethacin not only inhibits endogenous prostaglandin synthesis but also stimulates production of cytokines,[16-19,30] whereas pentoxifylline inhibits production of cytokines.[20-22] The increase in glucose production induced by indomethacin was not affected by pentoxifylline, despite the counteracting effects of indomethacin and pentoxifylline on cytokine production. Therefore, this observation supports the notion that indometha-

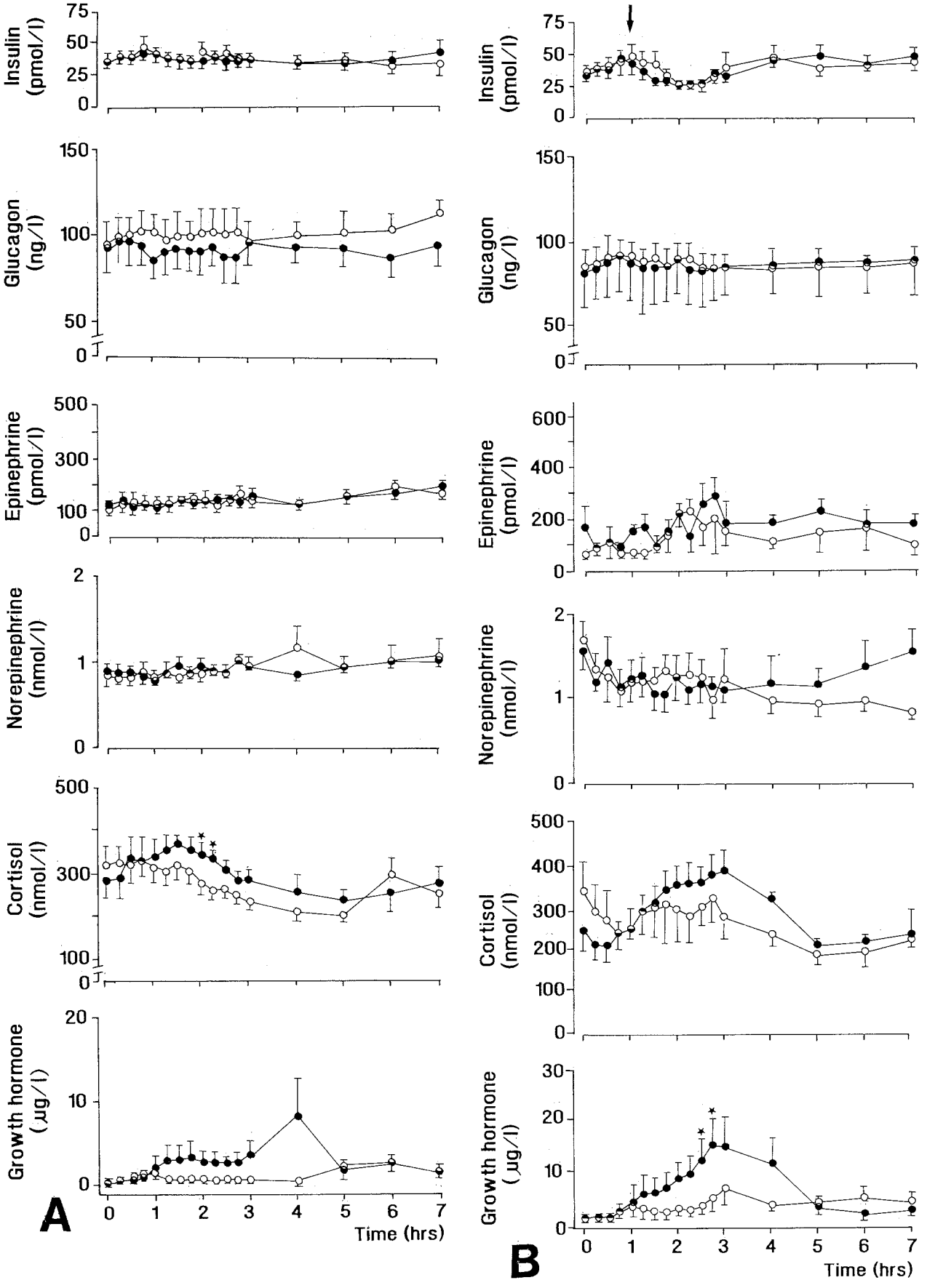
Insulin (pmol/l)
Glucagon (ng/l)
Epinephrine (pmol/l)
Norepinephrine (nmol/l)
Cortisol (nmol/l)
Growth hormone (μg/l)
A
B
Time (hrs)

Figure 2

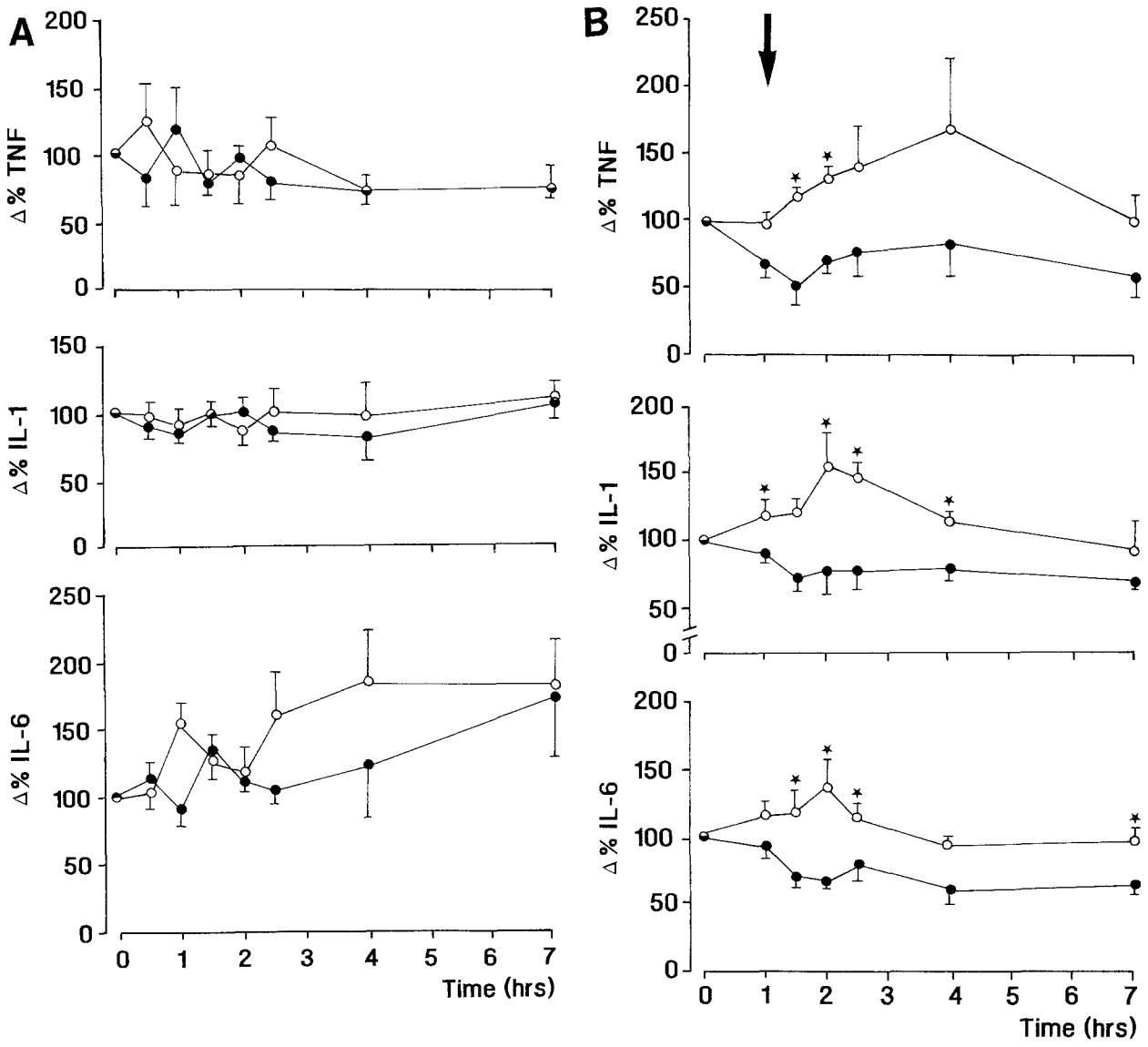

Fig 3. (A) Study 1: Effects of pentoxifylline infusion (○) versus saline infusion (●) on the relative change (%) in LPS-stimulated cytokine production (corrected for the number of monocytes). Pentoxifylline infusion (2.1 mg · min^{-1}) was started at t = 0 hours and continued throughout the study. There were no significant differences between the studies. (B) Study 2: Effects of indomethacin alone (○) versus effects of indomethacin and pentoxifylline (●) on the relative change (%) in LPS-stimulated cytokine production (corrected for the number of monocytes). Pentoxifylline infusion (2.1 mg · min^{-1}) was started at t = 0 hours and continued throughout the study; indomethacin (150 mg orally) was administered at t = 1 hour (arrow) (*P < .05, indomethacin v indomethacin and pentoxifylline).

cin does not modulate glucose production by modulation of cytokine production.

To provide support for this interpretation of the interaction of indomethacin and pentoxifylline, we measured cytokine production in blood obtained at regular intervals during both studies, because cytokine production in blood correlates with cytokine production by Kupffer cells after indomethacin administration.[17-19,30] Pentoxifylline, a xanthine oxidase inhibitor, inhibits "immediate early" gene activation by monocytes, resulting in decreased cytokine responses (eg, of TNF and IL-6) to endotoxin in vitro and in vivo, but also to other stimuli such as phytohemagglutinin.[34,35] The effects of pentoxifylline on indomethacin-induced changes in cytokine production have not been

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Fig 2. (A) Study 1: Effects of pentoxifylline infusion (●) versus saline infusion (○) on plasma concentrations of glucoregulatory hormones. Pentoxifylline infusion (2.1 mg · min^{-1}) was started at t = 0 hours and continued throughout the study (*P < .05, pentoxifylline v control). (B) Study 2: Effects of indomethacin alone (○) versus effects of indomethacin and pentoxifylline (●) on plasma concentrations of glucoregulatory hormones. Pentoxifylline infusion (2.1 mg · min^{-1}) was started at t = 0 hours and continued throughout the study; indomethacin (150 mg orally) was administered at t = 1 hour (arrow) (*P < .05, indomethacin v indomethacin and pentoxifylline).

documented previously. The effect of indomethacin and pentoxifylline on cytokine levels was not detectable in unstimulated blood in healthy volunteers. However, pentoxifylline has been shown to inhibit TNF mRNA expression in vivo.[36] Because we did not have this assay available, we used the model of LPS-stimulated blood. It is of interest that the effects of indomethacin on in vitro cytokine production but not on HGO were reversed by pentoxifylline.

Theoretically, the possibility cannot be excluded that pentoxifylline and/or indomethacin affect the volume of distribution of 3-^{3}H-glucose. However, since this would affect tracer and tracee similarly, it would not influence glucose specific activity and, as a consequence, the calculation of hepatic glucose production. Although pentoxifylline may increase splanchnic perfusion independently of changes in cardiac output,[37] no relationship has been shown between physiological changes in splanchnic blood flow and HGO. Even when pentoxifylline would increase splanchnic blood flow, it seems unlikely that an increase in blood flow inhibits HGO.

In addition to an effect on cytokine production,[20-22] xanthine derivatives like pentoxifylline block the adenosine receptor.[38] In vitro experiments in cultured hepatocytes show that adenosine has a transient stimulatory effect on basal glycogenolysis, lasting only about 30 minutes.[39,40] Remarkably, the inhibition of basal HGO by pentoxifylline occurred in the absence of changes in cytokine production and lasted only approximately 45 minutes. Therefore, it is possible that the initial inhibition of basal HGO by pentoxifylline was mediated by other paracrine mechanisms (eg, by blockade of the adenosine receptor).

In conclusion, indomethacin stimulates HGO without affecting plasma concentrations of glucoregulatory hormones. This increase in HGO by indomethacin is not affected by pentoxifylline, despite counteracting effects of indomethacin and pentoxifylline on in vitro cytokine production. Therefore, indomethacin stimulates HGO by mechanisms unrelated to glucoregulatory hormones, prostaglandins, or cytokines.

ACKNOWLEDGMENT

We are indebted to the Laboratory of Endocrinology for technical assistance and to M. Ackermans for performing the pentoxifylline assay. We thank W.A. Buurman for kindly donating the TNF antibodies.

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