Indomethacin Stimulates Glucose Production in Adults With Uncomplicated Falciparum Malaria

Evelien Dekker, Johannes A. Romijn, Huynh Van Thien, Mariette T. Ackermans, Erik Endert, Piet A. Kager, Le Thi Diem Thuy, and Hans P. Sauerwein

In healthy subjects, basal hepatic glucose production is (partly) regulated by paracrine intrahepatic factors. It is unknown if these paracrine factors also influence basal glucose production in infectious diseases with increased glucose production. We compared the effects of 150 mg indomethacin (n = 9), a nonendocrine stimulator of glucose production in healthy adults, and placebo (n = 7) on hepatic glucose production in Vietnamese adults with uncomplicated falciparum malaria. Glucose production was measured by primed, continuous infusion of [6,6-$^2H_2$]glucose. After indomethacin, the plasma glucose concentration and glucose production increased in all subjects from 5.3 ± 0.1 mmol/L to a maximum of 7.1 ± 0.3 mmol/L ($P < .05$) and from 17.6 ± 0.8 μmol · kg^{-1} · min^{-1} to a maximum of 26.2 ± 2.5 μmol · kg^{-1} · min^{-1} ($P < .05$), respectively. In the control group, the plasma glucose concentration and glucose production declined gradually during 4 hours from 5.4 ± 0.2 mmol/L to 5.1 ± 0.1 mmol/L ($P < .05$) and from 17.1 ± 0.8 μmol · kg^{-1} · min^{-1} to 15.1 ± 1.0 μmol · kg^{-1} · min^{-1} ($P < .05$), respectively. There were no differences in plasma concentrations of insulin, counterregulatory hormones, or cytokines between the groups. We conclude that indomethacin administration results in a transient increase in glucose production in patients with uncomplicated falciparum malaria in the absence of changes in plasma concentrations of glucoregulatory hormones or cytokines. Thus, this study indicates that in uncomplicated falciparum malaria, the rate of basal hepatic glucose production is also regulated by paracrine intrahepatic factors.

GLUCOSE PRODUCTION is regulated by the interplay of several mechanisms. Major factors involved in the regulation of glucose production are the gluconeogenic precursor supply, the classic glucoregulatory hormones, and the plasma glucose concentration. In healthy adults, gluconeogenic precursor supply does not play a major role in the regulation of overall glucose output in the postabsorptive state unless the supply diminishes below a certain level.[1,2] Of all the classic hormones, the ratio between plasma insulin and glucagon concentrations seems to be the main determinant of glucose production.[3] However, when somatostatin is infused, glucose production decreases only transiently, suggesting that these hormones are not pivotal for maintenance of basal glucose production.[4] This suggestion is supported by the observation that changes in plasma glucose influence glucose production independently of changes in glucoregulatory hormones, a process frequently referred to as autoregulation.[5] These data together indicate that other, probably intrahepatic, mechanisms must be operative in maintaining basal glucose production. Potential mediators of this process are Kupffer cell products. 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. In these studies, it has been shown that stimulated Kupffer cells produce prostaglandins,[6] which in turn modulate hepatic glycogenolysis.[7-9] Other Kupffer cell products are cytokines (like tumor necrosis factor [TNF] and interleukin-6 [IL-6]) and nitric oxide,[6,10] which also affect glucose production.[11-13] In vivo in healthy adults, indomethacin (a prostaglandin synthesis inhibitor) stimulates hepatic glucose production by mechanisms unrelated to factors outside the liver.[14] This observation suggests that in healthy adults basal glucose production is not maximally stimulated, but is partly inhibited, possibly by paracrine intrahepatic factors like prostaglandins. It is unknown if these paracrine factors also influence basal glucose production in infectious diseases with increased glucose production such as malaria.

In uncomplicated falciparum malaria, glucose production is increased by 25%.[15] Theoretically, in patients with malaria, as in healthy subjects, the rate of glucose production can also be influenced by intrahepatic paracrine factors like prostaglandins. In this case, indomethacin should be able to increase the rate of glucose production. As glucose production is maximized, it can be hypothesized that under circumstances of increased basal glucose production, the inhibiting influence of intrahepatic paracrine factors is lessened; the effect of indomethacin will then be reduced.

To evaluate the effects of indomethacin on glucose production, we measured glucose production by infusion of [6,6-$^2H_2$]glucose before and after oral administration of 150 mg indomethacin or placebo in patients with uncomplicated falciparum malaria.

SUBJECTS AND METHODS

Subjects

Sixteen consecutive patients with uncomplicated falciparum malaria admitted to Bao Loc General Hospital, Lam Dong Province, Vietnam, were recruited. Nine patients were allocated to the indomethacin protocol, and seven patients served as controls and received placebo. Exclusion criteria were as follows: complicated malaria according to World Health Organization criteria,[16] pregnancy, age less than 16 years, treatment with quinine (quinine stimulates insulin secretion[17]), concomitant infectious disease, and severe malnutrition. Each patient provided

From the Metabolism Unit, Department of Internal Medicine, and the Department of Infectious Diseases, Tropical Medicine and AIDS, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands; Bao Loc General Hospital, Lam Dong Province; and the Tropical Diseases Research Center, Cho Ray Hospital, Ho Chi Minh City, Vietnam.

Submitted April 12, 1997; accepted August 18, 1997.

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

Address reprint requests to Hans P. Sauerwein, MD, Metabolism Unit, Department of Internal Medicine (F4-222), Academic Medical Center, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands.

0026-0495/98/4702-0018$03.00/0

informed consent. The study protocol was approved by the institutional review board of Cho Ray Hospital, Ho Chi Minh City, under whose jurisdiction research in the Lam Dong Provincial Hospital is performed.

Study Design

Patients were recruited immediately after laboratory confirmation of the clinical diagnosis and exclusion of quinine use by a quinine dipstick test.[18] Each patient was treated with artemisinine derivatives.[19] On the day of admission, all subjects had a standard dinner at 6 PM, followed by a fast, except for water ingestion, until completion of the study.

The study design is shown in Fig 1. On the morning after admission, an intravenous cannula was inserted into a forearm vein for isotope infusion. A second cannula for blood sampling was introduced into a suitable vein of the contralateral arm. The catheters were kept patent by a slow isotonic saline infusion.

After obtaining a baseline blood sample for determination of background isotopic enrichment, plasma glucose, and basal hematologic and biochemical tests, a primed (3.2 mg/kg), continuous (40 $\mu g \cdot kg^{-1} \cdot min^{-1}$) infusion of [6,6-$^2H_2$]glucose (99%; Isotec, Miamisburg, OH) dissolved in sterile isotonic saline and sterilized by passage of the solution through a millipore filter (0.2 μm, Minisart; Sartorius, Göttingen, Germany) was administered by a motor-driven, calibrated syringe pump (Perfusor Secura FT; Braun, Melsungen, Germany). The rate of [6,6-$^2H_2$]glucose infusion was calculated from the measured concentration of glucose in the infusate. After 90 minutes of [6,6-$^2H_2$]glucose infusion for equilibration, three blood samples were collected at intervals of 15 minutes for determination of the plasma glucose concentration and [6,6-$^2H_2$]glucose enrichment. Blood samples for measurement of plasma concentrations of insulin, counterregulatory hormones, cytokines, alanine, and lactate were also collected after 120 minutes.

At time 0, after 2 hours of [6,6-$^2H_2$]glucose infusion, either 150 mg indomethacin or placebo was administrated. Blood samples for measurement of the plasma glucose concentration and [6,6-$^2H_2$]glucose enrichment were obtained every 15 minutes for the first 2 hours after the intervention and every 30 minutes for the last 2 hours of the study. Samples for determination of plasma insulin, counterregulatory hormones, and cytokines were collected every 30 minutes until the end of the study, and a blood sample for plasma alanine and lactate was obtained again at the end of the study.

Blood samples for plasma glucose, [6,6-$^2H_2$]glucose enrichment, insulin, counterregulatory hormones, and cytokines were collected in prechilled heparinized tubes, and samples for alanine and lactate in fluoride tubes. All samples were kept on ice and centrifuged promptly. Aliquots of separated plasma were stored at less than −20°C and were transported on dry ice before assay.

Assays

All measurements were performed in duplicate, and all samples from each individual subject were analyzed in the same run. The glucose concentration and [6,6-$^2H_2$]glucose enrichment in plasma were measured by gas chromatography/mass spectrometry using selected ion monitoring. The method was adapted from Reinauer et al,[20] using phenyl-β-D-glucose as an internal standard.

The plasma insulin concentration was measured by commercial radioimmunoassay (RIA) (Pharmacia Diagnostics, Uppsala, Sweden), glucagon by RIA (Daiichi Radioisotope Laboratories, Tokyo, Japan; glucagon antiserum raised in guinea pigs against pancreatic-specific glucagon, cross-reactivity with glucagon-like substances of intestinal origin < 1%), and cortisol by fluorescence polarization immunoassay on TDx (Abbott Laboratories, Chicago, IL). Catecholamines were determined by high-performance liquid chromatography with fluorescence detection.[21]

The plasma alanine concentration was determined by an amino acid analyzer (Chromocon 500; Tegimenta AG, Rotkreuz, Switzerland), and plasma lactate by an enzymatic method (Boehringer Mannheim, Almere, The Netherlands) on a Cobas Bio centrifugal analyzer (Boehringer Mannheim, Mannheim, Germany).

Cytokine assays. TNF concentrations were measured by an enzyme-amplified sensitivity immunoassay (EASIA; Medgenix, Amersfoort, The Netherlands) with a detection limit of 5 pg/mL. Soluble TNF receptors type I and type II were assayed by an EASIA (Medgenix) with a detection limit of 0.1 and 0.5 ng/mL, respectively. Plasma concentrations of IL-1 were measured by an immunoradiometric assay (Medgenix) with a detection limit of 10 pg/mL, and IL-6 was determined by an enzyme-linked immunosorbent assay (CLB, Amsterdam, The Netherlands) with a detection limit of 2 pg/mL.

Calculations and Statistics

Glucose output was calculated by the steady-state (baseline samples) and non–steady-state equations of Steele[22] in their derivative form. The effective volume of distribution for glucose was assumed to be 165 mL/kg.

Results are reported as the mean ± SEM unless otherwise stated. Data within the groups were analyzed by ANOVA for randomized block design, and by Fisher's least-significant difference test for multiple comparisons when indicated. Data between the groups were analyzed by the Mann-Whitney *U* test. Statistical significance was set at *P* less than .05.

RESULTS

Clinical Data

Sixteen Vietnamese adults with uncomplicated acute falciparum malaria were studied: nine (eight men) in the indomethacin group and seven (six men) in the control group. Clinical and laboratory characteristics of both groups are listed in Table 1. There were no significant differences between the groups for

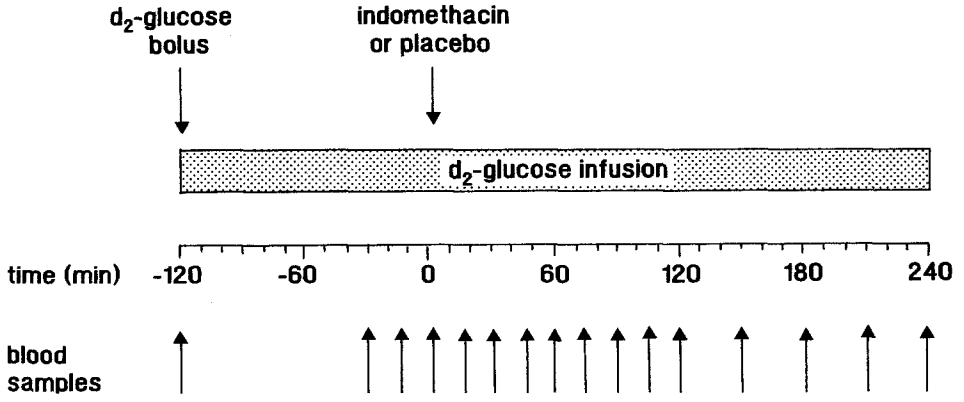

Fig 1. Study design.

any clinical or laboratory parameters. In both groups, values obtained in the women were not different from those in the men. Therefore, they are not described separately. All patients responded quickly to therapy and had an uneventful recovery.

Glucose Kinetics

The baseline plasma glucose concentration and glucose production rate were not different between the two groups. After indomethacin, the plasma glucose concentration and glucose production increased in all subjects from 5.3 ± 0.1 mmol/L to a maximum of 7.1 ± 0.3 mmol/L (or 34% ± 4%, $P < .05$) and from 17.6 ± 0.8 μmol · kg^{-1} · min^{-1} to a maximum of 26.2 ± 2.5 μmol · kg^{-1} · min^{-1} (or 61% ± 25%, $P < .05$; Fig 2). The maximal rate of glucose production after indomethacin occurred at different time points in the different patients, varying from $t = 30$ to $t = 120$ minutes. Compared with the control values, the plasma glucose concentration and glucose production increased significantly after indomethacin administration (Fig 2).

In the control group, the plasma glucose concentration and glucose production declined gradually during 4 hours from 5.4 ± 0.2 mmol/L to 5.1 ± 0.1 mmol/L (or 5% ± 2%, $P < .05$) and from 17.1 ± 0.8 μmol · kg^{-1} · min^{-1} to 15.1 ± 1.0 μmol · kg^{-1} · min^{-1} (or 12% ± 2%, $P < .05$), respectively (Fig 2).

Hormones

Baseline plasma concentrations of insulin and counterregulatory hormones were not different between the two groups (Fig 3). Plasma concentrations of insulin, cortisol, glucagon, and adrenaline were not significantly different between the two groups at any time point. Plasma noradrenaline concentrations were different between the groups only at $t = 120$ minutes ($P = .04$).

Cytokines

Baseline plasma concentrations of TNF and IL-6 were not different between the two groups, and plasma concentrations of these cytokines were not significantly different between the two groups at any time point (Fig 4).

Table 1. Clinical and Laboratory Characteristics of 16 Adult Patients With Uncomplicated Malaria

Characteristic	Indomethacin (n = 9)	Placebo (n = 7)
Age (yr)	28.3 ± 2.8	24.3 ± 1.9
BMI	18.2 ± 0.8	18.9 ± 0.3
Body temperature (°C)	37.7 ± 0.3	37.7 ± 0.3
Duration of illness (d)	3.6 ± 0.5	4.6 ± 1.1
Parasitemia (/μL)	3,500 (60-81,120)	4,425 (351-23,916)
Hemoglobin (g/dL)	13.2 ± 0.7	13.2 ± 0.2
AST (U/L)	9 ± 1	8 ± 1
ALT (U/L)	11 ± 3	9 ± 2
Bilirubin (mg/dL)	1.2 ± 0.3	0.9 ± 0.1
Creatinine (mg/dL)	1.0 ± 0.1	1.0 ± 0.1

NOTE. Values are the mean ± SEM, except for parasitemia (median and range). There were no significant differences between the groups.

Abbreviations: BMI, body mass index; AST, aspartate transaminase; ALT, alanine transaminase.

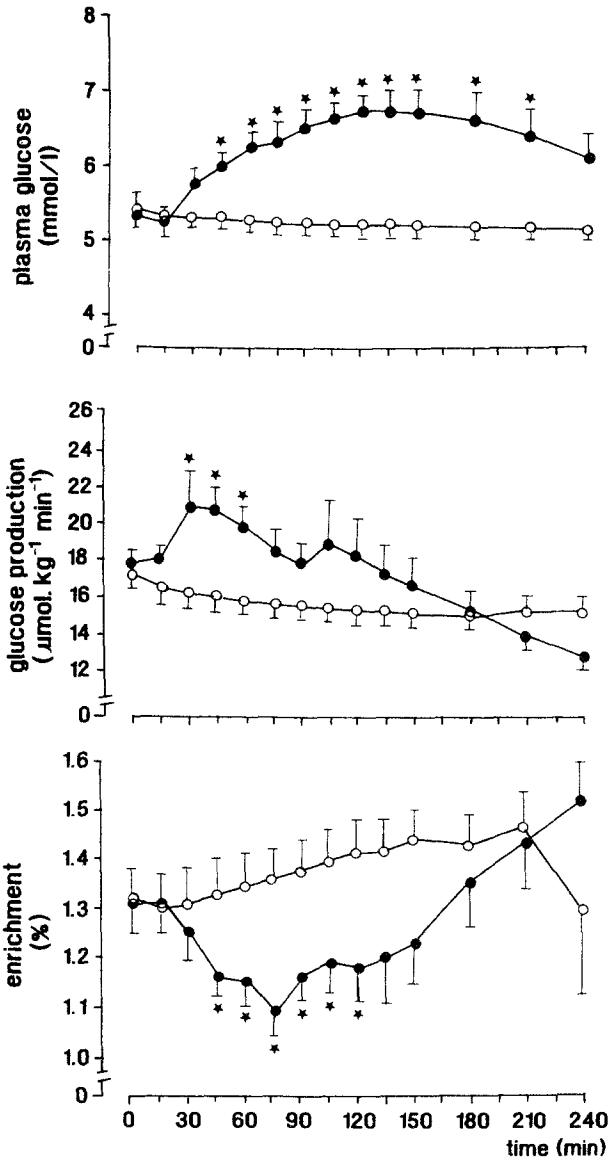

Fig 2. Effects of indomethacin (●) and placebo (○) on the plasma glucose concentration, glucose production, and enrichment in adults with uncomplicated malaria. Values are the mean ± SEM. *$P < .05$ *v* placebo.

DISCUSSION

Administration of the prostaglandin synthesis inhibitor indomethacin to patients with uncomplicated falciparum malaria resulted in a transient 3-hour 61% increase in glucose production associated with increased plasma glucose. This stimulatory effect of indomethacin on glucose production was not explained by any change in the plasma concentration of insulin, counterregulatory hormones, or cytokines. Therefore, from the data obtained in our study, we conclude that indomethacin stimulates glucose production in patients with uncomplicated falciparum malaria through mechanisms unrelated to changes in the plasma concentration of glucoregulatory hormones or cytokines. However, since no samples were obtained from the portal vein, these data do not preclude the possibility that pancreatic hormones or cytokines in the portal vein were different between the two

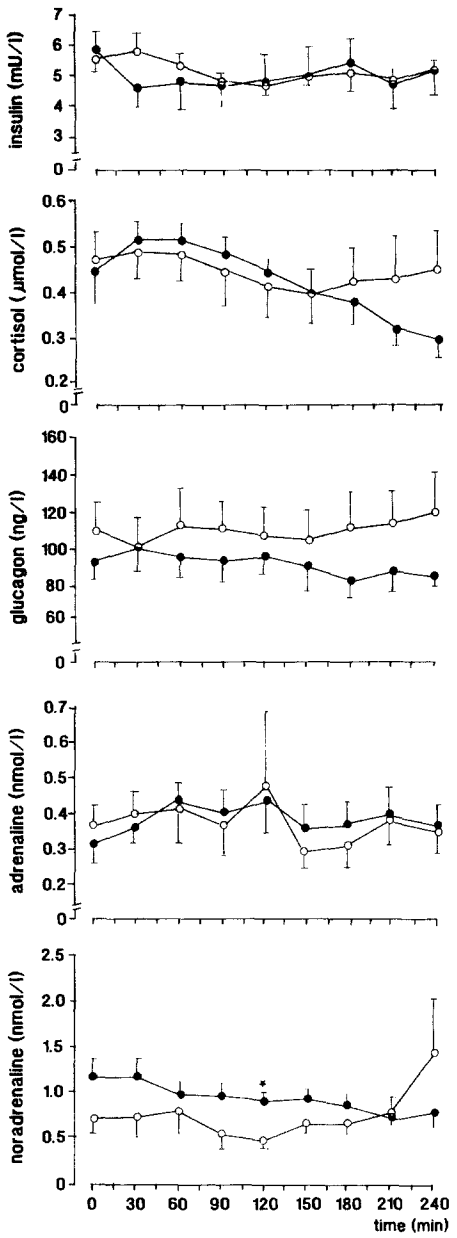

Fig 3. Effects of indomethacin (●) and placebo (○) on the plasma concentration of insulin and counterregulatory hormones in adults with uncomplicated malaria. Values are the mean ± SEM. *$P < .05$ *v* placebo.

groups. This study indicates that in uncomplicated falciparum malaria, the rate of basal hepatic glucose production is also regulated by prostaglandins.

Theoretically, the possibility cannot be excluded that indomethacin affects the volume of distribution of [6,6-$^2H_2$]glucose. However, since this effect of indomethacin would affect the tracer and tracee similarly, this would not influence glucose enrichment and, as a consequence, the calculation of glucose production.

The waning effect of indomethacin evident 30 minutes after administration is probably not due to diminishing drug levels. Following oral administration, absorption of the drug is rapid and complete, with peak plasma levels achieved after 1 to 2 hours. The biological half-life of the drug is about 5 to 10 hours.[23] The waning effect on glucose production can be ascribed to an autoregulatory response by the liver, as it is well known that increased plasma glucose inhibits glucose production in humans independently of changes in glucoregulatory hormones.[24] The absence of an increase in plasma insulin despite a significant increase in plasma glucose is explained by the inhibiting effect of indomethacin on glucose-stimulated insulin secretion.[25]

The relative change in glucose production and plasma glucose (61% and 34%, respectively) suggests that the increase in plasma glucose is caused by the increase in glucose production rather than by a decrease in glucose uptake. However, an effect on peripheral glucose uptake cannot be excluded. The published data on the effects of indomethacin on peripheral glucose uptake are conflicting. Some studies described an inhibitory effect of indomethacin on insulin-stimulated glucose uptake in muscle/adipose tissue,[26,27] whereas another study reported no effect of indomethacin on insulin-stimulated glucose uptake.[28] Consequently, the possibility exists that the peripheral effects of indomethacin contribute to the degree of increase in plasma glucose in addition to the change in hepatic glucose production.

Previously, we have shown that glucose production in Vietnamese adults with uncomplicated falciparum malaria is increased by 25%.[15] We have also shown that in healthy caucasian adults, fasting from 14 to 20 hours decreases glucose production by 18%.[14] In the present study, glucose production

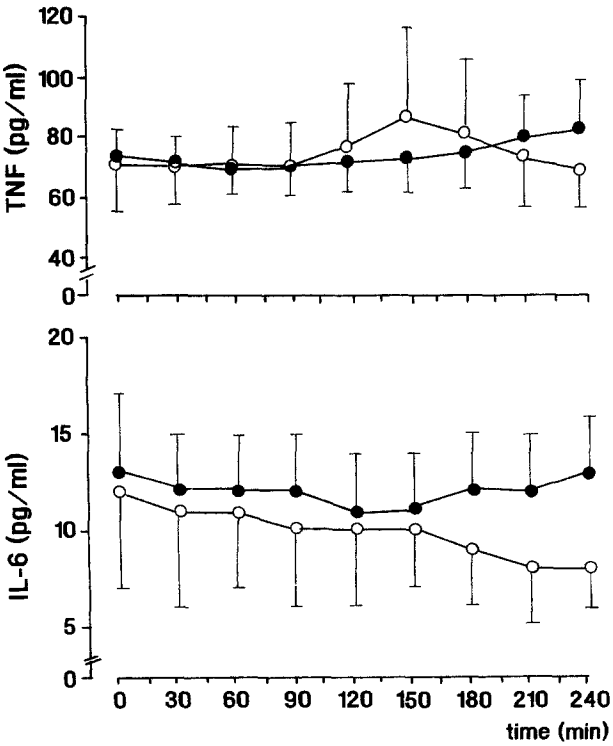

Fig 4. Effects of indomethacin (●) and placebo (○) on the plasma concentration of TNF and IL-6 in adults with uncomplicated malaria. Values are the mean ± SEM.

decreased gradually by 12% in Vietnamese subjects with uncomplicated malaria who did not receive indomethacin. These data indicate that the response to short-term fasting is similar in healthy caucasian adults and Vietnamese subjects with uncomplicated falciparum malaria, despite higher basal glucose production rates in the latter. We have also shown that administration of indomethacin to healthy caucasians induces a 31% increase in glucose production that lasts for 1 hour.[14] In the present study, indomethacin induced a 61% increase that lasted for about 3 hours. These data suggest that, contrary to expectation, the role of prostaglandins in the regulation of basal glucose production is more important in uncomplicated falciparum malaria patients than in healthy subjects.

In this study, we administered indomethacin, a prostaglandin synthesis inhibitor. Inhibition of prostaglandin synthesis by indomethacin resulted in an increase in glucose production and plasma glucose in patients with uncomplicated falciparum malaria. These results are in contradiction with in vitro animal studies, in which it has been shown that stimulated Kupffer cells produce prostaglandins, which in turn stimulate hepatic glycogenolysis.[7-9] However, our data are in accordance with data obtained in healthy adults, in whom indomethacin stimulated glucose production.[14] The discrepancy between the effects of prostaglandins in vitro and the modulation of prostaglandin synthesis in vivo could be explained by differences in the regulation of these processes between animals and humans or by other effects of indomethacin besides its influence on prostaglandins.

Indomethacin not only inhibits prostaglandin synthesis but also modulates cytokine production, probably indirectly by inhibiting the synthesis of prostaglandins.[29-31] Kupffer cells produce several cytokines.[6] TNF and IL-6 can stimulate glucose production in humans.[11,12] Basal levels of TNF and IL-6 in this study were elevated concomitantly with the increase in glucose production. These cytokines could therefore contribute to the elevated glucose production before indomethacin administration in our malaria patients. After indomethacin administration, plasma concentrations of TNF and IL-6 did not change, and changes in the plasma concentration of these cytokines therefore do not explain the increase in glucose production induced by indomethacin in these patients. Several studies have shown changes in the production of cytokines within tissues without a concurrent elevation of the circulating levels.[32-34] Therefore, the absence of changes in the plasma level of the cytokines after indomethacin does not preclude the possibility that a paracrine influence by cytokines inside the liver is an operative mechanism in uncomplicated falciparum malaria.

In this respect, Kupffer cell products are probably important mediators. In the literature, there is evidence that *Plasmodium falciparum* pigment from parasites sequestered in the host microvasculature stimulates monocytes and macrophages to release TNF and IL-1.[35] Malaria pigment is also taken up by Kupffer cells in the liver.[36,37] After stimulation, Kupffer cells produce prostaglandins, various cytokines, and nitric oxide,[38] products with a known influence on glucose production.[7-9,11-13] Therefore, these mediators may contribute to the regulation of glucose production in falciparum malaria. However, since it is difficult to evaluate the paracrine interaction of Kupffer cells and hepatocytes in vivo, this remains an interesting speculation.

In conclusion, indomethacin administration produced a transient increase in glucose production, resulting in increased plasma glucose in uncomplicated falciparum malaria patients. This stimulatory effect of indomethacin on glucose production was not explained by any change in the plasma concentration of glucoregulatory hormones or cytokines. Thus, basal glucose production in patients with uncomplicated falciparum malaria is possibly regulated also by other, most likely intrahepatic, factors, probably including prostaglandin.

ACKNOWLEDGMENT

We are indebted to the doctors, nurses, and laboratory staff of Cho Ray Hospital, Ho Chi Minh City, and Bao Loc General Hospital, Lam Dong Province, Vietnam, for their collaboration; to An Ruiter, Jan de Jong, and the other technicians of the Endocrinology Laboratory in the Academic Medical Center for their assistance; and to Theunis Eggelte for providing the quinine dipsticks.

REFERENCES

1. Jahoor F, Peters EJ, Wolfe RR: The relationship between gluconeogenic substrate supply and glucose production in humans. Am J Physiol 258:E288-E296, 1990

2. Jenssen T, Nurjhan N, Consoli A, et al: Failure of substrate-induced gluconeogenesis to increase overall glucose appearance in normal humans. J Clin Invest 86:489-497, 1990

3. Cherrington AD, Chiasson JL, Liljenquist JE, et al: The role of insulin and glucagon in the regulation of basal glucose production in the postabsorptive dog. J Clin Invest 58:1407-1418, 1976

4. Liljenquist JE, Mueller GL, Cherrington AD, et al: Evidence for an important role of glucagon in the regulation of hepatic glucose production in normal man. J Clin Invest 59:369-374, 1977

5. Müller MJ, Möring J, Seitz HJ: Regulation of hepatic glucose output by glucose in vivo. Metabolism 37:55-60, 1988

6. Decker K: Biologically active products of stimulated liver macrophages (Kupffer cells). Eur J Biochem 192:245-261, 1990

7. Casteleijn E, Kuiper J, van Rooij HC, et al: Hormonal control of glycogenolysis in parenchymal liver cells by Kupffer and endothelial liver cells. J Biol Chem 263:2699-2703, 1988

8. Casteleijn E, Kuiper J, van Rooij HC, et al: Conditioned media of Kupffer and endothelial liver cells influence protein phosphorylation in parenchymal liver cells. Biochem J 252:601-605, 1988

9. Kuiper J, Zijlstra FJ, Kamps JA, et al: Cellular communication inside the liver. Binding conversion and metabolic effects of prostaglandin D_2 on parenchymal liver cells. Biochem J 262:195-201, 1989

10. Magilavy DB, Rothstein JL: Spontaneous production of tumor necrosis factor α by Kupffer cells of MRL/lpr mice. J Exp Med 168:789-794, 1988

11. Van der Poll T, Romijn JA, Endert E, et al: Tumor necrosis factor mimics the metabolic response to acute infection in healthy humans. Am J Physiol 216:E457-E465, 1991

12. Stouthard JML, Romijn JA, Van der Poll T, et al: Endocrinologic and metabolic effects of interleukin-6 in humans. Am J Physiol 286:E813-E819, 1995

13. Horton R, Titheradge A: Inhibition of hepatic gluconeogenesis by nitric oxide: A comparison with endotoxemic shock. Biochem J 299:735-739, 1994

14. Corssmit EPM, Romijn JA, Endert E, et al: Indomethacin stimulates basal glucose production in humans without changes in concentrations of glucoregulatory hormones. Clin Sci 85:679-685, 1993

15. Dekker E, Romijn JA, Ekberg K, et al: Glucose production and

gluconeogenesis in adults with uncomplicated malaria. Am J Physiol 272:E1059-E1065, 1997

16. World Health Organization: Severe and complicated malaria. Trans R Soc Trop Med Hyg 80:3-50, 1996

17. Henquin JC, Horemans B, Nenquin M, et al: Quinine-induced modifications of insulin release and glucose metabolism by isolated pancreatic islet cells. FEBS Lett 57:280-284, 1975

18. Silamut K, Hough T, Eggelte T, et al: Simple methods for assessing quinine pre-treatment in acute malaria. Trans R Soc Trop Med Hyg 89:665-667, 1995

19. Hien TT, White NJ: Qinghaosu. Lancet 341:603-608, 1993

20. Reinauer H, Gries FA, Hübinger A, et al: Determination of glucose turnover and glucose oxidation rates in man with stable isotope tracers. J Clin Chem Clin Biochem 28:505-511, 1990

21. Somsen GA, Dubois EA, Brandsma K, et al: Cardiac sympathetic neuronal function in left ventricular volume and pressure overload. Cardiovasc Res 31:132-138, 1996

22. Steele R: Influences of glucose loading and of injected insulin on hepatic glucose output. Ann NY Acad Sci 82:120-130, 1959

23. Helleberg L: Clinical pharmacokinetics of indomethacin. Clin Pharmacokinet 6:245-258, 1981

24. Sacca L, Hendler R, Sherwin RS: Hyperglycemia inhibits glucose production in man independent of changes in glucoregulatory hormones. J Clin Endocrinol Metab 47:1160-1163, 1978

25. Topol E, Brodows RG: Effects of indomethacin on acute insulin release in man. Diabetes 29:379-382, 1980

26. Richelsen B, Hjollund E, Pedersen O, et al: Effects of prostaglandin E_2, indomethacin and adenosine deaminase on basal and insulin-stimulated glucose metabolism in human adipocytes. Biochim Biophys Acta 844:359-366, 1985

27. Segal S, Blair A, Weinberg A: In vitro effects of salicylate on carbohydrate metabolism. Metabolism 9:1033-1046, 1960

28. Zorzano A, Balon TW, Jakubowski JA, et al: Effects of insulin and prior exercise on prostaglandin release from perfused rat muscle. Biochem J 240:437-443, 1986

29. Shirahama M, Ishibushi H, Tsuchiya Y, et al: Kupffer cells may autoregulate interleukin I production by producing interleukin I inhibitor and prostaglandin E_2. Scand J Immunol 28:719-725, 1988

30. Callery MP, Mangino MJ, Kamei T, et al: Interleukin-6 production by endotoxin-stimulated Kupffer cells is regulated by prostaglandin E_2. J Surg Res 48:523-527, 1990

31. Endres S, Cannon JG, Ghorbani R: In vitro production of IL Iβ, IL Iα, TNF and IL 2 in healthy subjects: Distribution, effect of cyclooxygenase inhibition and evidence of independent gene regulation. Eur J Immunol 19:2327-2333, 1989

32. Keogh C, Fong Y, Marano MA, et al: Identification of a novel tumor necrosis factor α/cachectin from the livers of burned and infected rats. Arch Surg 125:79-85, 1990

33. Tracey KJ, Cerami A: Tumor necrosis factor and regulation of metabolism in infection: Role of systemic versus tissue levels. Proc Soc Exp Biol Med 200:233-239, 1992

34. Suter PM, Suter S, Girardin E, et al: High bronchoalveolar levels of tumor necrosis factor and its inhibitors, interleukin 1, interferon, and elastase, in patients with adult respiratory distress syndrome after trauma, shock, or sepsis. Am Rev Respir Dis 145:1016-1022, 1992

35. Pichyangkul S, Saengkrai P, Webster HK: Plasmodium falciparum pigment induces monocytes to release high levels of tumor necrosis factor-α and interleukin-1β. Am J Trop Med Hyg 51:430-435, 1994

36. Ramachandran S, Perera MVF: Jaundice and hepatomegaly in primary malaria. J Trop Med Hyg 79:207-210, 1976

37. Boonpucknavig V, Boonpucknavig S: The histopathology of malaria, in Wernsdorfer WH, McGregor IA (eds): Malaria, vol 4. London, UK, Churchill Livingstone, 1988, pp 673-707

38. Roland CR, Goss JA, Mangino MJ, et al: Autoregulation by eicosanoids of human Kupffer cell secretory products. A study of interleukin-1, interleukin-6, tumor necrosis factor-alfa, transforming growth factor-beta, and nitric oxide. Ann Surg 219:389-399, 1994