

1.1 ± 0.2 were bound to the column and were eluted by 30 mM and 1 M HCl, respectively.

We concluded that the amount of unsaturated FA in each fraction ($\approx 50\%$ of FA bound to glycogen, $\approx 90\%$ of FA in eluted fractions) may have accounted for the inhibition of Glc6Pase since it was shown that free but not bound unsaturated FA could inhibit the enzyme in vitro in relevant concentrations.

Effects of lipid infusion on postabsorptive glycemia in non insulin dependent diabetes mellitus (NIDDM). V Rigalleau, E De Tinguy, A Iron, J Aubertin, H Gin (*Clinique médicale, Tripode, 33000 Bordeaux, France*)

As proposed by Randle, lipid–glucid interactions may play a role in the hyperglycemia of NIDDM. We previously reported a hyperglycemic effect of a lipid infusion in the postabsorptive state in NIDDM patients [Rigalleau (1994) *Metabolism* 43, 1300]. This paper describes how we studied its mechanism in 30 NIDDM patients. Fifteen received a 180 min lipid infusion ('Ivélip 20%'; 0.015 mL/kg/min) and 15 received saline (controls). Glucose, TGs, FFAs levels were measured and continuous indirect calorimetry was performed beginning 30 min before the start of the infusion and continuing to the end of the testing period. Lipid infusion significantly ($P < 0.05$) slowed the postabsorptive glycemic decline (lipid: 10.5 ± 1.1 mmol/L to 10.2 ± 1.0 at 180 min, NS; saline: 11.2 ± 0.8 to 9.8 ± 0.7 , $P < 0.01$). The response was heterogeneous, six 'responders' showed an absolute hyperglycemic response (10.8 ± 1.0 to 11.8 ± 0.8), while nine 'nonresponders' did not, in a similar manner to the saline controls (11.4 ± 1.2 to 10.5 ± 1.1). The lipidic effects of the lipid infusion differed in these two groups. In 'responders', the lipid infusion produced a

greater ($P < 0.01$) increase in FFAs ('responders': 839 ± 218 μ mol/L to $3\ 335 \pm 840$; 'nonresponders': 954 ± 109 to $1\ 731 \pm 206$). In contrast, TGs ('responders': 2.20 ± 0.19 mmol/L to 8.56 ± 1.54 ; 'nonresponders': 1.76 ± 0.18 to 6.67 ± 0.89 ; NS), total lipid oxidation ('responders': 0.74 ± 0.09 mg/kg/min to 0.90 ± 0.06 ; 'nonresponders': 0.59 ± 0.16 to 0.79 ± 0.10 ; NS) and glucose oxidation ('responders': 1.27 ± 0.28 mg/kg/min to 1.14 ± 0.20 ; 'nonresponders': 1.40 ± 0.35 to 1.20 ± 0.30 ; NS) did not evolve differently in the responder and nonresponder groups. Lipid infusion modified postabsorptive glycemia in NIDDM patients. The response was heterogeneous, and needed lipolysis of the infused triglycerides. This did not occur the same way in all subjects, as previously shown in normal subjects [Peterson (1990) *Proc Natl Acad Sci USA* 87, 909]. In contrast, an elevation of lipid oxidation did not seem necessary. The normality of total lipid oxidation in NIDDM patients, therefore [De Fronzo (1988) *Diabetes* 37, 667], did not exclude a role of lipid–glucid interactions during hyperglycemia. Interaction at the oxidative level did not seem sufficient to elevate glycemia, indicating an additional effect of lipid infusion on endogenous glucose production or nonoxidative glucose disposal.

Effects of glucagon on fructose-induced alterations of glucose metabolism in man. N Paquot¹, P Schneider², E Jéquier², L Tappy² (¹ *Division of Diabetes, CHU-Sart Tilman, 4000 Liège, Belgium*; ² *Institute of Physiology, University School of Medicine, Bugnon 7, 1005 Lausanne, Switzerland*)

Gluconeogenic substrates increase gluconeogenesis but fail to enhance the overall endogenous glucose production (EGP). The mechanisms responsible for this autoregulation remain unknown. In order to assess the effects of hyperglucagonaemia on autoregulation of EGP, eight healthy sub-

jects (4M/4F, 23.1 ± 2.4 years, 23.7 ± 3.5 kg/m² of BMI) were studied i) during hourly ¹³C fructose ingestion (0.3 g/kg fat free mass/h) for 3 h (F); ii) during ¹³C fructose ingestion and glucagon infusion (F + G); iii) during glucagon infusion alone (G). EGP levels were assessed by 6.6 ²H glucose and the contribution of fructose gluconeogenesis to EGP from ¹³C plasma glucose. Basal levels of glucagonaemia were similar in F, F + G and G and remained unchanged during fructose ingestion (F); F + G and G significantly increased glucagonaemia (from 112 ± 5 to 233 ± 9 ng/L with F + G, from 107 ± 4 to 210 ± 26 ng/L with G). EGP increased by $19.8 \pm 1.5\%$ with F + G (from 9.7 ± 1.2 to 11.8 ± 2.2 $\mu\text{mol/kg/min}$, $P < 0.001$) but remained unchanged during F or G. Gluconeogenesis from fructose represented about 80% of EGP with F + G. Plasma ¹³C glucose levels were identical with F and F + G, indicating a similar relative contribution of fructose gluconeogenesis to the glucose-6 phosphate pool. It was concluded that i) both an increased glucagonaemia and an enhanced supply of gluconeogenic precursors are required to increase EGP; ii) F + G increase EGP without changing the relative proportion of glucose-6 phosphate production from fructose and from other sources (ie, glycogenolysis + gluconeogenesis from non-fructose precursors). This suggested that alterations in the rates of glycogen synthesis or glucose-6 phosphate hydrolysis are involved.

Role of glucose-6 phosphatase and glucokinase in the regulation of hepatic glucose production in insulin-resistance.

C Minassian, G Mithieux (*Faculté de médecine René-Laënnec, Inserm, Unité 449, rue Guillaume-Paradin, 69372 Lyon cedex 08, France*)

We assessed the insulin sensitivity of hepatic glucose production (HGP) and the com-

ponents of the glucose–glucose-6 phosphate (Glc6P) cycle in rats fed a standard hyperglucidic diet (S) or a high-fat diet for 3 weeks, supplemented (HFM) or not (HF) with oral metformin (50 mg/kg/day) during the last week. HGP was assessed by [³-³H]glucose dilution after saline or insulin infusion during 45 min euglycemic clamps.

Basal HGP was similar in the three groups: 75 ± 8 , 65 ± 9.5 and 71 ± 3 $\mu\text{mol/kg/min}$ (mean \pm SEM, $n = 5$) for S, HF and HFM rats, respectively. Upon insulin infusion (35 mU/h), HGP decreased by 35% in S rats (49 ± 4.5 $\mu\text{mol/kg/min}$, $P < 0.05$ vs basal), did not decrease in HF rats (60 ± 12 $\mu\text{mol/kg/min}$, NS vs basal) and decreased by 68% in HFM rats (22.5 ± 10 $\mu\text{mol/kg/min}$, $P < 0.01$ vs basal). Upon insulin infusion at 70 mU/h, HGP was similarly suppressed in the three groups: 5.5 ± 7 , 6.5 ± 8 and 14 ± 7 $\mu\text{mol/kg/min}$, respectively.

Total Glc6Pase activity levels, assayed in intact microsomes isolated from fresh livers, were 30% lower ($P < 0.01$) in HF and HFM rats (0.15 ± 0.01 and 0.16 ± 0.01 $\mu\text{mol/min/mg prot}$) than in S rats (0.23 ± 0.02 $\mu\text{mol/min/mg}$), with similar Kms (≈ 2 mM). Glucokinase (GK) activity was 65% lower ($P < 0.01$) in HF and HFM rats (0.54 ± 0.13 and 0.60 ± 0.17 U/g wet weight) than in S rats (1.63 ± 0.4 U/g), with similar Kms (≈ 8 mM). Insulin had no effect on Glc6Pase and GK. Glc6P, assayed in a freeze-clamped liver lobe, was similar in the three groups after saline or insulin perfusions. Plasma Glc was similar in the three groups, before and after the perfusions. Insulin had no significant effect on the theoretical glucose output, calculated from the enzyme kinetics and the substrate concentrations, in any of the three groups.

We concluded that: i) mechanisms additional to total enzyme activities and substrate concentrations control the Glc–Glc6P cycle; ii) HF rats exhibited insulin resistance to HGP and that normal insulin sensitivity