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Are Kupffer cells involved in the metabolic adaptation of the liver to dietary carbohydrates given after fasting?

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Abstract

In rats, a high carbohydrate fat-free (HCFF) diet, given after fasting, induces both hepatic lipogenic and glycogenic enzymes. In the present study, we evaluated the involvement of Kupffer cells in the metabolic events occurring in the liver during the fasting–refeeding transition. Male Wistar rats were fasted for 48 h and received an intravenous injection of either NaCl 0.9% (Gd−) or 10 mg/kg $GdCl_3$ (Gd+), an inhibitor of Kupffer cells, then fed for 12 h with a HCFF diet. The comparison of colloidal carbon uptake was similar in rats fasted and in rats fasted and then refed a HCFF diet, thus indicating that refeeding does not affect per se Kupffer cell phagocytic activity. The inhibition of Kupffer cells by $GdCl_3$ did not affect fatty acid synthase (FAS) induction, as shown by the analysis of both FAS mRNA and activity; refeeding a HCFF diet increased the hepatic triglyceride and glycogen content to the same extent in Gd+ and Gd− rats. Our results do not support the involvement of Kupffer cells in the metabolic events occurring in the liver tissue by feeding a HCFF diet after fasting. However, the discussion supports the involvement of Kupffer cells in the modulation of the hepatic lipid metabolism by other nutrients than carbohydrates.

Keywords: Kupffer cell; Fasting–refeeding; Gadolinium chloride; Glycogen; Triglyceride

1. Introduction

Although the liver is mainly composed of hepatocytes, the other cell types distributed along the hepatic sinusoid, like Kupffer cells, seem to play an important role in the regulation of the hepatic metabolism namely through the release of paracrine factors [1–3]. First, the paracrine interaction between hepatocytes and macrophages is a prerequisite for the stimulation of the hepatocellular lipogenesis by thyroglobulin [4]. Moreover, several bioactive compounds (substances like cytokines, oxygen radicals and prostaglandins) are secreted by Kupffer cells during the infection or after lipopolysaccharide administration, and are involved in the metabolic adaptative response to an inflammatory process: prostaglandin E_2 (PGE_2) and NO have been shown to decrease both glycogenolysis and gluconeogenesis inside the hepatocytes [5–8]; on the other hand, interleukin-6 (Il-6) directly induces hepatic lipogenesis, whereas PGE's antagonize the acute inhibition of lipogenesis by glucagon [9]. However, the putative role of Kupffer cells in the modulation of lipid or glucose metabolism, occurring out of situations mimicking infection or inflammation, remains to be studied.

In rats, a high carbohydrate fat-free (HCFF) diet, given after a fasting period, has been shown to induce lipogenic enzyme gene expression and, subsequently, to produce triglyceride (TG) accumulation in the liver tissue [10,11]. Moreover, it also leads to glycogen accumulation in liver cells, through the post-transcriptional regulation of glycogen synthase gene expression [12]. When rats receive an i.v. injection of tumor necrosis factor alpha (TNF-α), a cytokine which is mainly produced by Kupffer cells, fatty acid synthase (FAS) activity, a key regulatory enzyme of fatty acid synthesis, increases by 33% [13]. These results lead us to postulate the involvement of Kupffer cells in the metabolic events occurring in the liver during the specific dietary manipulation, namely the fasting–refeeding transition. In order to test this hypothesis, Kupffer cell phagocytic activity was histochemically and biochemically assessed in rats fasted for 48 h prior to refeeding with a

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high carbohydrate fat-free diet for 12 h. Moreover, the modifications of carbohydrate and lipid metabolism occurring after refeeding were compared in control rats and in rats previously treated with gadolinium chloride ($GdCl_3$), a specific inhibitor of Kupffer cells in the liver tissue known to block phagocytosis and to reduce serum cytokine release [14–16].

2. Materials and methods

All chemicals used were the purest grade available and were purchased from Sigma (Filter Service, Belgium) or Boehringer (Mannheim, Germany).

2.1. Animals and diet

Nutrients required for the preparation of a semi-synthetic diet, and a standard chow diet (AO4) were all obtained from UAR (Villemoisson-sur-Orge, France). A semi-synthetic high carbohydrate fat-free (HCFF) diet was prepared by mixing saccharose (40% w/w), starch (40%), casein (16%), mineral and vitamin mix (4%) in proportion suggested by the UAR in order to provide adequate amounts of micronutrients. The caloric value of AO4 and HCFF diets was 3.73 and 3.88 kcal/g, respectively.

Male Wistar rats (Iffa Credo, les Oncins, France), weighing 220–240 g at the beginning of the experiment, were fed the AO4 standard diet and tap-water ad libitum before the experiment. The rats were either fasted for 48 h or in a second group were fasted for 48 h then refed ad libitum for 12 h with the HCFF diet; $GdCl_3$ (10 mg/kg body weight) or NaCl 9‰ were administered intravenously to rats 12 h before refeeding. Animals were killed under pentobarbital (60 mg/kg) anesthesia; blood was collected from the descending vena cava and the liver was excised and clamped immediately in liquid nitrogen and stored at −80°C for further total RNA isolation or measurement of hepatic enzyme activities and metabolite concentration. All the animals received care in compliance with the Institution's guidelines from the National Academy of Sciences (NIH publication 86-23).

2.2. Biochemical methods

Serum TGs were measured by using a kit coupling enzymatic and spectrophotometric detection of reaction endproducts (Triglycerides EliTech diagnostics, Brussels, Belgium). The same kit was used for liver TG content, after chloroform–methanol extraction according to Folch et al. [17].

The hepatic glycogen content was assayed using a modification of a previously described method [18]. Freeze-clamped liver tissue was homogenized in ice-cold buffer (pH 7) containing 0.1 M KH_2PO_4, 0.1 M K_2HPO_4 and 2 mM EDTA. The homogenates were heated at 100°C for 10 min in 1 M KOH. After neutralization with acetic acid and centrifugation, the supernatant was incubated in the presence of α-amyloglucosidase in pH 5 acetate buffer; the glucose was produced and was quantified by an enzymatic reaction as previously described.

The procedure described by Linn was used for the measurement of FAS activity in cytosolic fractions [19].

Protein was assayed by the method of Lowry et al., using bovine serum albumin as standard [20].

2.3. Histological analysis

Liver pieces were taken directly after killing the rats and either fixed in 10% buffered neutral formalin, embedded in paraffin and sliced into 3–4 μm sections for hematoxylin–eosin staining, or frozen in liquid nitrogen and cut in the cryostat for fat detection by Sudan Red 7b (Janssen Chimica, Belgium) and for glycogen detection by periodic acid Schiff reagent (PAS).

2.4. Semi-quantification of colloidal carbon uptake by Kupffer cells

To test for the phagocytic capacity of Kupffer cells, colloidal carbon (Pelikan No. 17 dissolved in saline 1:10; 1.5 ml/kg) was injected in the portal vein 20 min before blood collection; liver samples were kept in 10% formalin, embedded in paraffin and then sliced into 3–4 μm sections for further histological study. Semi-quantification of Kupffer cells colored in black through carbon colloidal uptake, was performed by scanning histological photography (Sharp JX 325) and the optical density corresponding to Kupffer cells containing colloidal carbon was determined by using a densitometer (Image Master, Pharmacia Biotech). As colloidal carbon absorbs at a maximum wavelength of 630 nm, the measurement of the optical density at this wavelength in the serum allows quantification of the amount of colloidal carbon that escaped macrophage uptake.

2.5. RNA isolation and reverse transcriptase-polymerase chain reaction (RT-PCR) quantification of FAS mRNA

Total RNA was isolated from frozen liver tissue (200 mg), using the guanidine thiocyanate method initially described by Chomczynski and Sacchi [21] and modified as described for RNAgent total RNA isolation system (Promega). Total RNA was quantified by UV absorption at 260 nm and the purity of RNA was checked at 280 nm ($A_{260}/A_{280} = 1.6–2$). One step RT-PCR was performed on 1 μg total RNA as described in the detailed procedure from Access RT-PCR system kit (Promega). The reverse transcription reaction was performed at 48°C for 45 min, followed by a single denaturing step at 94°C for 2 min.

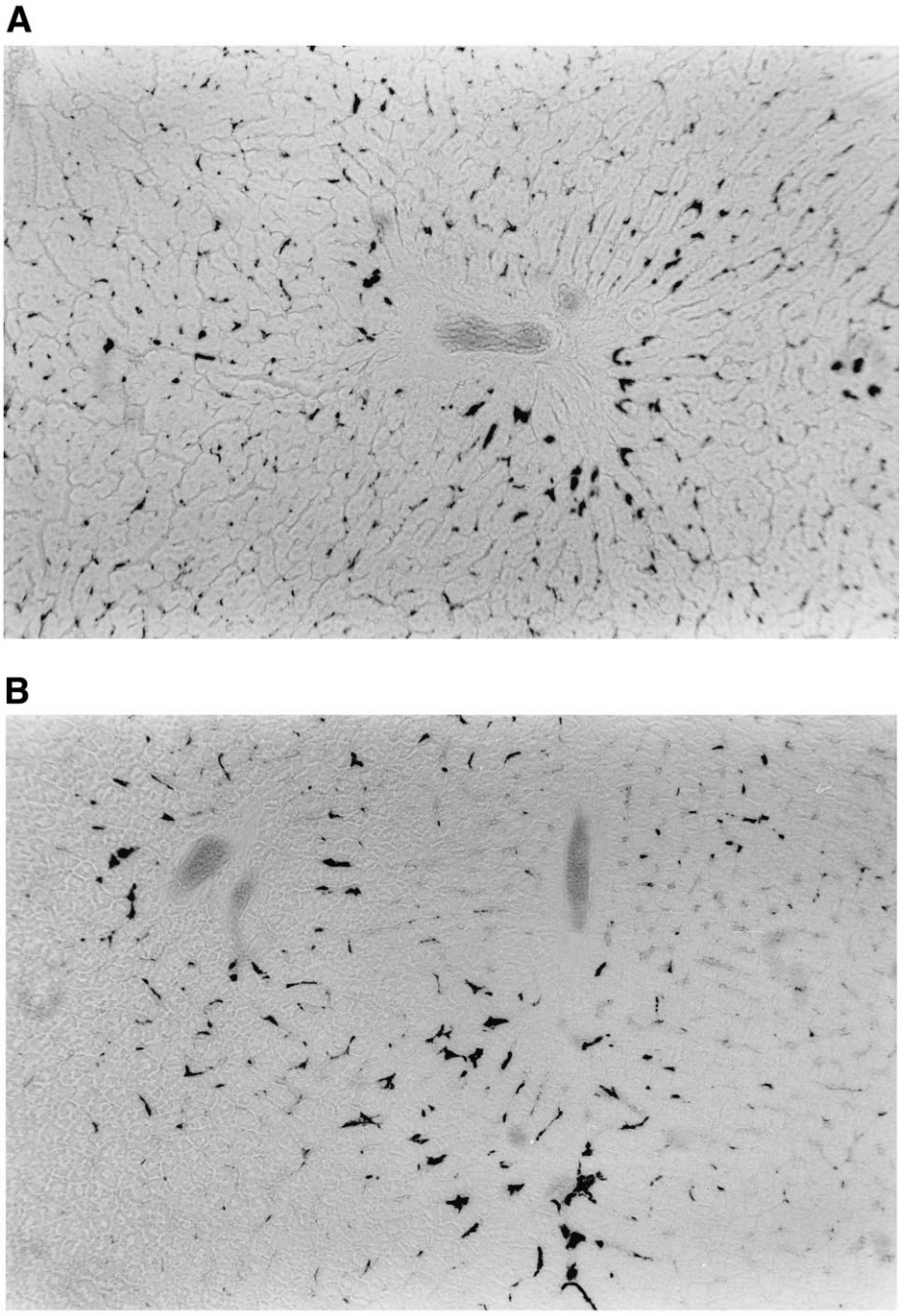

Fig. 1. Distribution of colloidal carbon in the liver 20 min after intravenous injection. Rat fasted for 48 h (A), rat fasted then refed for 12 h with HCFF diet after saline injection (B) and rat fasted then refed for 12 h with HCFF diet after $GdCl_3$ injection (C). The carbon is mainly taken up in Kupffer cells (dark spots). ×1200.

Amplification was carried out under standard thermal cycling conditions, 23 cycles of the profile 94°C for 30 s, T°C for 1 min (T = hybridization temperature of primer), 68°C for 2 min and a final extension step at 68°C for 7 min. Specific primer pairs were as follows: FAS, sense 5′-CTCATGGGTGTGGAAGTGCGCCAG-3′ and antisense 5′-CCAGGCTGTGGAACA CAGTGATGGAAC-3′; β-actin, sense 5′-CTGACCGAGCGTGGCTACAG-3′ and antisense 5′-GGTGCTAGGAGCCAGGGCAG-3′. The cycle numbers used for each primer pair were adjusted to ensure linear amplification. Reaction products were separated on 1.8% agarose gel in TAE buffer (2 M Tris base; 5.7% acetic acid; 0.05 M EDTA, pH 8) containing 0.1 mg/ml ethidium bromide. RT-PCR products were visualized under short wave UV light and photographed. Photographs were scanned (Sharp JX 325) and the density of the bands was calculated using the program Image Master (Pharmacia Biotech). The FAS–β-actin

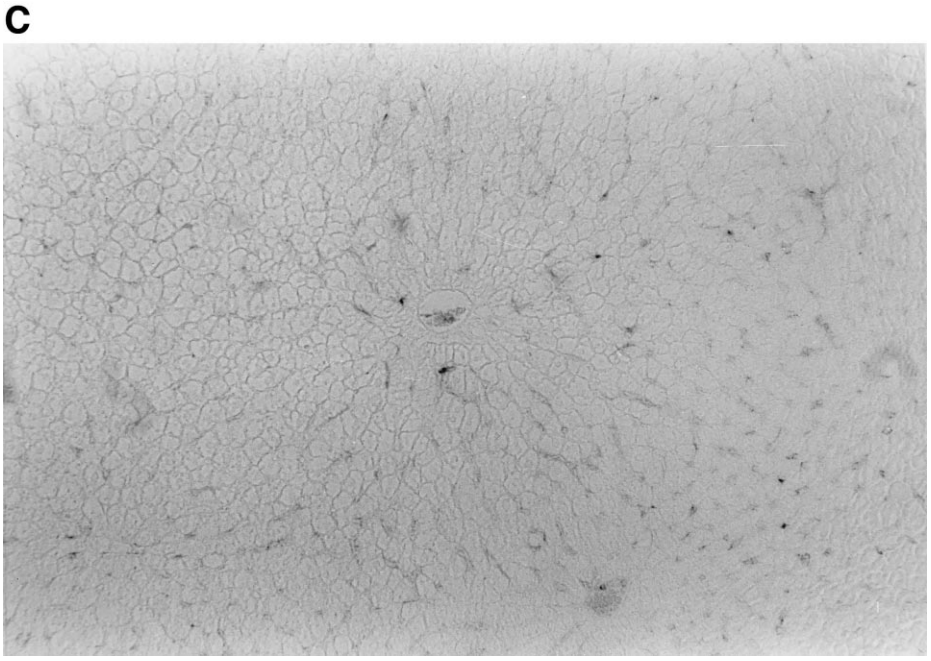

Fig. 1 (*continued*).

mRNA ratio was used as a relative estimate of FAS mRNA abundance.

2.6. Statistical analysis

Values are presented as means ± S.E.M. The statistical significance of observed variations was carried out by one-way ANOVA followed by a Scheffé test.

3. Results

The number and activity of Kupffer cells have been assessed in $GdCl_3$-treated animals and during fasting–refeeding transition 20 min after an injection of a single dose of colloidal carbon in the portal vein. The treatment of rats with $GdCl_3$ strongly decreased the uptake of colloidal carbon by Kupffer cells as shown by the histological analysis of liver sections (Fig. 1). The optical density of the cells having taken up colloidal carbon (colored in black) was significantly lower (Fig. 2A). Moreover, an accumulation of colloidal carbon in the serum occurred in $GdCl_3$-treated animals (Fig. 2B). The comparison of colloidal carbon uptake was similar in rats fasted and in rats fasted and then refed a HCFF diet, thus indicating that refeeding does not affect per se Kupffer cell phagocytic activity.

The dietary intake during the refeeding period was 16.8 ± 0.7 g in refed (Gd−) and 17.5 ± 0.5 g in refed (Gd+) groups ($P > 0.05$ one way ANOVA followed by the Scheffé test). In both groups, refeeding lead to a strong increase in liver weight, a phenomenon which is mainly correlated with the accumulation of glycogen in liver tissue, occurring to nearly the same extent in both refed (Gd−) and refed (Gd+) rats (Table 1); the histological detection of glycogen in liver tissue by PAS reagent confirmed this result (data not shown).

The induction of lipogenic enzymes was assessed by measuring both FAS mRNA and activity in the liver tissue (Table 1). FAS mRNA was not detectable under fasting conditions but was induced 12 h after refeeding a HCFF

Table 1
Effect of Kupffer cell inhibition by $GdCl_3$ on liver parameters (weight, TG and glycogen content, FAS activity) in carbohydrate-rich diet given after fasting of rats

	Fasted	Refed (Gd−)	Refed (Gd+)
Liver/body weight (%)	2.80 ± 0.05	5.36 ± 0.20[a]	5.94 ± 0.10[a]
TG (nmol/mg protein)	65.5 ± 8.1	86.4 ± 14.4	79.6 ± 9.3
Glycogen content (μg/mg protein)	2 ± 1	817 ± 106[a]	752 ± 149[a]
FAS activity (mUI/mg protein)	2.20 ± 0.29	8.27 ± 0.76[a]	9.68 ± 0.74[a]

Values are means ± S.E.M. for six rats in each group: rats fasted for 48 h, rats fasted then refed for 12 h with HCFF diet after saline injection (Gd−) and rats fasted then refed for 12 h with HCFF diet after $GdCl_3$ injection (Gd+).
[a]One way ANOVA followed by Scheffé test: $P < 0.05$ versus fasted rats.

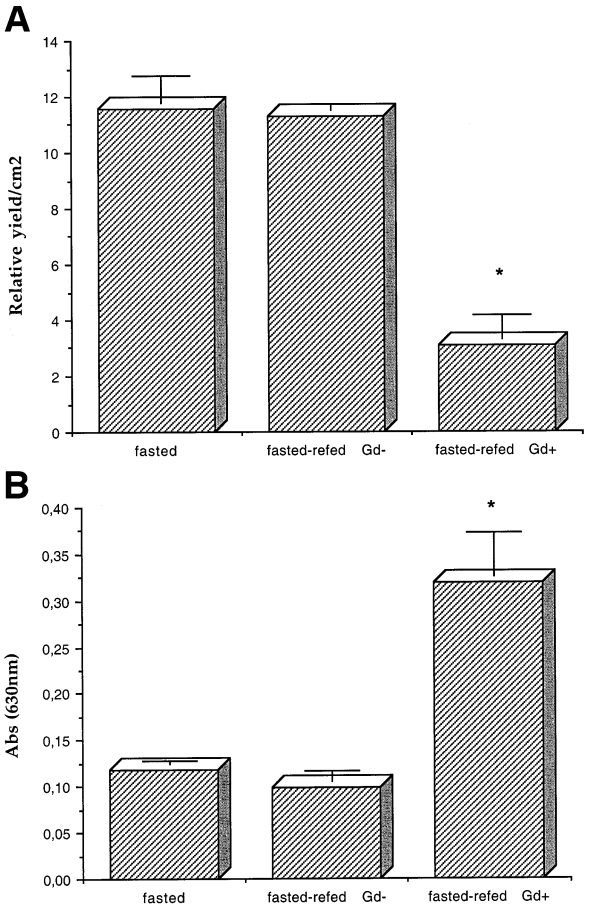

Fig. 2. Semi-quantification of colloidal carbon uptake by Kupffer cells by in situ densitometry on liver section and optical density in the serum. Relative yield of black cells per cm^2 corresponding to Kupffer cells containing colloidal carbon was calculated after scanning the photographs of liver slices (A). The absorbance of the serum was determined at 630 nm (B). Values are means ± S.E.M. for four rats in each group: rats fasted for 48 h, rats fasted then refed for 12 h with HCFF diet after saline injection (Gd−) and rats fasted then refed for 12 h with HCFF diet after $GdCl_3$ injection (Gd+). *One way ANOVA followed by Scheffé test: $P < 0.05$ versus fasted and refed (Gd−) rats.

diet (Fig. 3). Moreover, the hepatic FAS activity was increased four-fold in refed rats as compared to fasted rats. The inhibition of Kupffer cells by $GdCl_3$ does not affect FAS induction, as shown by analysis of both FAS mRNA and activity. Refeeding a HCFF diet only moderately modified the hepatic TG content after 12 h (Table 1), as confirmed by the histological detection of fat (data not shown); however, the serum TG concentration reached 1.34 ± 0.15 and 1.36 ± 0.11 mmol/l in refed (Gd−) and refed (Gd+) groups, respectively, as compared to the low level measured in the serum of fasted rats (0.28 ± 0.04 mmol/l).

4. Discussion

The induction of lipogenesis occurring in the liver of rats given a high carbohydrate diet after fasting is a well described metabolic process in vivo [10,11,22]. In vitro studies, performed in primary culture hepatocytes, have shown that nutrients (glucose) and hormones (T3, insulin) regulate this process by increasing the expression of genes coding for key lipogenic enzymes, like FAS [23–25]. One study reports that lipogenesis also occurs in Kupffer cells as shown by their capacity to incorporate [^{14}C]acetate into $CHCl_3$ extractable molecules [26] and other recent data suggest that a high carbohydrate diet induces glucose-6-phosphate dehydrogenase in sinusoidal endothelial and Kupffer cells, but this effect has been proposed to represent preconditioning of antioxidant pathways rather than a sign of increased production of NADPH for lipogenesis [27]. Moreover, Kupffer cells are important sources of PGE's and cytokines like TNF-α, Il-1 and Il-6, which are able to induce lipogenesis in vitro in cultured hepatocytes, and in vivo [9,28–30]; this phenomenon was proposed as a key mechanism explaining the hypertriglyceridemia occurring in patients with severe inflammation or infection [29,31]. TNF-α is also able to induce sterol regulatory element binding protein (SREBP-1) maturation in human hepatocytes; SREBP is a key transcription factor in the regulation of FAS gene expression [32–34]. In view of these data, the study was mainly devoted to analyzing the putative implication of Kupffer cells in the induction of lipogenesis and TG accumulation occurring by refeeding rats with a HCFF diet after fasting.

In a recent study, we had demonstrated that the previous inhibition of Kupffer cells by i.v. injection of $GdCl_3$ in vivo modified the metabolic status of the liver tissue in vitro, thus suggesting that Kupffer cells are able, per se

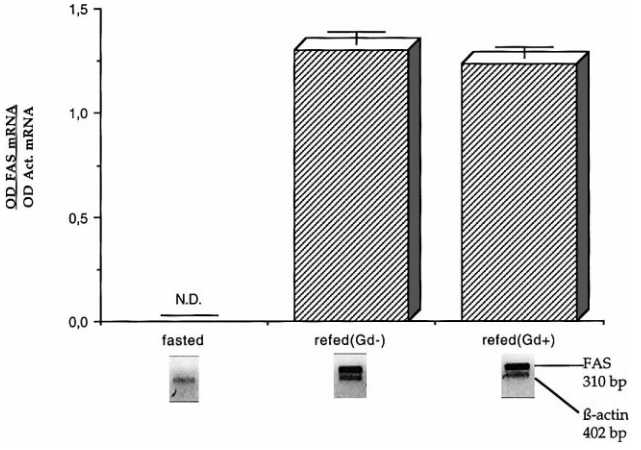

Fig. 3. Effect of Kupffer cell inhibition by $GdCl_3$ on relative quantification of FAS mRNA in the liver tissue in carbohydrate-rich diet given after fasting of rats. FAS–β-actin mRNA ratio was a semi-quantitative RT-PCR assay relative to FAS mRNA tissue levels. Details of the methods are described in Section 2. Values are means ± S.E.M. for four rats in each group: rats fasted for 48 h, rats fasted then refed for 12 h with HCFF diet after saline injection (Gd−) and rats fasted then refed for 12 h with HCFF diet after $GdCl_3$ injection (Gd+) (N.D., non-detectable). The picture of the agarose gel is presented under the graph showing the bands corresponding to the products for β-actin and FAS. The size was estimated by comparison with a standard molecular weight (∅ × 174 DNA/*Hin*fI Markers 24 bp → 726 bp, Promega).

and without any known activation, to modulate the metabolic pattern inside the liver tissue [35]; the same protocol of inhibition of Kupffer cells was applied here. A single i.v. $GdCl_3$ injection inhibited Kupffer cell numbers and phagocytic activity, as shown by both the histological analysis of liver sections and the accumulation of colloidal carbon in the peripheral serum. However, the pretreatment with $GdCl_3$ did not modify either the induction of FAS expression and activity, or its physiological consequences, namely TG accumulation in the liver or in the serum, occurring through refeeding a HCFF diet after fasting in rats.

Other arguments lead us to postulate that Kupffer cells could be involved in the modulation of carbohydrate metabolism: an in vitro study supported the hypothesis that PG's produced by Kupffer cells in response to glucagon might participate in a feedback loop inhibiting glucagon-stimulated glycogenolysis in hepatocytes [7]. Moreover, the increasing evidence for the existence of intrahepatic regulation of glucose metabolism by Kupffer cell products was also supported by the fact that NO inhibits gluconeogenesis from lactate and glycogen synthesis in freshly isolated fasted-rat hepatocytes [8]. However, no effect of $GdCl_3$ on glycogen accumulation occurring in the liver after refeeding was observed here. The discrepancy between the in vitro data obtained by Sprangers et al. and our in vivo data, could be due to the fact that $GdCl_3$ does not allow modulation of all the cells producing NO, including endothelial cells. In this view, it should be interesting to test for the putative influence of $GdCl_3$ pre-treatment on the capacity of precision-cut liver slices to produce NO, this model allowing the viability of the several hepatic cell types to be maintained [35]. It would be interesting to confirm this observation by using another Kupffer cell inhibitor like methylpalmitate [36], which may suggest that lipogenesis or glycogenesis induction due to carbohydrates is not dependent on the presence or the activity of Kupffer cells. Could any (positive or negative) influence of the Kupffer cells on lipogenesis or glycogenesis be masked by the acute induction of those metabolic pathways after the fasting–refeeding transition? The question remains open and will take part of our future objectives. Even if it is clear that the treatment with gadolinium interferes with the uptake of colloidal carbon, the effect of this treatment on the Kupffer cells generated mediators such as cytokines, prostaglandins or reactive oxygen intermediates, was not studied here. In fact, it is unclear whether this model of inhibition precludes a cytokine-mediated Kupffer cell–hepatocyte interaction which is not dependent on phagocytic stimulation. Nevertheless, in one of our previous studies and according to other authors, the pretreatment of rats with $GdCl_3$ has no influence on plasma TNF-α levels [16]; however, the precision-cut slices obtained from the liver of $GdCl_3$ pre-treated animals exhibited a lower release of TNF-α in the medium of incubation [35]. Moreover, when cultured rat Kupffer cells were treated with 10 μg/ml $GdCl_3$ for 12 h and further incubated with 10 μg/ml LPS, the production of Il-6, TNF-α and NO was completely inhibited [37]; $GdCl_3$ is thus able, at least in vitro, to preclude mediator release by Kupffer cells upon activation (LPS).

The lack of involvement of Kupffer cells in our study also supported the fact that we were unable to show any modification of Kupffer cell phagocytic activity, assessed by analyzing colloidal carbon uptake by the liver, due to the fasting–refeeding transition. In view of our results, the fasting–refeeding transition does not modify the phagocytic activity of Kupffer cells; even if the metabolic response to this nutritional transition is complex, no modification of the 'critical metabolic end-point' (such as hepatic TG or glycogen accumulation; FAS induction), with no idea of the kinetics of the phenomenon, occurs when the phagocytic activity of Kupffer cells is down-regulated by $GdCl_3$ pre-treatment. This only suggests that the induction of lipogenesis may occur in different situations, in which Kupffer cell activity is promoted (LPS treatment) or not (fasting–refeeding transition). The involvement of Kupffer cells in the modulation of hepatic lipid metabolism by other nutrients or drugs, remains an attractive hypothesis. For example, dietary *n*-3 polyunsaturated fatty acids (PUFA) decrease FAS mRNA in adult rat liver [38] while altering eicosanoid and cytokine release from Kupffer cells [39–41]. Another example is the well described implication of Kupffer cells in the accumulation of TG in the liver of rats given ethanol orally [42,43]. Both *n*-3 PUFA and ethanol are known to promote lipid peroxidation in the liver tissue [43,44]; whereas refeeding a HCFF diet after fasting does not induce such an effect. Could this mean that Kupffer cells participate in the regulation of hepatic metabolism only when reactive species (NO, $O_2^{\bullet -}$, PGE_2, etc.) are involved? This question merits attention.

Acknowledgements

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