

Effects of fatty acids on liver regeneration in rats

Efeitos dos ácidos graxos sobre a regeneração hepática em ratos

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A B S T R A C T

Objective: To study the effects of polyunsaturated fatty acids (PUFA) omega-3 and omega-6 in the oxidative stress and in liver regeneration in rats subjected to 70% partial hepatectomy (PH, 70% hepatectomy, Higgins-Anderson partial hepatectomy). **Methods:** 72 young male Wistar rats were randomly divided into four equal-sized groups: control (G1), partially hepatectomized (G2), partially hepatectomized with two weeks daily intraperitoneal infusion of omega-3 (G3) and partially hepatectomized with two weeks daily intraperitoneal infusion of omega-6 (G4). In moments 36h (T1), 168h (T2) and 336h (T3) post-PH, thiobarbituric acid reactive substances (TBARS) and reduced glutathione (GSH) were measured in plasma and liver tissue, while glucose and total bilirubin were measured in blood. The mass of the residual liver in the same moments was the parameter used to estimate the evolution of liver regeneration. **Results:** omega-3 PUFA inhibited liver regeneration and induced reduction of hepatic GSH concentration seven days post-PH. Omega-6 PUFA, in contrast, showed no inhibitory effect on regeneration. There was an increase of lipid peroxidation both in blood and liver with administration of omega-6. **Conclusion:** Omega-3 PUFA retarded post-PH liver regeneration, probably through inhibition of oxidative stress. Omega-6 PUFA increased TBARS concentrations in blood and liver but did not alter the evolution of the liver regenerative process.

Key words: Liver regeneration. Oxidative stress. Fatty acids. Lipid peroxidation. Rats.

INTRODUCTION

The mammalian liver has a remarkable capacity for regeneration after tissue damage, including partial hepatectomy¹. After resection of the two largest lobes of the rat liver, left lateral and median (PH, 70% partial hepatectomy, Higgins-Anderson partial hepatectomy, 2/3 partial hepatectomy), the residual right lateral and caudate lobes trigger an essentially hyperplastic response with cell and tissue regeneration², culminating, in 3 to 14 days, in restoration of the original volume of the gland²⁻⁴. Reactive oxygen species (ROS), antioxidants and lipid peroxidation (LPO) have been implicated as influencing the mechanisms controlling cell growth and proliferation⁵⁻⁷. The administration of exogenous antioxidants such as alpha-tocopherol (vitamin E) and reduced glutathione (GSH) slows the progression of hepatic regeneration^{7,8}. Moreover, many studies have reported that the genesis and/or the formation of free radicals is an important factor in the phenomenon of liver regeneration and necessary for their natural course^{6,9}. Omega-3 and omega-6 PUFA were studied in a classical experimental model of partial hepatectomy

by Higgins and Anderson¹ to evaluate their influences on oxidative stress and liver regeneration.

METHODS

The study followed the standards of the Brazilian College of Animal Experimentation (COBEA) and was approved by the Ethics Committee on Animal Research (CEPA) under the number of CFU protocol 14/06 of August 11th, 2006.

We used 72 young (70 ± 10 days) male Wistar rats (*Rattus norvegicus var. Albinus, Rodentia mammalia*), with mass between 100 and 235g from the Central Animal Facility at the Federal University of Ceará. They were sheltered for the study at the vivarium of LABCEX in polypropylene cages with stainless steel lid and floor covered with sawdust shavings, leaving about 250 cm² free area. The animals were kept in circadian cycles of light and dark, with 12 hours of light with low intensity and 12 hours of darkness, both before and after surgery and throughout the period of experimentation. The cages were cleaned daily and the animals examined. The room

Work done at the Laboratory of Experimental Surgery (LABCEX) of the UFC Medical School, Fortaleza – CE – BR.

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temperature was maintained at $23 \pm 4^\circ \text{C}$, relative humidity between 40 and 70% and free access to water and balanced chow proper for the species composed of 4% lipids, 21% protein, 52% carbohydrate and the remaining of non-digestible residue (Guabi Nutrilabor®, Mogiana Alimentos, São Paulo, SP)

The animals were randomly distributed to four groups of 18 rats. Group 1 (G1) was the control group: the animals underwent only laparotomy (without PH) at time T0. All other groups underwent the classical Higgins-Anderson 70% hepatectomy (PH)¹ at time T0 and received, for 14 days, intraperitoneal (ip) injections of: NaCl 0, 9% (saline), 0.1 ml/kg (Group 2 – G2); omega-3 PUFA, 0.1 g/kg (Group 3 – G3); and omega-6 PUFA, 0.1 g/kg (Group 4 – G4).

Six randomly picked anesthetized rats of each group underwent complementary hepatectomy (HC) - except for G1, who underwent total hepatectomy (TH) - in each of the following moments: 36h (T1), 168h (T2) and 336h (T3) after the initial procedure (T0). In T1, T2 and T3 samples were collected from blood and residual liver tissue. Blood collection was performed under direct vision by puncturing the abdominal vena cava just before the residual or total hepatectomy. All surgeries were performed under inhalation anesthesia of diethyl ether and PH consisted in the removal of the two anterior lobes of the rat liver, as originally described by Higgins and Anderson¹, via bilateral subcostal oblique transverse laparotomy (bilateral Kocher incision) with approximately 4cm extension. Blood glucose and bilirubin were used as parameters for evaluation of liver metabolism and regeneration under the action of the GSH antioxidant, and Thiobarbituric Acid Reactive Substances (TBARS), both in liver and blood, to measure oxidative stress. Blood samples were heparinized and, after 10 minutes of centrifugation (4,000 rpm), placed in sealed test tubes and frozen in liquid nitrogen at 70°C for further preparation and analysis. The hepatic tissue samples were in the same way frozen and stored in test tubes. Thiobarbituric acid (TBA) was purchased from Sigma Chemical Co., St. Louis, USA. TAP kit (TA-01) was purchased from Oxford Biomedical Research (Oxford, MI, USA). Saline (NaCl 0.9%) was obtained from Pharmaceutical Chemistry (Gaspar Viana, Brazil) and Omegaven® (omega-3) and Lipovenos® (omega-6) were purchased from Fresenius Kab (GmbH, Austria).

Lipid peroxidation (LPO) was determined by measuring malondialdehyde (MDA) as the reactive substance to TBA¹⁰. For determination of GSH, we calculated the content of non-protein sulfhydryl groups by the technique of Sedlak & Lindsay¹¹. D glucose was estimated according to the method of Slein as described by Vasconcelos¹² and total bilirubin levels were determined via the Meiteis modification of the Mallory and Evelyn procedure¹³. Liver regeneration was evaluated by measurements of residual masses in the livers of mice.

GraphPad Prism 4.0 (GraphPad Software, San Diego, California, USA) was used for computer analysis and statistical comparisons with the Dunnett test. The regeneration of liver tissue after PH is represented by linear regression lines obtained by the method of the least squares; after the distribution of the full set of groups was guaranteed to be approximately normal (not shown), the lines were compared in pairs by Student t test for angular coefficients (â). Statistical significance was set at 95% ($p < 0.05$).

RESULTS

The comparison between G1 and G2 (Figure 1) represents "non-hepatectomy vs. hepatectomy".

Figure 2 shows a statistically significant increase in hepatic GSH concentration of G2 at moment T2. Similar significant increases occurred in T1 and T3 (not shown). In addition, hepatic GSH decreased in a statistically significant way in G3 at moment T2 (Figure 2), which also occurred at moments T1 and T3 (not shown).

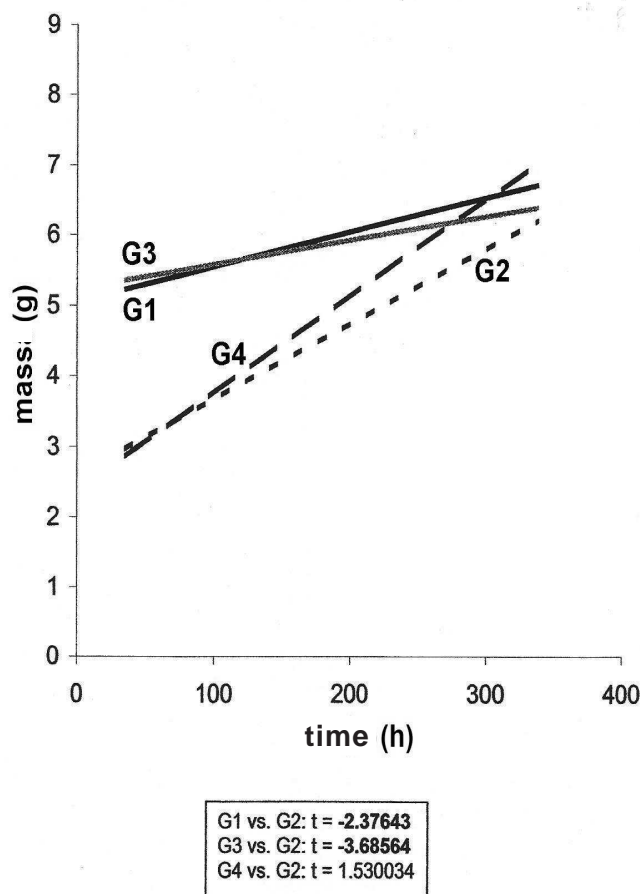


Figure 1 - Evolution of the Post-PH residual livers. G1 = laparotomy group (without PH) = control group; G2 = PH + saline, G3 = PH + Omega 3, G4 = PH + Omega 6; Student t test of angular coefficients of the regression lines shows statistic significance G1xG2 and G3xG2, $p < 0.05$ (t values in bold).

The concentrations of liver TBARS was significantly increased ($p < 0.01$) in G4 (Figure 3) at moment T2, but this growth also occurred at T1 (not shown).

Plasma GSH after PH was significantly higher ($p < 0.01$) in G2 in T1 and T2 and at all times in G3. Figure 4 presents these facts at moment T2.

Both G2 and G3 did not have significant changes in plasma TBARS after PH, but the MDA was shown with significantly increased concentrations in G4 at moments T1 and T2. Figure 5 shows this at T2.

Statistically significant hyperglycaemia ($p < 0.01$) occurred with G2 rats at T2 and T3, while significant hypoglycaemia ($p < 0.01$) was evident in G3 and G4 at all times. Figure 6 displays these facts at T2.

Total bilirubin levels did not change significantly in either group at any time (not shown).

DISCUSSION

Figure 1 shows the evolution of residual livers in each group by means of regression lines (interpolation). As expected, the G1 did not show regenerative behavior once their line of evolution of liver mass is practically horizontal. In fact, the animals in this group did not undergo any surgery of the liver or were subjected to any injection of drug. The slope of G1 is not null - it's small, but positive - probably because it expresses the small natural growth of the liver in young rats. G2, in contrast, displays aggressive behavior of regeneration, with inclination (\hat{a}) significantly greater than G1 (Figure 1). It is the natural liver regeneration, without stimulating or inhibiting drugs.

G1 and G3 showed very similar slopes (Figure 1), indicating that the regenerative growth in these two groups (non-PH and PH omega 3) are not different. In other words, the administration of omega-3 PUFA resulted in inhibition of liver regeneration, since in G1 there is not, strictly speaking, any ongoing regeneration. The slopes of G4 and G2 lines, on the other hand, are not significantly different, which in essence confirms that the intake of PUFA omega-6 (G4) does not interfere significantly with the natural development of liver regeneration (G2).

Partial hepatectomy per se is related to the formation of free radicals^{14,15}, and the animals only partially hepatectomized (G2) showed increased GSH, both in plasma and liver (Figures 4 and 2, respectively), which can be understood as an attempt to mitigate the oxidative stress caused by PH. In general, cells respond to oxidative stress with higher concentration of GSH in order to inhibit potential oxidative injury. In fact, many studies have shown increased production of free radicals after partial hepatectomies^{9,16,17}.

The present study demonstrates that the phenomenon of liver regeneration was significantly reduced after infusion of omega-3 (Figure 1, G3 compared to G2); at the same time, there was a decrease of hepatic GSH (Fig. 2, G3 compared to G2). Omega-3 PUFA thus functions

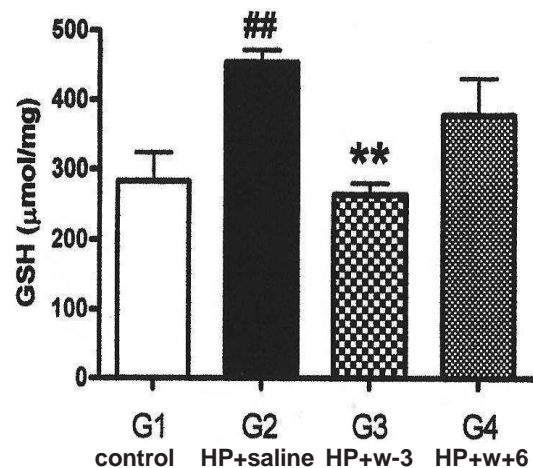


Figure 2 - Post-PH Hepatic GSH, T2. Statistically significant ($p < 0.01$) increase of GSH in G2 compared to G1; significant decrease ($p < 0.01$) in G3 and no significant changes in G4, both compared to G2.

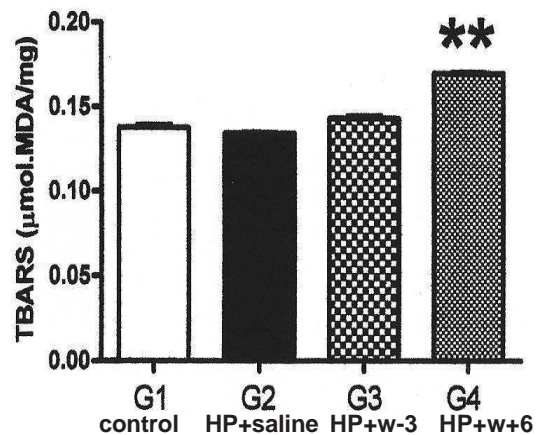


Figure 3 - Post-PH Hepatic TBARS, T2. Statistically significant increase ($p < 0.01$) of TBARS in G4 compared to G2. Absence of significant changes in G3 compared to G2 and in G2 compared to G1.

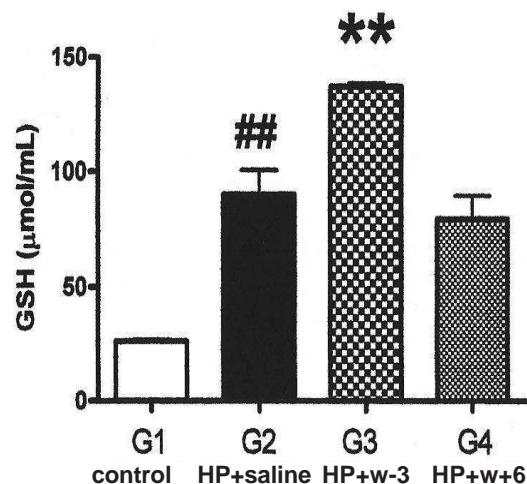


Figure 4 - Post-PH Plasmatic GSH, T2. Statistically significant increases ($p < 0.01$) in G2 compared to G1 and in G3 compared to G2. Absence of significant changes in G4 compared to G2.

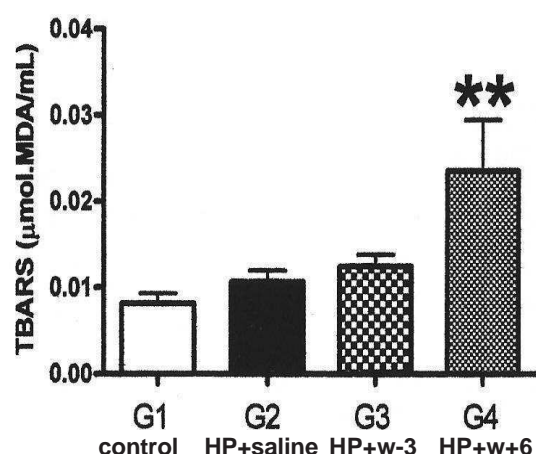


Figure 5 - Post-PH Plasmatic TBARS, T2. Absence of statistically significant changes in G2 compared to G1 and in G3 compared to G2. Significant increase of TBARS in G4 compared to G2.

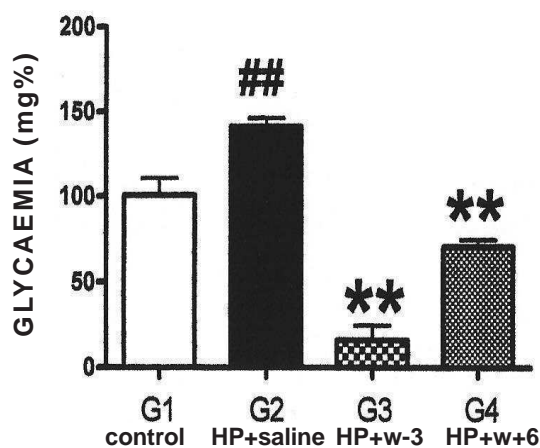


Figure 6 - Post-PH GLYCAEMIA, T2. Statistically significant ($p < 0,01$) hiperglycaemia in G2 compared to G1 and hipoglycaemia in G3 and G4, both compared to G2.

as an antioxidant agent that inhibits rat liver regeneration after PH. Corroborating these findings, several researchers have shown that omega-3 PUFA inhibits the generation of free radicals^{18,19} and, with respect to the regenerative process, many studies attest to the importance of lipid peroxidation (LPO)^{7,16,20}. Such papers are unanimous in pointing out the genesis and formation of free radicals among the prominent factors for natural, physiological liver regeneration^{6,9}. Furthermore, administration of exogenous antioxidant blocks hepatic regeneration^{5,6}. For example, the exogenous supply of vitamin E affects hepatic regeneration in partially hepatectomized rats⁷ and the administration of GSH blocks liver regeneration in rats⁸. Thus, omega-3 PUFA exerts an inhibitory factor on liver regeneration after PH in rats probably through its antioxidative properties.

Unlike omega-3, the results obtained here show that the administration of omega 6 PUFA did not inhibit the regeneration process of rat liver and since both plasma

and liver TABRS increased significantly with the infusion of omega-6 at T1 and T2 (Figures 5 and 3, respectively), this study confirms that omega-6, though inducing increased lipid peroxidation, does not interfere with the evolution of liver regeneration. Some studies have obtained even more conclusive results and showed that omega-6, besides increasing oxidative stress^{18,20}, increases liver regeneration in rats²⁰.

The divergent behavior of omega-3 and omega-6 in relation to oxidative stress and liver regeneration can be summarized as follows: while omega-3 inhibits liver regeneration and acts as an antioxidant, omega-6 does not interfere with changes in the liver regenerative process and has pro-oxidant properties.

Epidemiological studies with the Greenland Eskimo population²¹ as well as investigations in clinical nutrition^{22,23} and laboratory research with cytokines and eicosanoids^{24,25} have shown that omega-6 has proinflammatory properties, while omega-3 exhibits anti-inflammatory activities²⁶. Similar properties were seen here. They explain the differences between these PUFA on liver regeneration.

Malignancies are living examples of major cell proliferation as it occurs in the liver regeneration phenomenon. Several investigators have suggested that omega-3 works to suppress cancer cells while omega-6 stimulates carcinogenesis²⁷⁻²⁹. There is evidence suggesting that the incidence of aggressive carcinoma correlates in a straightforward way with the intake of omega-6³⁰ and, on the other hand, there is a study reporting decreased proliferation of tumor cells in the colon of rats fed with fish oil (omega-3) when compared to corn oil (omega-6)³¹. Several surveys are therefore conclusive in pointing out that diets rich in omega-6 PUFA induce tumor growth (cell proliferation), whereas diets high in omega-3 PUFA show inhibitory effects³². Such studies are in line with this research in relation to cell proliferation – the compensatory hyperplasia of the liver regenerative process: omega-3 blocks, omega-6 does not.

A large number of studies have reported that the residual liver lobes after hepatectomy maintain all the liver functions necessary to keep homeostasis in normal organic levels despite the ongoing regeneration process^{3,33,34}. In partially hepatectomized rats, plasma insulin concentrations have a significant decrease^{35,36}, while the levels of glucagon increase^{37,38}, which probably constitutes part of the homeostatic response resulting, among other things, in proper blood glucose levels³⁶. In the group with omega-3 intake, as well as in the one with omega-6, plasma glucose values were significantly decreased (Figure 6). These are probably consequences of the hypoglycemic action of lipids on the mechanism of insulin secretion. In fact, research has revealed that the secretion of insulin, previously deemed to be dependent on a unique and essential glucose stimulus, is now being more and more related to the interaction of glucose and lipid metabolism³⁹. When high levels of

circulating free fatty acids in rats fasted for one day are suddenly reduced via infusion of a lipolytic agent (i.e., nicotinic acid), a subsequent stimulation of glucose secretion by insulin is totally inhibited, but it becomes normal if the concentration of free fatty acids is kept high by co infusion of lipid emulsion with heparin^{40,41}. Clinical trials show similar results with two day fasting humans⁴². In fed rats, since the level of circulating free fatty acids is low, the response of insulin secretion after a glucose stimulus is normal⁴⁰, but an artificial increase in the concentration of circulating free fatty acids results in dramatic increase in insulin secretion after a glucose stimulus⁴³. Moreover, the insulinotropic power of fatty acids is directly correlated to the length of their chains and their degree of saturation⁴¹. Presumably, all animals of groups G3 and G4, nourished daily with proper chow plus the artificial intraperitoneal infusion of omega-3 or omega-6 PUFA, consequently presented with higher insulin

secretion and therefore hypoglycaemia (Figure 6). In addition, antioxidants induce greater insulin action⁴⁴ due in part to the protection of beta cells from free radicals' injuries⁴⁵. Omega-3 PUFA, possessing the two properties, should, in theory, have higher hypoglycemic potential: in fact, the G3 mice displayed a steeper glycemic fall.

Total plasma bilirubin showed no significant change at all moments. Recent researches show that the administration of fish oil or vitamin E or eicosapentaenoic acid (EPA) did not induce any significant change in hepatic function tests³⁴, which agrees with this study on oxidative stress^{46,47}.

Thus, the present experimental results corroborate the hypothesis that oxidative stress plays a significant role in the phenomenon of liver regeneration in rats after partial hepatectomy, and that the influence of omega-3 and omega-6 are distinct, both in oxidative stress as in liver regeneration itself.

R E S U M O

Objetivo: Estudar os efeitos dos ácidos graxos poli-insaturados (PUFA) ômega-3 e ômega-6 no estresse oxidativo e na regeneração hepática em ratos submetidos à hepatectomia parcial à 70% (HP, hepatectomia a 70%, hepatectomia parcial à Higgins-Anderson). **Métodos:** 72 ratos Wistar machos jovens foram aleatoriamente distribuídos em quatro grupos de mesmo tamanho: controle, parcialmente hepatectomizados, e parcialmente hepatectomizados com aporte diário intraperitoneal, por duas semanas, de ou ômega-3 ou ômega-6. Nos tempos 36h (T1), 168h (T2) e 336h (T3) pós-HP, substâncias reativas ao ácido tiobarbitúrico (TBARS) e glutatona reduzida (GSH) foram medidos no plasma e no tecido hepático, enquanto glicose e bilirrubina total foram aquilatados no sangue. A massa do fígado residual, nos mesmos tempos, foi o parâmetro utilizado para estimar a evolução da regeneração hepática. **Resultados:** PUFA ômega-3 inibiu a regeneração hepática e induziu redução na concentração de GSH hepático sete dias pós-HP. PUFA ômega-6, ao contrário, não mostrou efeito inibitório sobre a regeneração. Houve aumento da peroxidação lipídica tanto no sangue como no fígado com a administração de ômega-6. **Conclusão:** PUFA ômega-3 retardou a regeneração hepática pós-HP provavelmente por inibição do estresse oxidativo. PUFA ômega-6 aumentou as concentrações de TBARS no sangue e no fígado mas não alterou a evolução do processo regenerativo hepático.

Descritores: Regeneração hepática. Estresse oxidativo. Ácidos graxos. Peroxidação de lipídeos. Ratos.

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