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IMMUNOLOGY AND HOST-PARASITE INTERACTIONS - ORIGINAL PAPER

Mice chronically fed a high-fat diet are resistant to malaria induced by *Plasmodium berghei* ANKA

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Abstract

C57BL/6 mice infected with *Plasmodium berghei* ANKA (PbA) develop neurological symptoms and die 6-–7-day post-inoculation in the absence of high parasitemia. The effects of chronic intake of a high-fat diet on this process are largely unknown. In this study, we assessed the effect of a high-fat diet on the host-parasite response to malarial infection. Mice were fed ad libitum with either standard or a high-fat diet for 8 weeks and afterwards were infected with PbA. PbA-infected mice feeding a standard diet presented blood parasitemia, hepatic and cerebral histopathological alterations, and hepatic injury with increased hemozoin deposition in the liver. By contrast, these changes were not observed in the malaria high-fat diet group. In addition, mice fed a high-fat diet did not develop the expected neurological symptoms of cerebral malaria and were resistant to death. Taken together, our results indicate that chronic ingestion of high-fat diet prevents the development of experimental malaria induced by PbA injection, suggesting a relationship between a high-fat diet and malaria, which is an interesting subject for further study in humans.

Keywords Experimental malaria · *Plasmodium berghei* ANKA · High-fat diet

Introduction

Despite real progress in the control of malaria, this disease remains a major public health problem in many tropical countries. In 2013, there was a record of 584,000 malaria deaths worldwide, 90% of which occurred in sub-Saharan Africa (WHO 2014).

Sub-Saharan Africa is a region with a high malaria prevalence and is also one of the poorest regions in the world, with an extremely high rate of malnutrition; therefore, the relationship between malaria and malnutrition has been widely studied in this area (Genton et al. 1998) (Tanner et al. 1987; Mbago and Namfua 1992). In humans, chronically malnourished children present with an increased risk of developing malaria, and the prevalence of malaria is associated with poor weight gain in children (Deen et al. 2002; Rowland et al. 1977). A cross-sectional study in Sudan showed an association between poorer nutritional status and a history of malaria (el Samani et al. 1987). Similarly, in Gambia, children admitted to the hospital with malaria had a lower mean weight compared with a control group (Man et al. 1998). By contrast, it was demonstrated that children with stunting, which is a common manifestation of malnutrition, presented protection against *Plasmodium falciparum* malaria and that the mechanism may be related to an improved ability of malnourished children to produce specific cytokines in response to malarial antigens (Deen et al. 2002; Genton et al. 1998). However, the exact mechanism by which malnutrition interferes with malaria immunopathology remains unclear.

Although nutritional status in Africa is primarily characterized by under-nutrition, there is evidence of ongoing

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nutritional transition in this area (Popkin 2004; Popkin 1998; Nnyepi et al. 2015; Bosu 2014). The nutrition transition is characterized by a shift to highly refined diets, which are high in fat, salt, and caloric sweeteners and low in fiber, in rapidly growing economies (Nnyepi et al. 2015). The increasing urbanization, technological developments, and changes in dietary patterns and physical activity are potential factors that cause an increase in the prevalence of overweight and obese children and adults. In addition, there is evidence of increasing consumption of dietary energy, fat, sugars, and protein in Africa (Bosu 2014; Nnyepi et al. 2015).

Considering the nutrition transition in the African regions that present with a high prevalence of malaria, clarifying the underline mechanisms of crosstalk between high-fat diet chronic intake and the incidence of malaria is relevant. Furthermore, whereas many studies have been performed to evaluate the association between under-nutrition and malaria, the effect of a chronic high-fat diet on malarial outcomes remains to be elucidated.

Experimental models of malaria have provided invaluable data for understanding malaria pathogenesis (Langhorne et al. 2011). The *Plasmodium berghei* ANKA strain induces a progressive increase in parasitemia, an accumulation of inflammatory cells in the brain microvasculature, and the development of neurological symptoms, leading to death, in C57BL/6 mice (Langhorne et al. 2011).

In this study, using the experimental model of malaria induced by *P. berghei* ANKA infection, we evaluated the effect of a chronic high-fat diet on malaria progression in mice, by evaluating parasitemia, clinical symptoms, brain and liver histopathological changes, and liver injury. Although during the blood stage of experimental malaria, *P. berghei* do not parasitize hepatocytes, the liver pathology was also investigated because the infection is able to induce severe liver damage (Jacobs et al. 2004; Adachi et al. 2001).

Material and methods

Animals and diets

Female C57BL/6 mice (3 weeks old) were obtained from the Animal Care Facilities of Universidade Federal de Minas Gerais, Minas Gerais, Brazil. The animals were housed in cages in temperature-controlled rooms and received water and food ad libitum. The animals were randomly assigned to receive a high-fat diet (PRAGSOLUÇÕES®, Jaú, São Paulo, Brazil) or a standard diet (NUVILAB®, CR-1-NUVITAL Nutrients Ltd., Paraná, Brazil) for 8 weeks. The composition of the standard chow was 57.5% carbohydrates, 30% protein, and 12.5% of fat. The high-fat diet comprised 17% carbohydrates, 30% protein, and 35% of lipids. The detailed composition of the standard diet and high-fat diet is shown in supplementary material. All procedures were performed with the approval of the Animal Ethics Committee of the Federal University of Minas Gerais (UFMG), Brazil (reference number 05/2014).

Evaluation of body weight and retroperitoneal fat

Body weight and retroperitoneal fat content were evaluated after 8 weeks of dietary consumption. The delta body weight is represented as percentage of gain in relation to the basal weight (mice aging 3 weeks old), using the following index: Δ of body weight gain (%) = [Final weight − basal weight(× 100)]/basal weight.

To measure the retroperitoneal fat, mice were euthanized by cervical disruption and retroperitoneal fat was collected and promptly weighed.

Serum cholesterol determination

Mice were anesthetized via an i.p. injection with a mixture of ketamine (150 mg/kg) and xylazine (10 mg/kg), and the blood was collected by cardiac puncture into ethylenediamine tetraaceticacid (EDTA) containing tubes. Serum total cholesterol and high-density lipoprotein (HDL) cholesterol were measured using commercial kits (Labtest), as previously described (Fazio et al. 1997). The non-HDL cholesterol fraction was calculated as total cholesterol minus HDL cholesterol (Baker and Forbes 2010). The results are expressed as milligrams per deciliter (mg/dl).

Experimental infection

After 8 weeks feeding on a high-fat or standard diet, mice were infected with *Plasmodium berghei* ANKA (PbA) by an i.p. injection of 10^6 parasitized red blood cells (pRBC) resuspended in 0.2 mL of PBS. The percentage of parasitemia in the infected mice was monitored on Giemsa-stained blood films from day 3 onward and estimated at 1000 RBCs under immersion oil. The mice were evaluated daily regarding body weight, body temperature, survival, and clinical neurological signs of ECM using the Rapid Murine Coma and Behavior Scale for Quantitative Assessment of Murine Cerebral Malaria (Carroll et al. 2010).

Histopathology

At 5 dpi, PbA-infected mice fed with standard or high-fat diet were anesthetized with a mixture of ketamine and xylazine and perfused through the heart with 10% buffered formalin. The brain and liver were quickly removed and fixed in 10% formalin for 48 h. After fixation, coronal sections of the brain and transverse sections of the left liver lobe were obtained, embedded in paraffin, cut into 4-μm sections, and then stained with

hematoxylin and eosin (H&E) or Prussian blue to visualize the malarial pigment, hemozoin, which is synthesized during the degradation of hemoglobin (Parekh et al. 2010). An experienced pathologist examined all slides and histological sections. Images were captured using an Olympus BX51 microscope, and digital images were acquired for documentation using Image-Pro Express 4.0 (Media Cybernetics, MD, USA).

Morphometric analysis

For morphometric examination, twelve images at × 40 magnification per specimen were obtained with an Olympus BX51 microscope, and digital images were acquired for documentation using Image-Pro Express 4.0 (Media Cybernetics, MD, USA). The hemozoin area (μm^2) stained with Prussian blue was measured using ImageJ 1.49S software.

Serum alanine aminotransferase activity

Plasma serum alanine aminotransferase (ALT) activity was measured and used as an index of liver cell injury using commercial diagnostic kits (Opera Clinical Chemistry System) as previously described (Oliveira-Lima et al. 2013). Enzyme activity is expressed as international units per liter (IU/l).

Statistical analysis

Data are reported as the mean ± SEM, except for the survival curves. The survival rate is expressed as the percentage of live animals, and a log-rank test was performed to determine survival curve differences. Treatment group means were compared via two-way ANOVA, followed by Bonferroni's post-test. Data obtained from two different groups were compared via Student's *t* test. Data obtained from the hemozoin analysis were compared using the Kruskal-Wallis test (non-parametric ANOVA). Statistical significance was established at $p < 0.05$.

Results

Body weight gain and retroperitoneal fat content increase in mice fed high-fat diet

The high-fat diet or standard diet was introduced at 3 weeks of age in different groups of female C57Bl/6 mice. After 8 weeks ingesting a high-fat diet, body weight gain percentage was significantly increased in these animals (162.50% ± 11.65%) compared with the mice that were fed a standard diet (98.88% ± 6.59%) ($p < 0.0001$) (Fig. 1a). Similarly, retroperitoneal fat content was increased in the mice that were fed a high-fat diet (0.98 ± 0.21 g) compared with the mice that were fed a standard chow diet (0.11 ± 0.02 g) ($p = 0.009$) (Fig. 1b).

High-fat diet-fed mice present increased serum levels of total cholesterol, HDL, and non-HDL cholesterol

After8 weeks of a high-fat diet, the animals were euthanized, and their blood was collected to determine serum levels of total cholesterol, HDL cholesterol, and non-HDL cholesterol. The mice that were fed a high-fat diet presented with increased serum levels of total cholesterol (155.30 ± 8.42 mg/dl) ($p < 0.0001$), HDL cholesterol (104.30 ± 7.36 mg/dl) ($p < 0.0001$), and non-HDL cholesterol (55.77 ± 7.34 mg/dl) ($p = 0.0433$) compared with the mice that were fed a standard diet (total cholesterol 73.76 ± 3.56 mg/dl; HDL 38.91 ± 3.67 mg/dl; and non-HDL 34.85 ± 5.64 mg/dl) (Fig. 2).

Absence of clinical symptoms in PbA-infected mice fed a high-fat diet

After 8 weeks of high-fat diet, the animals were infected with PbA by an i.p. injection of 10^6 pRBCs. The mice that were fed a high-fat diet were resistant to the clinical neurological symptoms ($p < 0.001$) (A), body temperature decreases ($p < 0.001$) (B), and body weight decreases ($p < 0.001$) (C) induced by

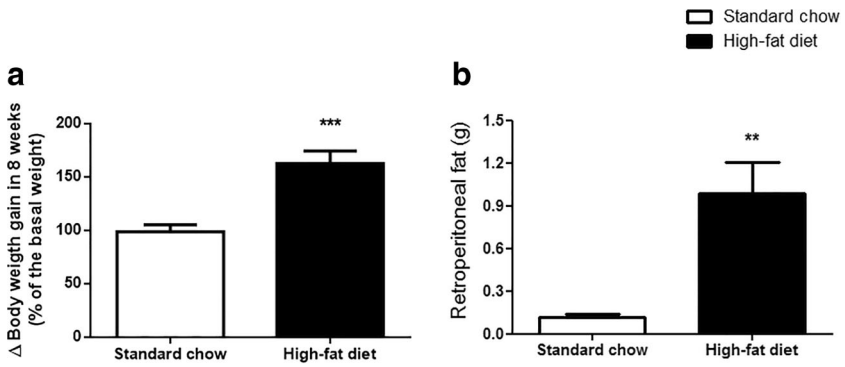

Fig. 1 Body weight gain and retroperitoneal fat content in mice fed a high-fat diet for 8 weeks. The Δ of body weight gain is represented as the % gain in relation to the basal weight (when mice was aging 3 weeks old). Body weight (**a**) and retroperitoneal fat content (**b**) were significantly increased in the mice fed a high-fat diet compared with mice fed standard chow. The data are presented as the means ± SEM (**a**, $n = 17$ mice/group) (**b**, $n = 5$ mice/group). Significant differences between groups are indicated (**$p < 0.005$; ***$p < 0.001$)

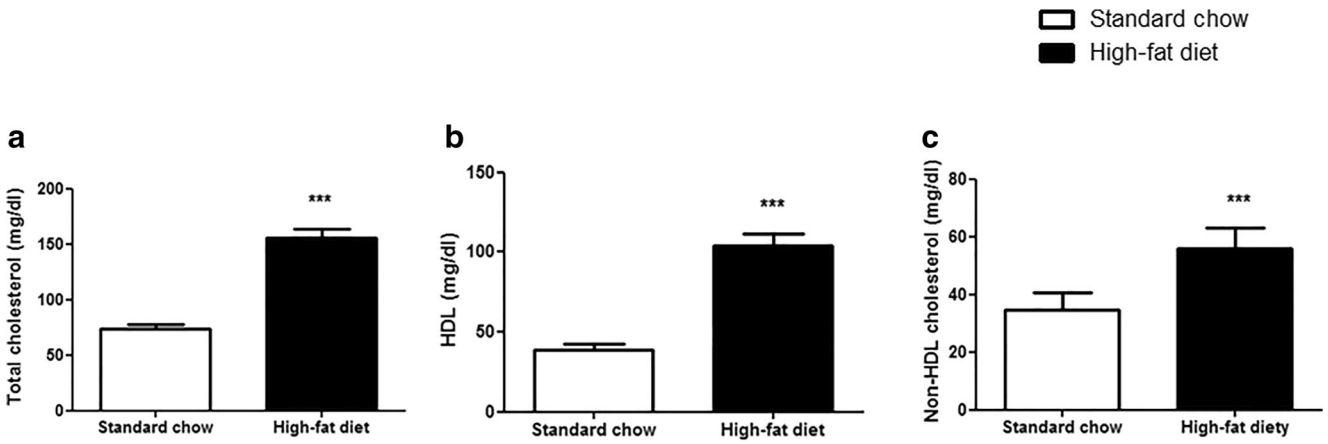

Fig. 2 Cholesterol serum levels in mice fed high-fat diet. After 8 weeks of high-fat diet ingestion, the serum levels of total cholesterol (**a**), HDL cholesterol (**b**), and non-HDL cholesterol (**c**) significantly increased compared with standard diet. The data are presented as the means ± SEM ($n = 8$ mice/group). Significant differences between groups are indicated (***$p < 0.001$)

malaria infection. However, the animals fed a standard diet presented body weight reduction of 10.83 ± 0.28% at 5 dpi, whereas the mice fed high-fat diet showed an increase in body weight of 4.33 ± 1.16%, which was similar to the results for control non-infected group (Fig. 3).

Absence of parasitized red blood cells and null mortality in infected mice fed a high-fat diet

The mice that were fed a high-fat diet did not show parasitized red blood cells, which were measurable by Giemsa staining. In addition, these animals were resistant to death after malaria infection ($p < 0.0001$) (Fig. 4). Those animals fed high-fat diet were monitored 3 months after malaria infection, and exhibited no clinical symptoms, parasitemia, or mortality throughout.

Hepatic histopathology of infected mice fed high-fat diet

Hematoxylin and eosin-stained liver sections revealed that infected mice fed standard diet present diffuse hepatic vascular congestion, leukocyte adhesion in the centrolobular venules, and perivascular inflammatory cell infiltration. On the other hand, infected mice fed a high-fat diet showed focal vascular congestion, mainly in the smaller vessels, very discrete leukocyte adhesion, and focal steatosis. Liver steatosis with hepatocellular

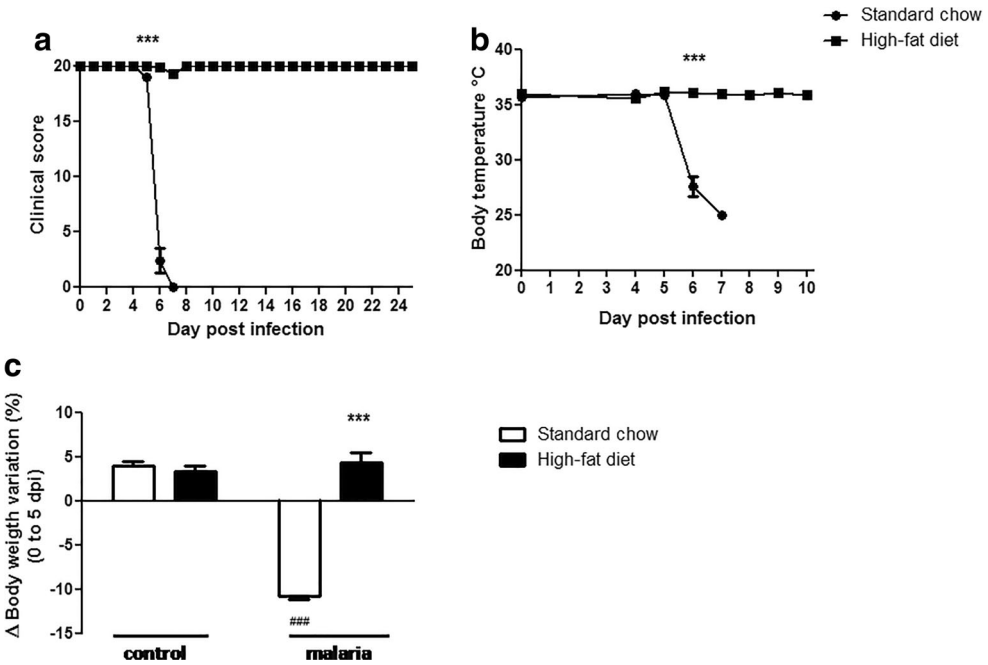

Fig. 3 Mice fed a high-fat diet are resistant to clinical symptoms induced by malaria infection. Mice fed a high-fat diet were resistant to the clinical neurological symptoms (**a**), body temperature decreases (**b**), and body weight decreases (**c**) induced by malaria infection**.** The data are presented as the mean ± SEM ($n = 9$ mice/group). Significant differences between groups are indicated (***$p < 0.001$ vs. malaria standard chow; $^{###}p < 0.001$ vs. respective control)

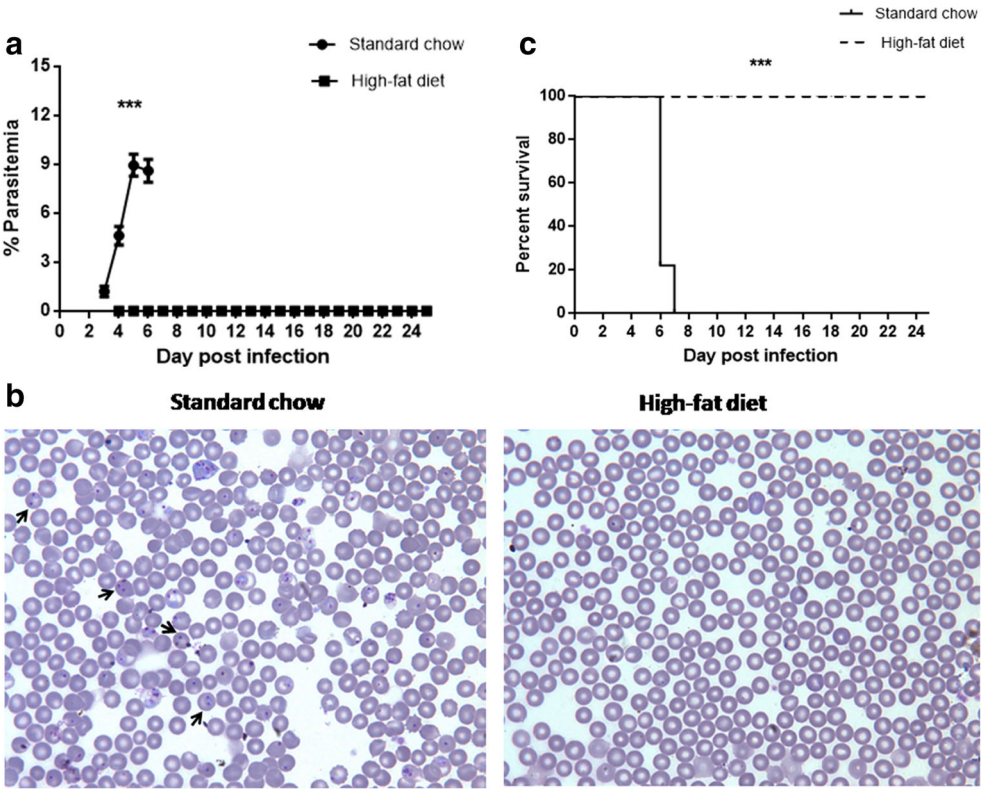

Fig. 4 Absence of parasitemia and mortality induced by malaria infection in animals fed a high-fat diet. Animals fed a high-fat diet did not show parasitized red blood cells as observed in mice fed standard chow (**a**). Red blood cells parasitized by *P. berghei* ANKA observed in mice fed a standard diet (arrow), while mice fed standard chow injected with *P. berghei* ANKA presented non-parasitized red blood cells (**b**). Animals fed a high-fat diet were resistant to death induced by malaria infection (**c**). The data are presented as the mean ± SEM ($n = 9$ mice/group). Significant differences between groups are indicated (***$p < 0.001$)

ballooning was also observed in the non-infected group fed the high-fat diet. The non-infected control group fed the standard chow diet presented normal hepatic histological characteristics, with hepatocytes arranged in radiating plates from the central vein separated by vascular sinusoids (Fig. 5). Significant hemozoin deposition was observed in the PbA-infected mice fed standard chow but not in the mice that were fed a high-fat diet following malaria infection or the controls.

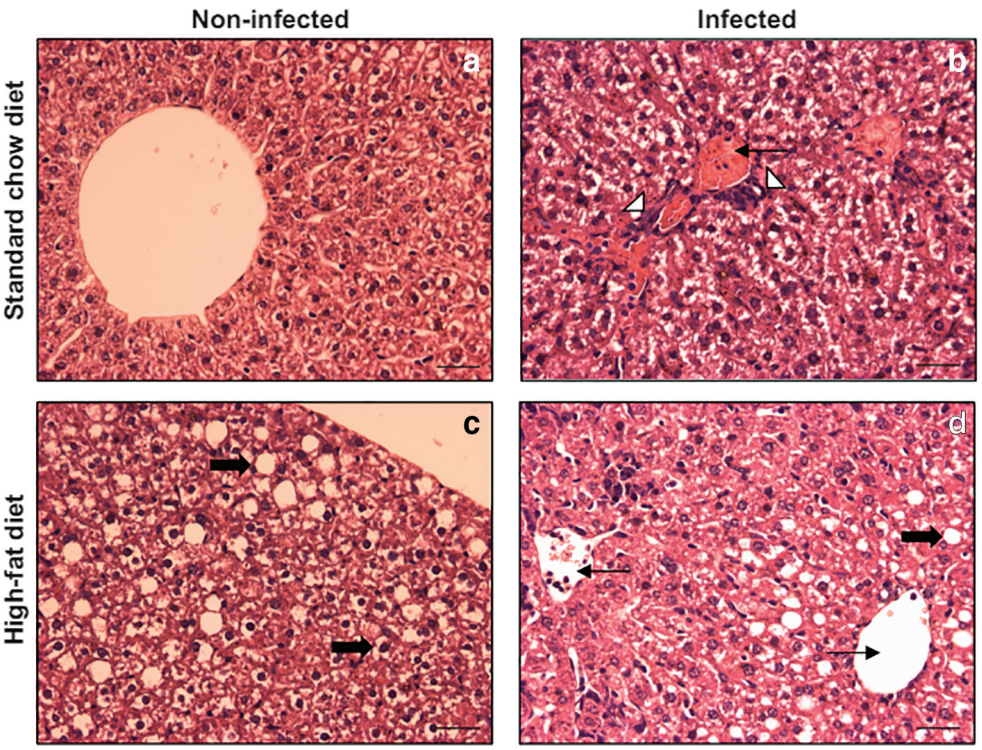

Fig. 5 Effect of chronic ingestion of a high-fat diet on histological aspects of the liver in Pb Anka-infected mice. Non-infected (a, c) and infected (b, d) mice fed a standard diet or a high-fat diet. Vascular congestion (arrow) and perivascular inflammation (arrow head) in infected mice fed standard chow (b). Discrete leukocyte adhesion (arrow) and focal steatosis (thick arrow) can be observed in infected mice fed a high-fat diet (d). Liver steatosis with hepatocellular ballooning (thick arrow) in the non-infected group fed a high-fat diet (c). Non-infected mice fed standard chow presented with normal histological characteristics (a). Bars indicate 30 μm

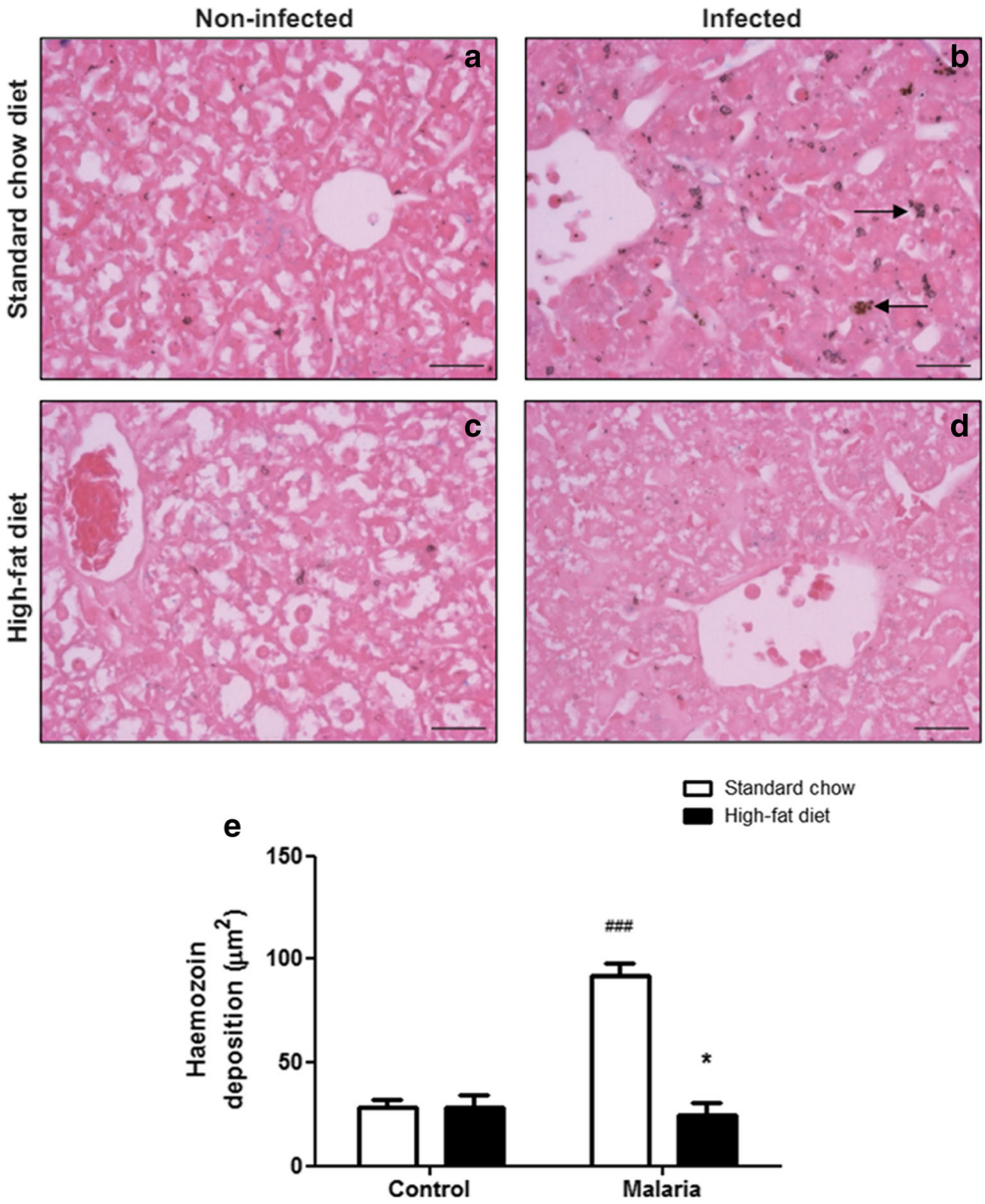

Fig. 6 Hemozoin deposition induced by malaria infection. Non-infected (a, c) and infected (b, d) mice fed a standard diet or a high-fat diet. Hemozoin deposition (b, arrows) in the PbA-infected mice fed standard chow but not in the mice fed a high-fat diet following malaria infection (d). Morphometrical examination of hemozoin deposition shows an increase in hemozoin area in the PbA-infected mice fed standard chow compared with the other groups (e) ($n = 6$ mice/group). Significant differences between groups are indicated (*$p < 0.05$ vs. malaria standard chow; ###$p < 0.001$ vs. respective control). Bars indicate 20 μm

Morphometric examination confirmed the qualitative analysis and revealed an increased area of hemozoin deposition in the liver parenchyma in the PbA-infected mice fed with standard chow (91.76 ± 6.09 m) compared with the infected mice fed with high-fat diet (28.34 ± 5.81 μm) (Fig. 6).

Serum alanine aminotransferase activity in control (non-infected) mice or infected mice

At 5 dpi, serum ALT activity in infected mice feeding high-fat diet (32.69 ± 1.28 IU/L) was similar to control non-infected group (35.97 ± 3.29). By contrast, the mice that were fed a standard chow diet presented higher ALT activity (43.35 ± 2.93 IU/L) compared with the non-infected mice (33.18 ± 0.57) ($p < 0.005$) or with infected mice feeding a high-fat diet ($p < 0.005$) (Fig. 7).

Cerebral alterations in infected mice fed a high-fat diet

The infected mice that were fed standard chow showed leukocyte infiltration in the parenchymal and pia vessels and endothelium-adherent leukocytes. Some meningeal vessels showed vascular congestion. The infected mice that were fed a high-fat diet showed very discrete leukocyte adhesion to the brain endothelium. In addition, the perivascular space was preserved in the cerebral parenchyma, and vascular congestion was not observed in this group. The non-infected groups

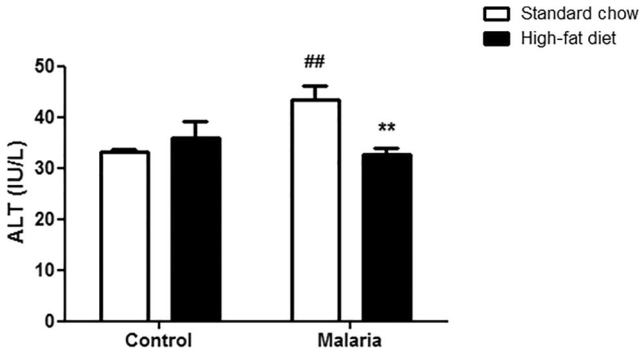

Fig. 7 Mice fed a high-fat diet do not present with an increase in the serum ALT activity induced by malaria infection. Mice fed a high-fat diet infected with PbA did not present with an increase in ALT activity in the serum on 5 dpi as observed in the standard chow group. The data are presented as the mean ± SEM ($n = 8$ mice/group). Significant differences between groups are indicated (**$p < 0.01$vs. malaria standard chow; ##$p < 0.01$ vs. respective control)

presented with normal histological characteristics, regardless of the type of diet (Fig. 8).

Discussion

In the present study, we report for the first time that C57BL/6J mice fed a high-fat diet are resistant to severe cerebral malaria induced by PbA infection. Surprisingly, these animals were not permissive to infection by the *Plasmodium berghei* ANKA parasite and did not develop the expected neurological signs, liver and brain histopathological changes, or mortality induced by malaria. A significant modifications of lipid metabolism, such as hyperlipidemia in mice that are chronically fed a high-fat diet, may be involved in this protection. In fact, injection of fatty acids during the first 3 days after infection can protect lean C57BL/6 mice infected by *P. berghei* ANKA from cerebral symptoms; however, the same treatment had no effect in BALB/c mice, indicating that the protective effect may be related to modifications of the host cells (Moumaris et al. 1995).

In our study, the histopathology analysis showed that hemozoin deposition in the liver increased significantly after malaria infection in mice fed with a standard diet, but not in mice fed a high-fat diet. Hemozoin is a biocrystal synthesized during the degradation of hemoglobin by malaria parasite, and accumulates in the liver through Kupffer cells and macrophage phagocytosis, as well as through aggregation of the parasitised erythrocytes in the liver sinusoids (Olliaro et al. 2000; Moore et al. 2008). Thus, this result provides evidence of parasite presence in the liver of mice fed a standard diet, but not in hepatic tissue of high-fat diet animals, which is consistent with the absence of blood parasitemia. Previous data obtained from *P. chabaudi* AS–infected mice found a strong positive correlation between hepatic hemozoin levels, hepatocyte damage, and liver inflammation. Moreover, intravenous injection of *P. falciparum*–derived hemozoin in malaria-free C57BL/6J mice induced inflammatory gene transcription in the liver, suggesting that hemozoin may be involved in malaria hepatopathy by inducing inflammation (Deroost et al.

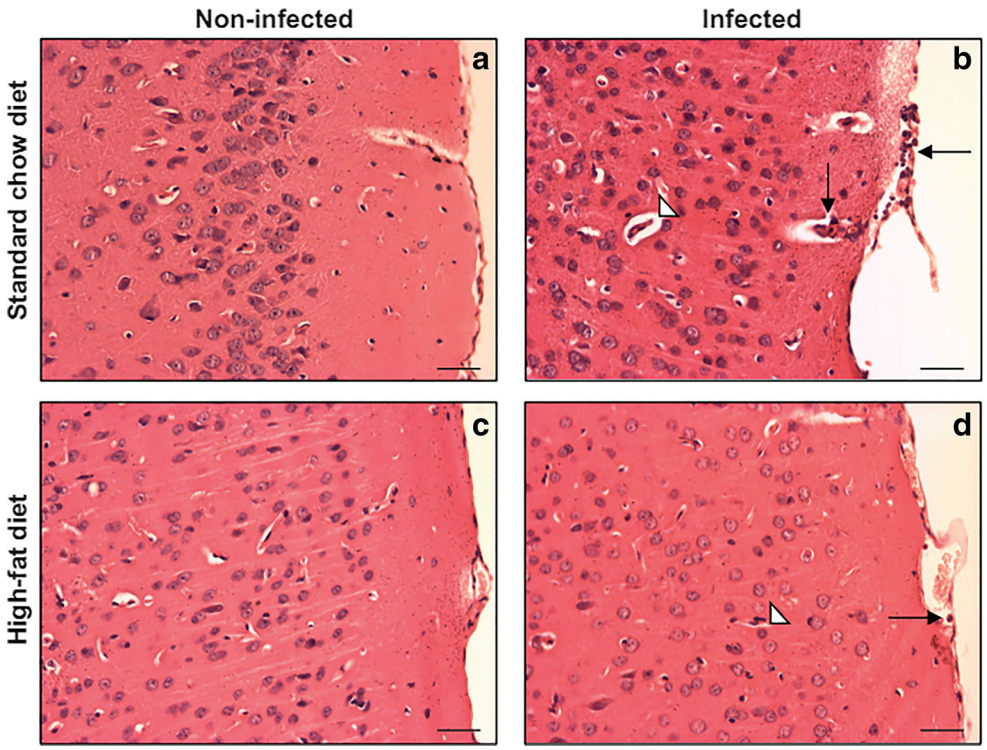

Fig. 8 Effect of chronic ingestion of a high-fat diet on cerebral histological changes induced by PbAnka infection. Non-infected (a, c) and infected mice (b, d) fed standard or a high-fat diet. Leukocytes within the cerebral parenchymal and pial vessels, endothelium-adherent leukocytes (arrow), and wide perivascular spaces (arrow head) in the infected mice fed standard chow (b). Very discrete leukocyte adhesion in the pia and brain vessels and preserved perivascular space (arrow head) in the infected mice fed a high-fat diet (d). Non-infected groups presented with normal histological characteristics (a, c). Bars indicate 30 μm

2014). In our study, the high intensity of hepatic hemozoin deposition in the malaria-infected mice that were fed standard chow was associated with vascular congestion and perivascular inflammation in the liver of these animals; such histopathological alterations were not pronounced in the malaria high-fat diet group. These histopathological changes were also associated with increased serum levels of alanine aminotransferase, indicating pronounced liver injury in the malaria-infected mice that were fed standard chow. By contrast, the serum ALT levels in the high-fat diet PbA-infected mice were similar to those found in the non-infected group. Serum ALT levels have been frequently used in experimental and clinical studies as a marker for liver damage following malaria infection (Giannini et al. 2005; Iwalokun et al. 2006). The histopathology analysis showed liver steatosis in mice chronically fed a high-fat diet. From a physiological viewpoint, visceral liver steatosis is caused by an imbalance between lipid availability and lipid disposal and occurs when excessive triglyceride accumulation occurs inside liver cells (Ferre and Foufelle 2010; Ha et al. 2014; Ibrahim et al. 2012). The fact that chronic intake of a high-fat diet causes resistance to malaria infection deserves special attention because it can cause deep modifications in lipid metabolism and may compromise liver function. Similar to the liver, the infected mice that were fed a standard diet showed brain pathological features typical of cerebral malaria, such as adherent leukocytes in the cerebral microvasculature and vascular congestion, which precede the neurological signs of cerebral malaria. By contrast, these signs were absent in the mice on a high-fat diet. Similar to our findings, a recent study demonstrated that administration of a high-fat diet to mice for a period of 4 days significantly reduces *Plasmodium* liver stage infection. Following this short-term of high-fat diet administration, the mice do not show signs of severe disease such as neurological signs of cerebral malaria, resulting in an extended overall survival when compared with mice fed a standard chow diet. In this study, the high-fat diet-induced reactive oxygen species was identified as the mechanism mediating the impairment of *Plasmodium* liver infection (Zuzarte-Luis et al. 2017). Previous data showed that obese leptin-deficient mice (ob/ob) are resistant to cerebral malaria, presenting progressive parasitemia resulting in death 18–25 days after PbA injection when compared with control animals (Robert et al. 2008). Different results were found in another study, in which the authors demonstrated that mice displaying hypothalamic obesity (induced by post-natal injections of monosodium glutamate) died earlier, and presenting lower red blood parasitemia levels than the controls (de Carvalho et al. 2015). It is interesting to note that those obese mice died following malaria infection, while in our study, mice that were chronically fed a high-fat diet were completely resistant to malaria symptoms, with no parasitized red blood cells and no deaths after having been inoculated with PbA. It is possible that the different mechanisms associated with the induction of obesity, e.g., leptin genetic deficiency; post-natal injections of monosodium glutamate or chronic ingestion of high-fat diet could be one of the key factors that modulates different outcomes for pathology.

In summary, we report that chronic ingestion of a high-fat diet triggers resistance to malaria in PbA-injected mice. These findings provide new perspectives for the development of prophylactic agents against malaria and for understanding malaria pathology. However, further studies are necessary to elucidate the molecular mechanisms underlying the relationship between a high-fat diet and malaria resistance.

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Compliance with ethical standards All procedures were performed with the approval of the Animal Ethics Committee of the Federal University of Minas Gerais (UFMG), Brazil (reference number 05/2014).

Conflict of interest The authors declare that they have no conflicts of interest.

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