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Gluten diet alters the blood cytokine expressions in Spix's Saddleback Tamarin (*Leontocebus fuscicollis*) kept in captivity in the Amazon region

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ABSTRACT. Callitrichids represent a wide diversity of primates from the New World and are excellent models for biomedical studies, one being the effect of diets that contain gluten. The objective was to estimate blood cytokine gene expressions in Spix's Saddleback Tamarin (*Leontocebus*

fuscicollis) submitted to periods with a gluten diet (GD) and a gluten free diet (GFD). Ten animals were monitored for stool consistency and blood samples were collected. Gene expressions were determined using RT-PCR and analyzed statistically. The GD alters the consistency of stools to softened and diarrheic. All genes showed significant differences between the two diet periods. The *NEF2*, *CD83* and *HLA-DQB1* genes increased their expressions significantly in the shift from GFD to GD period, and when reintroduced to the GFD the expressions normalized and, *TNFSF13B* decreased significantly and decreased with the reintroduction of the GFD. The *HLA-DQA1* gene decreased its expression from the GFD to GD, but decreased significantly when reintroduced to the GFD. We conclude that some blood cytokine specifics for celiac patients also altered in *Leontocebus fuscicollis* with GD and may normalize with GFD reintroduction, or decrease their expressions, which is quite different from celiac humans who persist in high or low expressions for life.
Key words: Callitriquids, Gene expression, Gluten diet, Cytokine, Nohuman primates.

INTRODUCTION

Marmosets and tamarins (Callitrichids) constitute the most diverse subfamily of New World monkeys , and one of the most varied phylogenetically. They are distributed into six genera within the subfamily: *Callimico, Callithrix, Cebuella, Mico, Leontopithecus* and *Saguinus*. And the genus *Saguinus* has been further divided into three subgenera: *Leontocebus, Saguinus* and *Tamarinus* (Sampaio et al., 2015; Garbino, 2018). Callitriquids play an important role as an experimental model for studies of reproduction, behavior, physiological systems and various clinical diseases (Smith, 2020). They are also excellent models for studies on aging because they are small animals with a short lifespan and early maturation (Ross et al., 2012), in addition to studies of chronic diseases (Tardif et al., 2011; Ross et al., 2012). Because they are very similar in these respects to humans, especially regarding metabolic processes, they are also excellent models for understanding these disorders (Banton et al., 2016).

Callitrichids in their natural habitat adopt a variety of feeding strategies for obtaining food containing the essential nutrients they require. In captivity, they can develop gastrointestinal disturbances, when caretakers ignore the species' food biology (Power et al., 2019). According to Peres (1993), free-living Amazon tamarins exhibit varied dietary patterns compared to other callitrichids, including arboreal species, climbers on lianas, epiphytic and shrubby species. Additionally, they observed that these animals mainly feed on pulp of ripe fruit, floral nectar, and plant exudates from certain plant species. In a comparative study with wild groups of *Callimico goeldii, Saguinus labiatus* and *S. fuscicollis*, observed a predominance of fruit species in the rainy season. It is particularly noteworthy that *Callimico goeldii* consumes large quantities of the fungus more frequently in the dry season. In contrast, *Saguinus labiatus* and *Saguinus fuscicollis* rarely eat fungi, but have a high intake of nectar, arthropods and exudates during periods of low fruit availability.

One important disorder to study in callitrichids is the effect of some foods on the gastrointestinal tract, one of them being the presence of gluten in some food sources provided in

captivity (Kuenel et al., 2013). Kuenel et al., (2013) observed clinical changes in the animals when submitted to gluten diets, including recurrent diarrhea and dermatological problems (alopecia). However, clinical features are often restored with the reintroduction of a gluten-free diet. Recent studies have evaluated the effects of a gluten diet on the expression of innate immune system genes in the peripheral blood (Almeida et al., 2019). They observed that the expression of the Defensin gene increased substantially and then recovered over time until the reintroduction of a gluten-free diet. The study found that the presence of soft and diarrheal stools was significantly more frequent during the period when submitted to a gluten diet. Thus, when the gluten-free diet was reintroduced, firm stools were reestablished.

In humans, there are numerous studies studying the effect of gluten-containing diets on the inflammatory clinical characteristics of the gastrointestinal tract, which results in an immuno-enteropathy known as Celiac Disease (Makovicky et al., 2020). CD4 + T cells are responsible for the recognition of Gluten: Specific antigens (Risnes et al., 2018). They have variations, which persist for decades in celiac patients who are not eating gluten-containing foods (Makovicky et al., 2020). Several genetic markers have been described as references in blood samples and intestinal biopsies from patients with celiac disease (allergy to gluten proteins). Therefore, to draw a parallel between intestinal diseases in callitrichids and humans. The genes *NEF2*, *CD*83, *HLA-DQB1*, *HLA-DQA1*, *TNFSF13B* stand out (Bragde et al., 2014; Sangineto et al., 2018). In this context, the objective of our study was to verify the influence of the gluten diet on blood gene expression of some cytokines, which are useful as markers of celiac disease in humans, using Spix's Saddleback Tamarin (*Leontocebus fuscicollis*) raised in captivity.

MATERIAL AND METHODS

This work was carried out following the animal welfare guidelines for experiments established by CONCEA (National Council of Control of Animal Experimentation), Brazil. All experimental procedures were registered on the Biodiversity Authorization and Information System of the Chico Mendes Institute of Biodiversity (SISBIO / ICMBIO, protocol number 47969-1) and was approved by the Ethics Committee of Animal Use at the Evandro Chagas Institute (CEUA / IEC, Protocol Number 17/2015).

Experimental design

Ten *L. fuscicollis* were selected, five males and five females. The subjects were a mean ± SD body mass of 0.433±0.509 kg and age range of 26-36 months. All primate colonies at the National Primate Center (CENP, Ananindeua Pará, Brazil) are submitted to annual health screenings, including physical examination, hemogram, biochemical tests, and deworming treatment. The animals were young adults (24-36 months) and had not been mated since they were 18 months of age. None of the animals used in this study had a history of infectious diseases as per their last health screening (2 months before data collection). All individuals lived in family groups of up to 5 individuals. They were kept in sheds and positioned in a north-south orientation to receive ≤12 h of natural light, in enclosures measuring 1.5 m x 2.0 m x 1.0 m (length, height and width). The enclosures had external and internal water bottles and multiple bowls for food provisioning. The animals were fed according to CENP's standard management practices. And, the experimental diets are described in Almeida et al. (2019) as P25 Megazoo food, fruit juices, fruit mix supplement, and 50 g of gluten that were provided during the Gluen Diet period – Total of 160 kcal, with 25%

of protein, 65% of carbohydrate, and 10% of lipid content. Diet intake was monitored by 3 trained observers from National Primate Center. The animals had ad libitum access to water. Feeding of these diets was alternated between three periods represented in Figure 1. At the end of each period, 2 mL of blood from the femoral vein was collected in a vacuum tube containing EDTA and then kept in liquid nitrogen for transport to the laboratory where they were kept at -80 °C for the following laboratory procedures. Observations of stool consistency were performed in all periods (gluten diet and reintroduction of the gluten-free diet), over a total period of 45 days. Three observers were trained to evaluate stool consistency, which was monitored daily and classified as (1) Firm, (2) Softened or (3) Diarrheal (Figure 1).

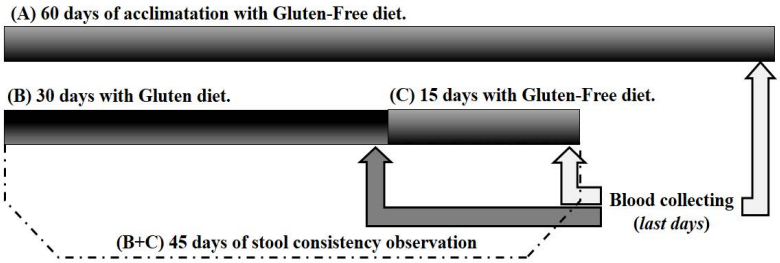

Figure 1. Experimental scheme: (A) acclimatization period with gluten-free diet, (B) period under gluten diet, and (C) period of reintroduction of the gluten-free diet. Also shown is the timing of blood collection and observations of stool consistency. Adapted from Almeida et al., (2019).

RNA extraction and RT-PCR for quantification

RNA extraction was performed from 300 uL of whole blood in a 1.5 mL microtube with TRIZOL reagent (Invitrogen, Carlsbad, CA, USA) following manufacturer recommendations. Next, RNA was treated with DNAse to obtain the pure RNA samples and evaluated for concentration and purity under a A260 / A280 ratio using a NanoDrop ND-1000 Spectrophotometer (Agilent, Santa Clara, CA, USA). Samples with a degree of purity equal to or greater than 1.9 were used for RT PCR.

The genes selected for analysis were based on results of gene expression in the blood of celiac humans (Bragde et al., 2014; Sangineto et al., 2018). The primer sequences were obtained using the PRIMER3 program (v.0.4.0.) available at http://bioinfo.ut.ee/primer3-0.4.0/. The sequences referring to drawing the primers were based on those of *Callithrix jacchus* deposited in Genbank by their respective identifiers, and the exons with the best primer confection patterns were selected. The sequences of primers and identifying information are given in Table 1.

RT-PCRs were performed for a final volume of 20 uL using the one-step Power Sybr® Green RNA-to-CT ™ kit (Applied Biosys-tems, Foster City, CA, USA), with the conditions of reagents and temperatures set according to the manufacturer's recommendations. All reactions were performed using the CFX96 TouchTM Real-Timer Detection System thermocycler (Bio-Rad, Hercules, CA, USA).

Ct (Threshold Cycle) values were determined through the baseline generated at the end of the exponential growth curve of RT-PCRs. Next, the relative expression values of the genes were

Table 1. Gene sequences of primers used to perform RT-PCRs.

Genes	Sequences 5'-3'	Size (bp)	Exon	Genbank (ID)
NFE2	F- AATGCTCCAAGTGAGCCATC	128	2	100414670
	R- TAAGGTGGTGGAGGAAGTGG			
TNFSF13B	F- AGCAGTCACGCCTTACTTCT	100	1	100399491
	R- TATCGGACAGAGGGGCTTTC			
CD83	F- ACTGGAGGGCAGTGAAGAGA	108	3	100405451
	R- AGGGAATAGAGCCTGCCACT			
HLA-DQA1	F- GAGATTCCAGCCCTACGTCA	137	4	100386508
	R- CTTGGTGTCTGGAAGCATCA			
HLA-DQB1	F- CGTGCGTCTTGTGACAGAAT	136	1	100386865
	R- CAGGATGTCCTTCTGGCTGT			
GAPDH	F- TCAAGAAGGTGGTGAAGCAG	155	8	100412621
	R- TTGACGAAGTGGTCGTTGAG			

NFE2 = nuclear factor, erythroid 2; *TNFSF13B* = TNF superfamily member 13b; *CD83* = CD83 antigen; *HLA-DQA1* = HLA class II histocompatibility antigen, DQ alpha 1 chain; *HLA-DQB1* = HLA class II histocompatibility antigen, DQ beta 1 chain; *GAPDH* = glyceraldehyde-3-phosphate dehydrogenase; bp= base pairs; ID= Identity.

estimated using the equation $2^{-\Delta Ct}$, where ΔCt is the difference between the Ct of the target genes and the Ct of the endogenous gene, where the GAPDH gene was used for this purpose. Relative expressions above and below 1.0 were considered up- and downregulation, respectively (Livak, 2001).

STATISTICAL ANALYSIS

The proportions of stool consistencies were compared using the chi-square test and the gene expression values were submitted to one-way ANOVA and the means were compared using the Tukey test. The level of significance was set at 0.05.

RESULTS

The average body mass of males was 0.450 kg (±0.02) and females were 0.428 kg (±0.05). It was observed that there was no significant difference ($P > 0.05$) between the body mass of males and females across the four collections. However, when comparing the average body masses between the collections, it was noted that there was a significant increase ($P < 0.05$) during the first fifteen days on the Gluten Diet. Subsequently, at the end of the 30-day diet period, a significant decrease ($P < 0.05$) in body mass was observed. Additionally, during the last fifteen days, when the animals were on the Gluten-Free Diet, they gained body mass compared to the acclimatization period with the Gluten-Free Diet.All genes were expressed in peripheral blood cells. Many of these genes showed both high expression at different stages of the study. Throughout the experiment, the expressions of all genes showed highly significant differences between test diet periods ($P <0.001$). In the gluten diet period had significant softened and diarrheic stool frequencies than firm stool, but when the gluten-free diet was reintroduced, the firm stool was more frequent ($P <0.001$).

Some genes increased their expression over the 30-day period with a gluten diet (*NEF2*, *CD83* and *HLA-DQB1*). The *NEF2* gene showed an upregulation, increasing about 60-fold the expression

in relation to the first period and then, when the gluten-free diet was reintroduced, the expression decreased and normalized. The *CD83* gene also increased its expression when the gluten-free diet was introduced by about 8-fold compared to the gluten-free diet and, then with the reintroduction of the gluten-free diet, the expression decreased significantly to a lower level than the initial one. The *HLA-DQB1* gene increased about 3-fold more with the introduction of gluten in the diet and when there was a reintroduction of the gluten-free diet, the expression returned to the initial level (Figure 2).

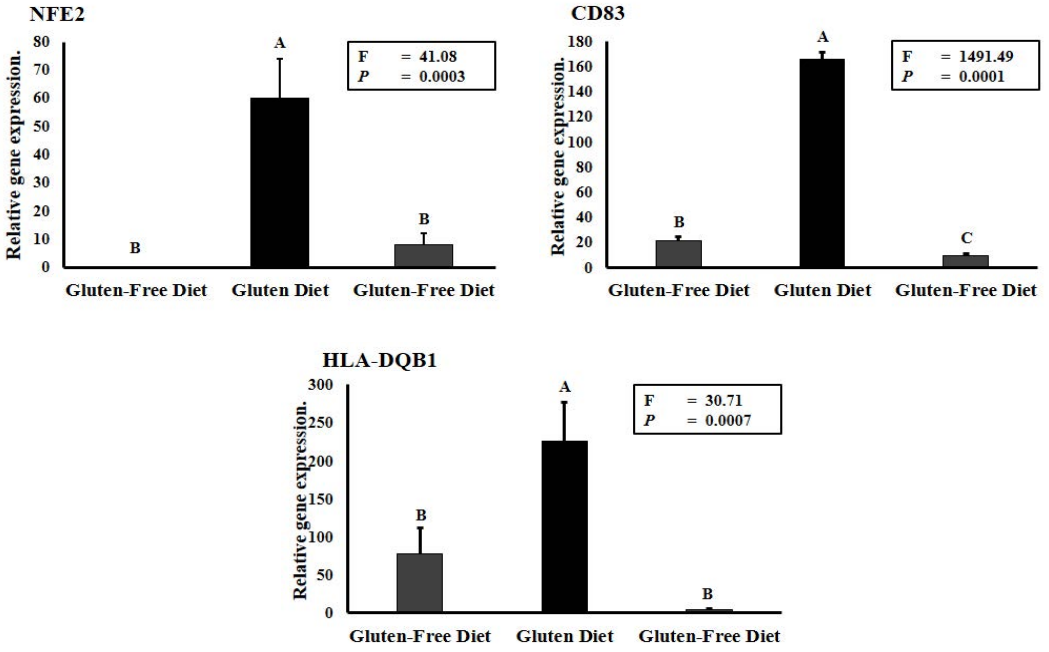

Figure 2. Genes that showed increased expression with the introduction of a gluten diet and decreased expression with the reintroduction of gluten-free diet. Different letters between diets mean significant differences between the means (N=10, df=6, ANOVA and Tukey tests).

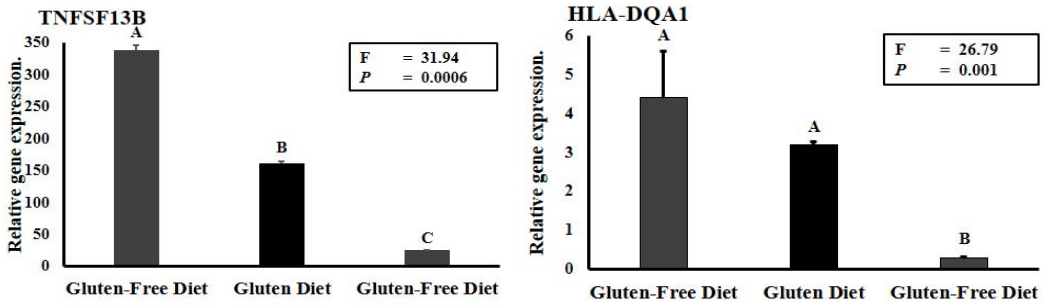

Figure 3. Genes that decreased in relative expression across the study with each change in the experimental diet. Different letters between diets mean significant differences between the means (N=10, df=6, ANOVA and Tukey tests).

During the acclimatization period, the animals are eating a gluten-free diet and the *TNFSF13B* gene has high gene expression (about 340 fold on the endogenous), however, when the gluten diet was introduced, the expression of this gene decreased significantly by half. Then, when the animals were reintroduced to a gluten-free diet, expression continued to decrease (Figure 3). The expression of the *HLA-DQA1* gene tended to decrease, but this decrease was not significant over the 30-day period with a gluten-containing diet, however the decrease still extended significantly to about 11% with the reintroduction of gluten-free diet (Figure 3).

DISCUSSION

Understanding the influence of a gluten diet on blood gene expression of cytokines in Spix's saddleback tamarin can provide valuable insights into potential biomarkers and mechanisms of celiac disease in humans. This unique primate model may offer significant parallels due to its genetic and physiological similarities to humans. The *NFE2* gene is an important regulator of genes involved in hematopoiesis (Gasiorek, 2015). Its high expression can be observed in a patient with myeloproliferative neoplasia (Peeken et al., 2018). In this study, it was possible to observe that the gluten diet regulates a highly significant increase in the expression of the *NFE2* gene. The findings by Sangineto et al., (2018) in humans with celiac disease demonstrate that the expression of the *NFE2* gene increased significantly; however, it was not an overexpression in relation to the control group (about 1.5-fold greater). This overexpression of *NFE2* in noh-human primates can also be justified by the condition of stress in captivity associated with the gluten diet. Chartoumpekis et al., (2011) associated stress conditions with high fat diets in increasing of the *NFE2* releasing factor in mice, thus generating a character of obesity in these animals.

The *CD83* gene, when expressed, is a molecular regulator of hyperactive immune responses, which can eventually lead to autoimmunity (Doebbeler et al., 2018; Wild et al., 2019). The same authors also revealed that the absence of *CD83* results in a more pro-inflammatory phenotype in dendritic cells leading to a strong induction of antigen-dependent T cells. In this context, it is possible to see that celiac patients have low expression of the *CD83* gene (Sangineto et al., 2018), whereas in this study, this gene increased significantly by about 8-fold its expression when the animals were fed a gluten diet. This demonstrates the difference in expression between celiac individuals who exhibit gluten autoimmunity (Khalkhal et al., 2019) of non-celiac non-human primates.

In celiac patients who have the allelic variations *HLA-DQA1*05* and *HLA-DQB1*02* in the genes, $CD4^+$ T lymphocyte cells specifically recognize gluten peptides through DQ2.5 molecules (Abadie et al., 2011). However, *DQA1* and *DQB1* gene expressions are not directly associated with DQ2.5 molecules in celiac patients (Pisapia et al., 2016). In this context, only the *HLA-* gene in this study was different, where *DQB1* was significantly upregulated in non-human primates that were subjected to a gluten diet. However, *DQA1* did not change at all between diets. Despite all this expression, the *DQB1* gene normalized with the reintroduction of the gluten-free diet.

The *TNFSF13B* gene is a 13b member of the Tumor Necrosis Factor superfamily, also known as BAFF (B-Cell Activation Factor) (Steri et al., 2017). In this study, the expression of *TNFSFS13B* decreased significantly with the addition of gluten and continued to decrease with the reintroduction of the gluten diet. This may have had an effect on B cells, as *TNFSFS13B* is produced by monocytes and neutrophils with the function of maintaining B cell homeostasis through regulation of B cell maturation, differentiation and survival (Woodland et al., 2006). But if we observe an experiment with celiac and non-celiac individuals, the expression of *TNSFS13B* may be up to 30% less in celiac

individuals (Castellanos-Rubio, 2012). In an evaluation of the expression of the *TNFSFS13B* gene in the plasma cells of non-celiac and non-celiac individuals there was a significant difference between the two groups.

Therefore, if the expressions were high, this could lead to increased levels of IgG and IgM, as well as reduced monocytes (Steri et al., 2017) and increased expression of the receptor for this cytokine, as observed in celiac individuals, however, it was much more expressed in individuals in the control group (Snir et al., 2019).

CONCLUSION

In conclusion, the animals submitted to the GD experiment did not present a clinical picture of CD, despite the alternating consistency of stools (softened and diarrheal), and the expressions of some cytokines during the GD period. However, the reintroduction of GFD normalized or decreased the expression of cytokines, normalizing them and restoring stools to a firm consistency. This study could provide a novel animal model for understanding the genetic and immunological underpinnings of celiac disease, potentially leading to better diagnostic markers and therapeutic strategies in humans.

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