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Hypertrophy of the neurons in the ileum of rats infected with cysts of *Toxoplasma gondii* (genotype II)

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ABSTRACT. This paper verified possible alterations caused by a genotype II *Toxoplasma gondii* strain with respect to the total number and morphometry of the myenteric neurons in the terminal ileum and descending colon of rats. Eight rats were divided into two groups: control (n = 4) and experimental (n = 4). This group was inoculated orally with 20 tissue cysts of *T. gondii* from a genotype II strain (ME-49). Whole mounted from the terminal ileum and the descending colon were stained with Giemsa. There was not any neuronal loss on both organs. The neurons became hypertrophied in the terminal ileum, whereas morphometric alterations were not observed for the neurons in the descending colon.

Key words: enteric nervous system, toxoplasmosis, morphology.

RESUMO. Hipertrofia de neurônios do íleo de ratos infectados com cistos de *Toxoplasma gondii* (genótipo II). Objetivou-se verificar as possíveis alterações causadas por uma cepa genótipo II de *Toxoplasma gondii*, sobre o número total e a morfometria de neurônios do plexo mientérico, do íleo terminal e do cólon descendente de ratos. Oito ratos foram divididos em dois grupos: controle (n = 4) e experimental (n = 4), sendo este inoculado, por via oral, com 20 cistos teciduais de *T. gondii* de uma cepa genótipo II (ME-49). Preparados totais do íleo terminal e cólon descendente foram corados com Giemsa. Não houve perda neuronal em ambos os órgãos. Os neurônios se tornaram hipertróficos no íleo terminal, enquanto nenhuma alteração morfométrica foi observada nos neurônios do cólon descendente.

Palavras-chave: sistema nervoso entérico, toxoplasmose, morfologia.

Introduction

Toxoplasmosis is cause for concern in public health and animal production. It is usually asymptomatic in humans; however, it may cause blindness, severe neurological disorders, hepatitis, and pneumonia in immunocompromised patients, as well as severe damage to fetuses (ASCENZI et al., 2005). On animals such as dogs, toxoplasmosis may cause fever associated with lassitude, anorexia, diarrhea, pneumonia, and neurological manifestations. In small ruminants, clinical toxoplasmosis is associated with fever, dyspnea, nervous symptomatology, and abortion, generally in sheep and perinatal mortality in lambs (URQUHART, 1998) whereas it presents diarrhea, cough, and dyspnea in pigs (WINGSTRAND et al., 1997).

This disease is caused by an obligate intracellular protozoan parasite named *Toxoplasma gondii*, which is scattered worldwide (DUBEY; BEATTIE, 1988). Its life cycle is facultatively heteroxenous: Felidae are definite hosts where the sexual reproduction of the parasite occurs with the formation of oocytes, which are eliminated via feces. All homoeothermic animals can be intermediary hosts, where the asexual reproduction of the parasite occurs with the formation of tachyzoites and bradyzoites (JACOBS, 1967; DUBEY, 1994). Tachyzoites present a high proliferation rate, what favors their dissemination within the host, characterizing the acute phase of the disease. Tissue cysts, full of bradyzoites, last for a long period of time, sometimes the entire life of the host, which characterizes the chronic phase of the disease (FERREIRA et al., 2003).

Infection by *T. gondii* may occur as a result of: (1) ingestion of food or water contaminated with oocytes from cat feces, (2) ingestion of tissue cysts in raw or undercooked meat, (3) via transplacentary (BARRAGAN; SIBLEY, 2003), (4) blood transfusion (DUBEY; BEATTIE, 1988), or (5) accidental inoculation during laboratorial manipulation. When oral infection occurs, the parasite crosses the intestinal epithelium, disseminates to other tissues, and may cross other biological barriers such as the placenta and the hematoencephalic barrier, and reach

immunologically privileged sites. The course of the parasitic infection is highly variable, mainly according to the type of host, immunological situation, the path and level of the infection, and parasite constitution (JOHNSON, 1984).

T. gondii presents a highly clonal population structure (HOWE; SIBLEY, 1995), which consists predominantly of three lines named type I, II, and III. As type I samples are often isolated from infections in human beings, samples from infections in animals are predominantly from either type II or III (HOWE; SIBLEY, 1995; HOWE et al., 1997; MONDRAGON et al., 1998; OWEN; TREES, 1999). Type II strains present low virulence (HOWE; SIBLEY, 1995) and high prevalence – either for human or animals – all around the world (HOWE et al., 1997; MONDRAGON et al., 1998; FUENTES et al., 2001). There is a considerable interest in determining how genotypes of *T. gondii* may differ concerning the capacity to induce pathologies or their occurrence in a certain animal species (SAEIJ et al., 2005).

It is common to observe signs and symptoms of alterations in the Central Nervous System (CNS) from patients infected with *T. gondii*; most commonly, headache, focal neurologic signs, confusion attacks evolving to coma, chorioretinitis, hydrocephaly, and encephalitis (DÄUBENER; HADDING, 1997). Moreover, the tissue cyst rupture may release the parasite and destroy the nervous tissue resulting in meningoencephalitis (GAZZINELLI et al., 1993). On the other hand, it is also common to observe diarrhea in animals infected by *T. gondii* (HASS et al., 1989; URQUHART, 1998). Thus, a possible alteration caused by the parasite on the Enteric Nervous System (ENS) – responsible for the digestive tube intrinsic innervation (FURNESS, 2006) – may be related to diarrhea pathophysiology. Therefore, this study was carried out in order to assess possible alterations caused by a genotype II *Toxoplasma gondii* strain on the total number and morphometry of the neurons of the myenteric plexus in the terminal ileum and the descending colon of rats.

Material and methods

Experimental groups

The experimental protocol as previously approved by the Unipar Ethics Committee in Research Involving Animal Experimentation.

Eight male 60-day-old Wistar rats (220.2 ± 24.5 g) were kept inside boxes with individual grids in a bioterium constantly at 25°C with 12-hours light/12-hours dark alternate cycles. The animals were divided into two groups: Control (CG, n = 4) and Experimental (EG, n = 4). In this, twenty genotype II (ME-49) *Toxoplasma gondii* strain tissue cysts were orally administered. All animals received rat chow (Nuvital®) and water *ad libitum*. After 24 hours, each specimen was anesthetized intramuscularly by using the following protocol: Acepram® 1.26 mL kg^{-1} + Ketalar® (10 mL) 1.26 mL kg^{-1} + Rompum® (2%) 0.42 mL kg^{-1} + Atropina® (1%) 0.22 mL kg^{-1} (PACHALY et al., 2003), for the removal of the terminal ileum and descending colon by laparotomy. The distal portion towards the ileocecal fold was considered as the terminal ileum. Then, the animals were submitted to euthanasia by anesthetic deepening.

Collecting whole mount preparations

The terminal ileum and the descending colon from each animal were measured with respect to their length and width by using a millimetric ruler right after being removed. As a result of the difficulty of anatomically distinguishing the terminal ileum from the jejunum, these measurements were performed by considering these two organs together. Then, they were washed in a 0.9%-NaCl solution, filled and immersed in a fixing solution containing ascetic formaldehyde for 48 hours. They were then dissected with the aid of a stereomicroscope by removing the mucosa and submucosa. The whole mounted – composed by muscle and serous – were stained according to the Giemsa technique (BARBOSA, 1978).

Quantitative analysis

The total number of myenteric neurons in 120 microscopic fields, uniformly distributed around the entire intestinal circumference of each specimen, totalizing 25.5 mm^2 per animal, was counted. Therefore, a Motic BL220A binocular microscope with 40x objective was used. The neurons positioned at the edges of each field were counted in alternated fields.

Morphometric analysis

The area of the soma, cytoplasm, and the nucleus of 300 neurons of the myenteric plexus of the terminal ileum and the descending colon (uniformly distributed all over the intestinal circumference) of the animals from each group was measured with the software Image Motic Plus, version 2.0. A microscope with a 2.0 Megapixel digital camera (Moticam 2000) connected to a computer was used for that purpose. From these values, neurons were divided into classes by considering the soma area (100 μm^2 interval) and the nucleus-soma ratio (0.10 intervals).

Statistical analysis

All data were first submitted to the Kolmogorov-Smirnov test in order to verify the type of distribution. Data with normal distribution were expressed in mean ± standard deviation. Data with free distribution were expressed as median as well as 25 and 75 percentiles (P25; P75). In order to compare the data between the Control Group and Experimental Group, Student's t-test (normal distribution data) and Mann-Whitney (free distribution data) were used by considering significant P-values lower than 0.05.

Results

The results of the measure of the dimensions of the collected organs through the quantitative and morphometric analysis are presented on Tables 1, 2, and 3, respectively. The number of neurons was divided in classes according to the soma area and according to soma-nucleus area ratio is presented on Figures 1 and 2, respectively.

Table 1. Length, width, and area of the ileum-jejunum and the total colon of healthy rats (Control Group – CG) and those submitted to infection by a genotype II *T. gondii* strain (Experimental Group – EG).

Organ	Group	Length (cm)	Width (cm)	Area (cm^2)
Ileum-jejunum	CG	107.25 ± 2.36	1.40 ± 0.08	150.10 ± 8.27
	EG	102.75 ± 3.77	1.33 ± 0.13	136.40 ± 16.97
Total colon	CG	15.45 ±1.32	2.15 ± 0.37	33.11 ± 5.74
	EG	14.75 ± 1.55	1.98 ± 0.34	28.75 ± 2.54

Values presented as mean ± standard deviation.

Table 2. Neuron population density in 25.2 mm^2 (120 microscopic fields) in the terminal ileum and descending colon of healthy rats (Control Group – CG) and those submitted to infection by a genotype II *T. gondii* strain (Experimental Group – EG).

Group	Organ	Number of Neurons in 25.2 mm^2
CG	Teminal ileum	3,912.8 ± 1,044.7
EG		4,602.4 ± 1,093.1
CG	Descending colon	4,983.8 ± 181.8
EG		4,772.3 ± 200.8

Values presented as mean ± standard deviation.

Table 3. Soma area, nucleus area, cytoplasm area, and the nucleus-soma area ratio of the myenteric neurons in the terminal ileum and descending colon of healthy rats (Control Group – CG) and those submitted to infection by a genotype II *T. gondii* strain (Experimental Group – EG).

Organ	Group	Soma area (μm^2)	Nucleus area (μm^2)	Cytoplasm area (μm^2)	Nucleus-soma area ratio
Terminal ileum	CG	238.9 (134.2; 826.5)⋆	95.3 (47.8; 330.2)⋆	145.3 (79.9; 466.0)⋆	0.39 (0.31; 0.49)
	EG	309.2 (142.3; 900.0)⋆	119.7 (55.3; 326.0)⋆	191.9 (85.5; 544.2)⋆	0.38 (0.31; 0.47)
Descending colon	CG	135.0 (98.3; 183.4)	69.9 (50.7; 94.6)	60.9 (42.8; 94.2)	0.52 (0.44; 0.59)
	EG	132.1 (88.3; 216.4)	69.4 (46.7; 101.2)	60.2 (36.4; 121.6)	0.52 (0.42; 0.61)

Values presented as median (25^{th} percentile; 75^{th} percentile). Values denoted by asterisks in the same column are significantly different ($p < 0.05$).

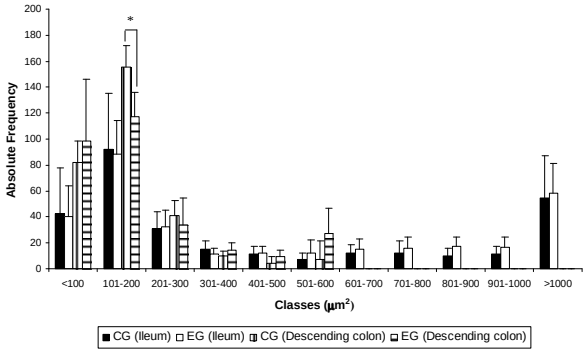

Figure 1. Histogram of the soma area of the myenteric neurons in the terminal ileum and descending colon of healthy rats (Control Group – CG) and those infected by a genotype II *T. gondii* strain (Experimental Group – EG). Columns denoted by asterisks differ significantly (⋆$p < 0.05$).

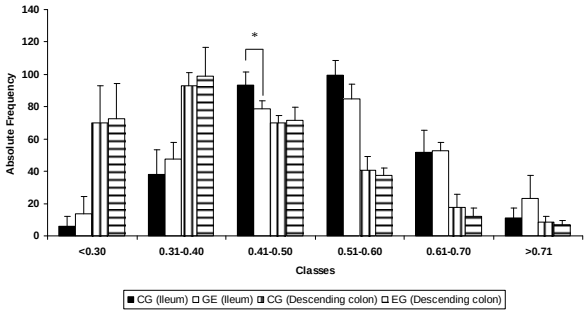

Figure 2. Histogram of the nucleus-soma area ratio of the myenteric neurons in the terminal ileum and descending colon of healthy rats (Control Group – CG) and those infected by a genotype II *T. gondii* strain (Experimental Group – EG). Columns denoted by asterisks differ significantly (⋆$p < 0.05$).

Discussion

Toxoplasma gondii is a parasite presenting antigenic and morphologic similarities; however, samples from distinct sources present differences in virulence either in animals or humans. This heterogeneity of the biological behavior from different samples suggests the existence of DNA polymorphism related to the pathogenicity of the infection by *T. gondii* (CRISTINA et al., 1991; HOWE; SIBLEY, 1995). By analyzing this polymorphism, Howe e Sibley (1995) subdivided *T. gondii* into three distinct clonal lines: I, II, and III.

Isolated type II are the most prevalent in several parts of the world (HOWE et al., 1997; MONDRAGON et al., 1998; FUENTES et al., 2001) and usually presents low virulence for mice (DUBEY, 1995); however, some authors have found progressive weight loss for mice with genotype II strains in spite of its possible association to the increase of the metabolism and the immune response to the parasite (ARSENIJEVIC et al., 2001; PICARD et al., 2002),

its impact on the Enteric Nervous System (ENS) is still not investigated.

In this study, it was observed that an infection caused by a ME-49 (genotype II) *T. gondii* strain did not alter the dimensions of the ileum-jejunum and the total colon of rats, as well as the number of the myenteric neurons in these organs. That is possibly due to the fact that the organs were collected after being infected for 24 hours; therefore, there was not enough time to cause a proliferative inflammatory response that would cause an increase of the intestinal area, mostly its width. Thus, it is possible to consider that the time of infection did not result in either necrosis or apoptosis of the nervous cells, what would be plausible since the immunological effector cells and their products are responsible for alterations in the nervous cells (SZABO; FEHER, 1991; BELAI et al., 1997; BORGES et al., 2000; GALEAZZI et al., 2000; BALEMBA et al., 2001; FURNESS, 2006). Perhaps this is a peculiar characteristic of *T. gondii*, as in experimental studies on rat colitis a loss of up to 50% of the myenteric neurons is observed between 48 hours and 35 days after the disease induction (SANOVIC et al., 1999).

On the other hand, significant increase of the cytoplasm and nucleus area resulting from the increase of the soma of the myenteric neurons in the terminal ileum was observed ($p < 0.05$), which was not observed for the descending colon. While observing the number of neurons by considering the classes according to the soma area, the majority of the neurons presents 200 μm^2 at most, either in the terminal ileum or descending colon; however, there are neurons reaching the interval which groups the neurons with an area even 1,000 μm^2. While comparing the groups, there was a decrease regarding the number of 101-200 μm^2 neurons in the descending colon from infected animals ($p < 0.05$). As there were not any neuronal losses, and, in general, there were not any alterations in the soma area of the myenteric neurons in the descending colon, it is suggested that part of the neurons from the mentioned class suffered morphometric alterations, and they were distributed almost uniformly among the other classes as, in these, there were not any significant differences among the groups. While comparing the number of neurons divided in classes according to the nucleus-soma area ratio, a prevalence of neurons in which the nuclei occupied 41-60% of the soma was observed in the terminal ileum in both groups, whereas most of the neurons in the descending colon present nuclei occupying less than 40% of the soma in both groups as well. By analyzing the Control Group and the Experimental Groups from each class, it was observed that (genotype II) *T. gondii* infection caused a reduction in the number of neurons with nuclei occupying 41-50% of the soma, which possibly migrate to the other classes after the morphometric alterations observed in the neurons from this organ.

Considering that the terminal ileum is marked by the presence of lymphoid nodules (Peyer's patches), the mentioned hypertrophy of the myenteric neurons of these organs probably occurred by an action of the immune system, and not by a direct action of the parasite on the neurons. Moreover, the experiment length of time (24 hours) might have been enough so that the infection would have altered the immune system of the descending colon as to module its ENS. Thus, it is worth remarking that little is known of the nature of the interactions between the ENS and the gastrointestinal tube; however, it is notorious that the response of the ENS is not uniform towards different stimuli of an inflammatory process (LOMAX et al., 2005). For instance, in patients with Crohn disease and ulcerative colitis, alterations in enteric ganglions such as neuronal hypertrophy and glial hyperplasia were observed (GEBOES; COLLINS, 1998).

With respect to *T. gondii,* the NF-κβ transcription factor plays a core part regarding the inflammatory, immune, and antiapoptotic response. The (type II) ME-49 strain induces the translocation of the NF-κβ to the nucleus of the splenocytes of mice (DOBBIN et al., 2002) and macrophages from the bone marrow (ROBBEN et al., 2004), thus stimulating the transcription of the genes involved in the proinflammatory response such as those which codify the Tumoral Necrosis Factor – TNF-α (SINAI et al., 2004), decreasing its pathogenicity. TNF-α is mainly produced by macrophages and monocytes, and secondarily stimulates the production of several other cytokines such as IL-6, IL-12 and IL-18 by developing a crucial role in the initialization and amplification of the inflammatory reactions.

Genotype II *T. gondii* strains also induce high levels of IL-10, IL-1β, IL-6 and IL-12 (SAEIJ et al., 2005). IL-12 is a proinflammatory cytokine that stimulates the production of interferon (IFN-γ), which directs the differentiation of the Th1 cells and forms the bindings between the innate and adaptive immunity (TRINCHIERI, 2003). IFN-γ is a key cytokine for the resistance against *T. gondii* (SUZUKI et al., 1988), that is, it is absolutely demanded for the effective activation of the

macrophages, which are critically important on defending the host against toxoplasmosis (SIBLEY et al., 1993; DECKERT-SCHLUTER et al., 1996).

Inflammatory cytokines (IL-1β e TNF-α) are numerous in the beginning of the inflammatory process and increase secretion of prostaglandins and leukotrienes, which contribute for the amplification of the tissue injury and inflammation interfering in the intestinal tract smooth muscle (SHEA-DONOHUE et al., 1997). Therefore, there are progressive alterations on the contractibility of the smooth muscles, resulting in a generalized reduction of the muscle response to the excitatory stimuli and the increase of the incidence of diarrhea (HOSSEINI et al., 1999). The effect of several cytokines has been analyzed in glial enteric cells in culture, and it was observed that TNF-α does not affect the expression of mRNA of IL-6, as IL-1β stimulated the protein and mRNA synthesis of IL-6 (RÜHL et al., 2001). On the other hand, there are reports on the literature showing that intestinal inflammation induces the secretion of cytokines such as IL-1β, TNF-α, IFN-α from the myenteric ganglions; however, it is still not known the exact identity of the cytokine secretion cell in the ganglion – either neurons or glia (EKBLAD; BAUER, 2004) – as well as possible target cells.

Thus, it would be reasonable to consider that: 1) the parasite may interact with the intestinal immune system inducing it to secret cytokines which will act on the ENS (paracrine action); 2) the parasite may interact with the ENS inducing it to secret cytokines; 3) the parasite will reach the systemic circulation and interact with either the immune system or the non-immune extra-intestinal cells, which will secret molecules (some cytokines) that will act on the ENS by an endocrine way. One or more of these ways may be the cause of the morphometric alterations observed in the myenteric neurons of the terminal ileum, what could be characterized as neural plasticity.

The results presented in this study demonstrate that the acute infection (during 24 hours) caused by a genotype II *T. gondii* strain provokes morphometric alterations in the myenteric neurons in the terminal ileum, but not in the descending colon. Moreover, there are not any neuronal losses in both organs. It is evident that further studies are necessary in order to better understand this phenomenon.

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