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Anterior subdiaphragmatic vagotomy decreases the IgA antibody response in the small intestines of BALB/c mice

Ivonne Maciel Arciniega-Martínez[a], Maria Elisa Drago-Serrano[b], Marisol Salas-Pimentel[a], Javier Ventura-Juárez[c], Aldo Arturo Reséndiz-Albor[a,*], Rafael Campos-Rodríguez[a,*,1]

[a] Laboratorio de Inmunidad de Mucosas. Sección de Estudios de Posgrado e Investigación, Escuela Superior de Medicina, Instituto Politécnico Nacional, Plan de San Luis esq. Salvador Díaz Mirón s/n, CP 11340 Ciudad de México, Mexico
[b] Departamento de Sistemas Biológicos, Universidad Autónoma Metropolitana, Unidad Xochimilco, Calzada del Hueso No. 1100 CP, 04960 Ciudad de México, Mexico
[c] Departamento de Morfología, Centro de Ciencias Básicas, Universidad Autónoma de Aguascalientes, Aguascalientes, Mexico

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ABSTRACT

To assess the impact of vagotomy on the IgA-response, male BALB/c mice underwent anterior vagotomy or a sham procedure were sacrificed on day 14 post-operation and the proximal and distal small-gut segments were dissected. In intestinal lavages IgA/IgM antibodies were analysed by ELISA; in Peyer's-patches and lamina-propria cell suspensions the intracellular IgA-associated interleukins (ILs) and pro-inflammatory cytokines in $CD4^+$ T cells were analysed by cytofluorometry. Vagotomy reduced the IgA or increased the IgM antibody concentration in both segments and reduced or increased the lamina- propria $CD4^+$ T cell pro-inflammatory cytokine responses in the distal or proximal segments, respectively. Data show the role of the vagus nerve on the IgA response.

1. Introduction

The vagus nerve is a prominent trunk of the parasympathetic nervous system that encompasses afferent and efferent branches that innervate the gastrointestinal tract (Berthoud and Neuhuber, 2000; Stakenborg et al., 2013). In regard to the afferent limb, the innervation of the efferent vagal branch is reduced in the gastrointestinal tract, and its distribution accounts for 100% in the stomach, 96% in the duodenum, 40% in the jejunum, 66% in the caecum, 16% in the descending colon and 0% in the rectum (Chang et al., 2003). The efferent vagal nerve includes left and right branches, which run along the oesophagus; after entering the abdominal cavity, they become the anterior and posterior trunks, respectively (Stakenborg et al., 2013). The anterior trunk of the vagus nerve innervates the proximal segment of the small intestine (Stakenborg et al., 2013). The vagus nerve provides signals that modulate intestinal immunity and dampen intestinal inflammation (Bonaz et al., 2017; de Jonge, 2013).

Immunoglobulin A (IgA) is an anti-inflammatory antibody that helps maintain intestinal homeostasis (Corthésy, 2013). The generation of IgA entails a complex interplay among antigen-presenting cells and the T and B lymphocytes; a cognate T and B cell interaction leads to the activation and class-switching of immature IgM^+ B cells to IgA^+ B cells in Peyer's patches, which are the major intestinal inductive site. Concomitantly, IgA^+ B cells migrate towards effector sites, such as the lamina propria, to mature into IgA^+ plasma cells, which release IgA antibodies that are eventually secreted towards the luminal milieu. The generation of IgA is modulated by transforming growth factor (TGF)-β, which orchestrates the class-switching of B cell precursors from the IgM^+ isotype to the IgA^+ isotype; interleukin (IL)-4, IL-5, IL-6, and IL-10 promote IgA^+ B cell proliferation and maturation in IgA plasma cells (Lycke and Bemark, 2017; Xiong and Hu, 2015). The distribution of IgA plasma cells, $CD3^+$ T cell precursors and Peyer's patches is a gradient that increases from the proximal to the distal small intestine (Matsui, 1991; Mowat and Agace, 2014; Tamura et al., 2003).

The impact of the parasympathetic modulation of the vagus nerve on intestinal immunity has been scarcely addressed in human trials and experimental animal models and has produced controversial findings. Patients who undergo vagus nerve resection, i.e., vagotomy, develop an intestinal IgA deficiency and severe diarrhoea (McLoughlin et al., 1976; McLoughlin et al., 1978). In animal models, the opposite effects of vagotomy on the intestinal IgA response have been reported (Gottwald et al., 1997; Enders et al., 1988; Somasundaram and Ganguly, 1987). Experimental studies conducted in rats showed that in the jejunal lamina propria, IgA plasma cells numbers are increased three weeks after

* Corresponding authors.
E-mail addresses: aresendiza@ipn.mx (A.A. Reséndiz-Albor), rcamposr@ipn.mx (R. Campos-Rodríguez).
[1] The author is deceased on July 4, 2019.

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resecting both vagal branches (Gottwald et al., 1997). In rats, both a proximal gastric vagotomy and a bilateral subdiaphragmatic vagotomy triggered the luminal increase in IgA, which resulted from changes in the intestinal permeability due to increased inflammation (Enders et al., 1988; Somasundaram and Ganguly, 1987).

Currently, the parasympathetic modulation of the IgA response by the vagus nerve is unclear, and its impact on the proximal and distal regions of the small intestine is unknown. Thus, this study aimed to assess the components of the IgA response at the inductive and effector sites of the small intestine in mice that underwent anterior subdiaphragmatic vagotomy.

2. Materials and methods

2.1. Animals

Two-month-old male BALB/c mice (20–25 g) were obtained from our Animal Breeding Unit (Escuela Superior de Medicina, Instituto Politécnico Nacional) and were housed in plastic cages in groups of five. All mice were kept in a 12 h light:dark cycle (lights on at 6 a.m.) for two weeks prior to any experimental manipulation. Food and water were provided ad libitum, and all manipulations and assays were conducted before 15:00 h to avoid the influence of the circadian cycles on ACTH and corticosterone. Animals were handled according to a protocol (ESM-CICUAL-04/13-01-2014) approved by the Institutional Animal Care and Use Committee.

2.2. Anterior subdiaphragmatic vagotomy

The surgical procedures were conducted under aseptic conditions as follows: The mice were anaesthetized by the intraperitoneal injection of a mixture containing 100 mg/kg ketamine and 10 mg/kg xylazine. The mice were positioned in dorsal recumbency, and a midline skin incision was made. The tissue layers were carefully retracted with clamps to reveal the stomach and oesophagus. With the help of a glass hook, the oesophagus was retracted to expose the two vagal trunks. With surgical clamps, the dissection of the peri-oesophagic connective tissue was accomplished. Thereafter, only the ventral or anterior branch, which is contiguous with the left cervical vagus (Berthoud and Neuhuber, 2000), was transected 0.5 cm above the gastroesophageal junction. The neural tissue (and the connective tissue) surrounding the oesophagus was removed to ensure the transection of most small vagal branches. An oesophagus from a mouse underwent vagotomy was embedded in paraffin and sectioned for histological analysis. The same surgical procedure was performed without the vagus nerve transection in the sham-operated group. The overall survival rate exceeded 95%. Mice from both the sham and vagotomy groups were sacrificed 14 days after surgery.

2.3. Surgery validation

The transection of the gastric vagal nerve branches causes food retention in the stomach (Martin et al., 1977; Mordes et al., 1979). Therefore, macroscopic changes in the stomach were monitored to validate the vagotomy. Additionally, a cholecystokinin (CCK) assay was conducted to validate the vagotomy. This assay relies on the ability of CCK to decrease food intake after satiety is reached and is completely dependent on vagus nervous integrity (Ghia et al., 2006). Fourteen days post-vagotomy, the mice were deprived of food for 20 h and were intraperitoneally injected with 8 μg/g body weight CCK8 (C2901-1MG, Sigma-Aldrich, Darmstadt, Germany). The sham-operated group mice treated with CCK8 were included. The food intake was estimated as the difference between food weight (g) before and after 2 h of CCK8 administration. The mice that underwent vagotomy and showed significantly decreased food intake were excluded from the experiments. At 14 days post-surgery, mice from both the vagotomy and sham groups were euthanized by an intraperitoneal injection of a lethal dose of sodium pentobarbital (100 mg/kg body weight) and were exsanguinated by cardiac puncture. The small intestine was dissected into segments of 5 cm in length at the proximal (after the pylorus) and distal (before the caecum) regions. Both intestinal segments were flushed with 5 mL of phosphate-buffered saline (PBS) containing 0.02% sodium azide and a protease inhibitor cocktail (04693124001 Complete Mini, Roche Diagnostics, Mannheim, Germany). The washout material was centrifuged at 10,000 xg for 20 min at 4 °C, and the supernatant corresponding to the intestinal secretion was stored at −70 °C until the measurement of the total IgA and IgM content was performed by ELISA. From each intestinal segment, the cells were isolated from Peyer's patches and the lamina propria to prepare cell suspensions for cytofluorometric assays.

2.4. Enzyme-linked immunosorbent assay

The concentrations of IgA and IgM in the intestinal secretions were determined based on a previously reported immunoenzymatic protocol (Arciniega-Martinez et al., 2016). The total concentrations of IgA and IgM in μg/mL from five mice per group were expressed as the mean and standard deviation (SD).

2.5. Flow cytometry assays

The isolation of cells from Peyer's patches and the lamina propria from the proximal and distal segments was conducted as described previously (Reséndiz-Albor et al., 2005). Single suspensions from two mice per group were pooled and adjusted to 1×10^6 cells/mL in PBS for cytofluorometric analysis.

The cytofluorometric analysis of the $CD3^+$ T, $CD4^+$ T, $CD8^+$ T, IgA^+ and IgM^+ plasma cells as well as the $CD4^+$ T cells intracellularly labelled with IgA-associated interleukins (IL-4, −5, −6, and − 10), transforming growth factor (TGF-β) and the pro-inflammatory cytokines IFN-γ, TNF-α and IL-12, was conducted using previously described protocols (Arciniega-Martinez et al., 2016; Reséndiz-Albor et al., 2010).

Briefly, the surface phenotypes of T cells were detected by using labelled monoclonal anti-CD3 FITC, anti-CD4 PerCP, and anti-CD8α PE antibodies; the plasma cells were labelled with anti-CD19 PE and anti-CD138 APC antibodies (all from BD Biosciences, San Jose, California, USA). For intracellular IgA^+ and IgM^+ detection, the cells were fixed, permeabilized and stained with anti-IgA FITC and anti-IgM PerCP according to the BD Bioscience protocol for intracellular staining. To detect the intracellular ILs and cytokines, the lymphocytes were first stimulated with a leukocyte activation cocktail (555,029, BD Pharmingen, San Jose, California, USA). Then, the cell surface marker antibodies anti-CD3 FITC and anti-CD4 PerCP were added and incubated. Subsequently, for the intracellular staining of T cells, fixation and permeabilization were performed using Cytofix and Cytoperm kits (554,722, BD Pharmingen, San Jose, California, USA) according to the manufacturer's instructions. These cells were incubated with anti-IL-4 PE, anti-IL-5 PE, anti-IL-6 PE, anti-IL-10 APC, anti-TGF-β APC, anti-IFN-γ APC, anti-TNF-α PE and anti-IL-12 PE. For all conditions, the expression of CD69 was measured as an activation control.

The fluorescent signal intensity was recorded and analysed by a FACSCalibur flow cytometer (Becton Dickinson, San Jose, California, USA). The events were collected from the lymphocyte gate on the FSC/SSC dot plot. A total of 20,000 gated events were acquired from each sample using BD FACSDIVA software (BD Biosciences). The data were analysed using Summit software v4.3 (Dako, Colorado Inc.).

2.6. Statistical analysis

Four independent experiments were performed ($n = 8$ mice per group, per experiment), and the data are presented as the mean and standard deviation (SD) from one representative experiment. Data were

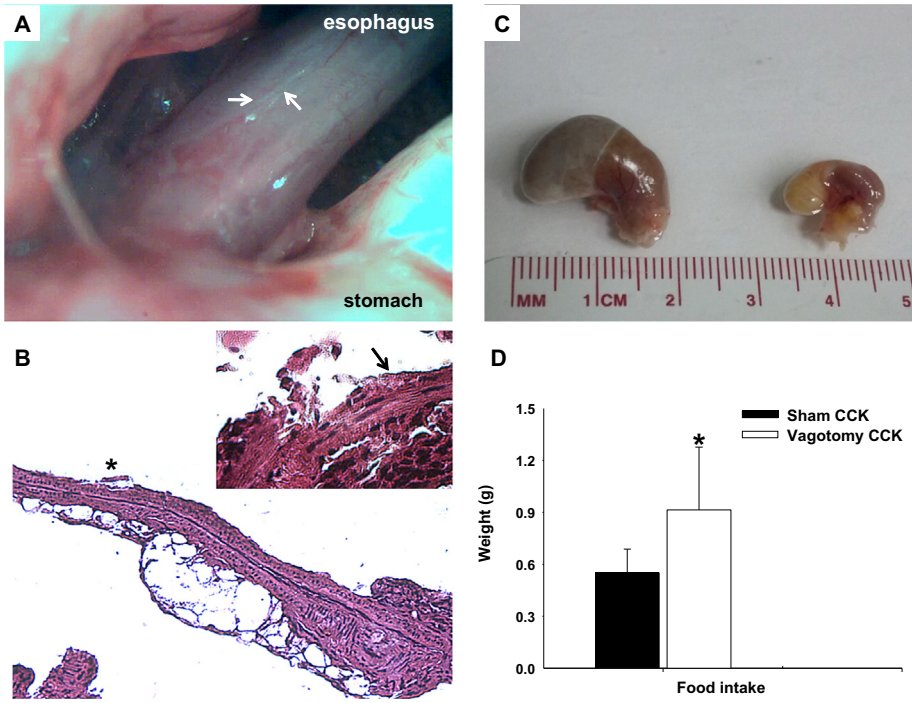

Fig. 1. Vagotomy surgery validation. A) A macroscopic visualization of the vagus nerve (arrowheads) at the oesophageal level near the stomach was performed. B) Location of the vagus nerve section site; the lower picture shows a panoramic view of the vagotomised oesophagus (X2.5), the asterisk (*) is the sectional site of the vagus nerve; the right upper picture shows an enlarged view of sectioned vagus nerve (arrow) (X400). C) representative macroscopic changes in the stomach from vagotomy (left) and sham (right) mice are shown. D) The food intake (g) of the sham CCK and vagotomy CCK mice are presented as the mean and standard deviation. *$p < .05$ versus the sham group.

analysed by Student's unpaired 2-tailed *t*-test for comparisons between the vagotomy and sham groups for the vagotomy validation test ($n = 8$ per group), ELISA (n = 8 per group) and cytofluorometry ($n = 4$ pools per group). The differences were considered significant at $p < .05$. All analyses were performed by using the statistical program SigmaPlot for Windows version 11 (Systat Software Incorporated, San Jose, California, USA).

3. Results

3.1. Vagotomy surgery validation

The location of the vagus nerve before surgery is depicted in Fig. 1A, and the vagotomised oesophagus and the sectional site of the vagus nerve after surgery is depicted in Fig. 1B. By macroscopic visualization, the dilatation of the stomach in the vagotomy group was observed to be higher than that in the sham-operated group (Fig. 1C). Food intake in the vagotomy CCK group (0.914 ± 0.363) was significantly greater ($p = .012$) than that in the sham CCK group (0.55 ± 0.138; Fig. 1D).

3.2. Anterior vagotomy impacted the antibody responses by decreasing the IgA or increasing the IgM concentration in both intestinal segments

Regarding the sham-operated group, vagotomy mice had either reduced IgA or increased IgM concentrations in the proximal and distal segments ($p < .001$, Fig. 2A and D). In comparison with that in the Peyer's patches of the sham-operated mice, the IgA^+ plasma cell response in the vagotomy mice was reduced in the proximal segment and increased in the distal segment, whereas the IgM^+ plasma cell response was increased in both regions ($p < .001$, Fig. 2B and C). In comparison with that of the sham-operated mice, the lamina propria of the vagotomy mice had lower IgA^+ plasma cell numbers and higher IgM^+ plasma cell numbers in both segments ($p < .001$, Fig. 2E and F).

3.3. Anterior vagotomy had a divergent impact on the CD4+ and CD8+ T cell populations in Peyer's patches or the lamina propria in both intestinal regions

Regarding the Peyer's patches, compared to the sham-operated mice, the vagotomy mice had increased $CD3^+$ and $CD8^+$ T cell numbers and reduced $CD4^+$ T cell numbers in both segments ($p < .001$, Fig. 3A-3C). In comparison with that of the sham-operated mice, the lamina propria of the vagotomy mice had either increased $CD4^+$ or reduced $CD8^+$ T cell responses in both segments, whereas the $CD3^+$ T cell response was found to be increased in the proximal region and reduced in the distal region ($p < .001$, Fig. 3D-3F).

3.4. Anterior vagotomy decreased the number of $CD4^+$ T cells expressing IgA-associated ILs in Peyer's patches from both intestinal regions

Compared to those the of the sham-operated mice, the Peyer's patches of the vagotomy mice had reduced IL-5, IL-6 and TGF-β responses in both segments, a reduced IL-4 $CD4^+$ T cell response at the proximal segment and a reduced IL-10 $CD4^+$ T cell response in the distal region ($p < .001$, Fig. 4A-4I). Comparisons of the lamina propria revealed that compared to those in the sham-operated group, the IL-4, IL-5 and IL-6 $CD4^+$ T cell responses in the vagotomy group were increased in the proximal segment and reduced in the distal region, whereas the IL-10 and TGF-β $CD4^+$ T cell responses were reduced in both segments ($p < .001$, Fig. 4B-4J).

3.5. Anterior vagotomy had the opposite effect on the $CD4^+$ T cells expressing pro-inflammatory cytokines in both regions of the lamina propria

Regarding the Peyer's patches, compared with the sham-operated mice, the vagotomy mice showed increased numbers of IFN-γ- and TNF-α-expressing $CD4^+$ T cells in the proximal region and decreased numbers in the distal segment, whereas IL-12-expressing $CD4^+$ T cell numbers were reduced in both segments ($p < .001$, Fig. 5A-5E). In comparison with that of the sham-operated mice, the lamina propria of the vagotomy mice had increased numbers of IFN-γ-, TNF-α- and IL-12-labelled $CD4^+$ T cells in the proximal region and reduced numbers in the distal segment ($p < .001$, Fig. 5B-5F).

4. Discussion

The transection of both vagal branches causes food retention in the stomach (Martin et al., 1977; Mordes et al., 1979). Therefore,

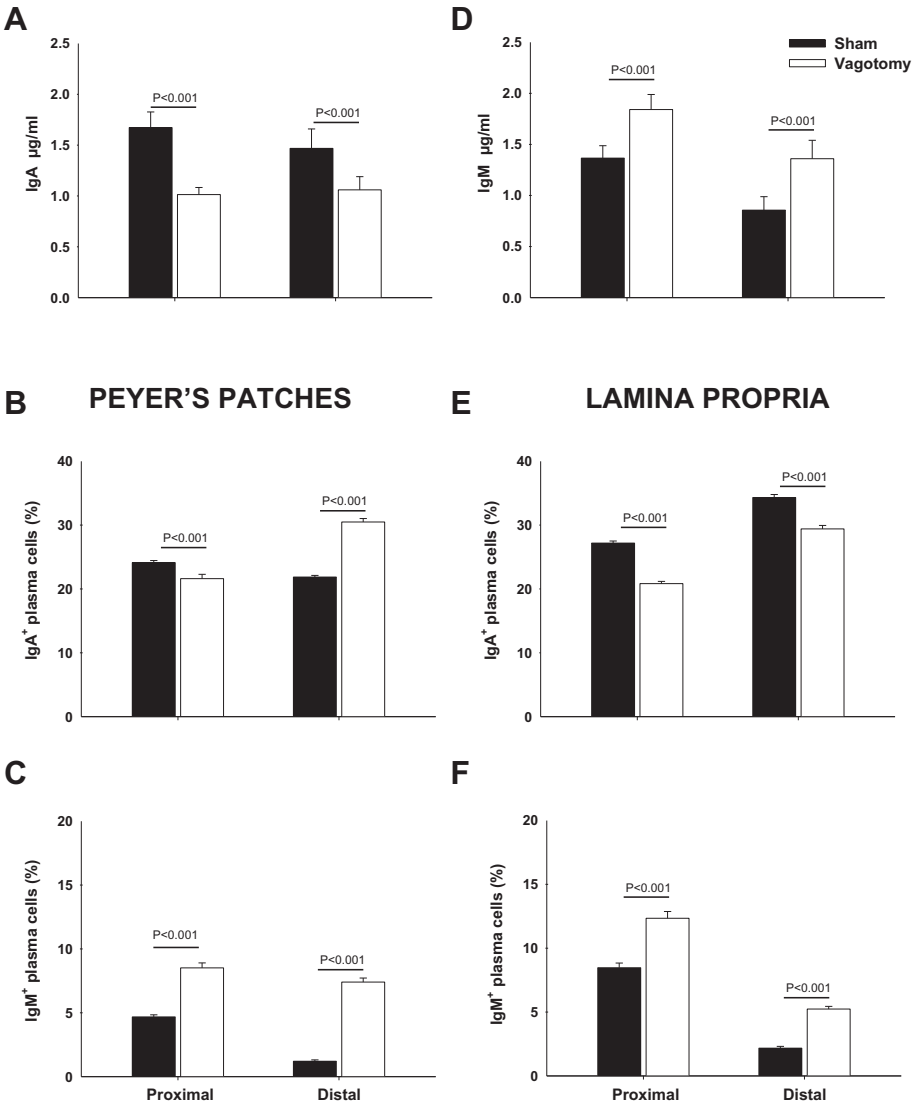

Fig. 2. Antibody concentration and the percentage of plasma cells in sham and vagotomy mice in the proximal and distal small intestine regions. The total concentration (µg/ml) of A) IgA and D) IgM in the proximal and distal small intestinal secretions of mice that underwent vagotomy or sham vagotomy are shown. The proximal and distal plasma cell percentages (%) in Peyer's patches and lamina propria are shown for the vagotomy and sham groups: B, E) IgA^+ isotypes and C, F) IgM^+ isotypes. The results are expressed as the mean and standard deviation (SD). The in-line *p* value indicates comparisons between the vagotomy versus the sham group within each region.

macroscopic changes in the stomach were monitored to validate the anterior vagotomy. As expected, a significant increase in food intake in the vagotomy mice was found.

A limited number of studies in animals that underwent either proximal gastric or bilateral truncal vagotomy have analysed the IgA antibody, IgA plasma cell or anti- and/or pro-inflammatory cytokine responses in the small intestine (jejunum and/or ileum) (Enders et al., 1988; Gottwald et al., 1997; Mitsui et al., 2014). Given that the anterior vagal trunk prominently innervates the proximal region of the small intestine (Stakenborg et al., 2013), we aimed, for the first time, to address the impact of anterior vagotomy on parameters of the IgA response in the proximal and distal small intestinal segments.

According to the findings, the anterior vagotomy displayed common effects on the proximal and distal segments by reducing the IgA concentration and IgA^+ plasma cell numbers (except in distal Peyer's patches) and by eliciting an IgM antibody response and increasing the number of IgM^+ plasma cells. These findings may be the result of the impact of anterior vagotomy on IgM/IgA class-switching given the reduced $CD4^+$ T and TGF-β^+ $CD4^+$ T cell response in the Peyer's patches. TGF-β determines the T cell-dependent IgM/IgA class-switching in Peyer's patches (Lycke and Bemark, 2017; Xiong and Hu, 2015). In addition, the effects of vagotomy on the IgA response may result from a decreased proliferation and/or maturation of IgA^+ B cell precursors derived from the reduced numbers of $CD4^+$ T cells expressing IgA-producing ILs in Peyer's patches, as found in both segments. It is thought that these ILs are involved in the proliferation and maturation of IgA^+ cell precursors in the lamina propria (Xiong and Hu, 2015). The vagotomy also decreased the number of lamina propria $CD8^+$ T cells, which are potential sources of IgA-associated ILs, such as IL-10, in both intestinal regions (Asigbetse et al., 2010). In rats that underwent proximal gastric or bilateral vagotomy, the jejunal lamina propria IgA^+ plasma cell numbers or IgA antibody concentrations were found to be increased (Enders et al., 1988; Gottwald et al., 1997). The opposite findings reported in this assay in regard to the decrease in the IgA response may be because of differences in the experimental settings, including surgery type and time of the parameter estimation, as stated below.

In the current study, stimulatory effects of the vagotomy were also observed for several parameters, including lamina propria $CD4^+$ T cells and Peyer's patch $CD8^+$ T cells in both regions and $CD4^+$ T cells expressing pro-inflammatory cytokines in the proximal lamina propria. The impact of bilateral vagotomy on triggering the production of pro-inflammatory cytokines has been described in the jejunum, ileum and throughout the whole length of the small intestine in a murine model of chronic haemorrhagic shock or post-operative ileus (Du et al., 2013; The et al., 2011). Conversely, the anterior vagotomy decreased the number of $CD4^+$ T cells expressing most pro-inflammatory cytokines in the Peyer's patches and lamina propria from the distal region. Apparent

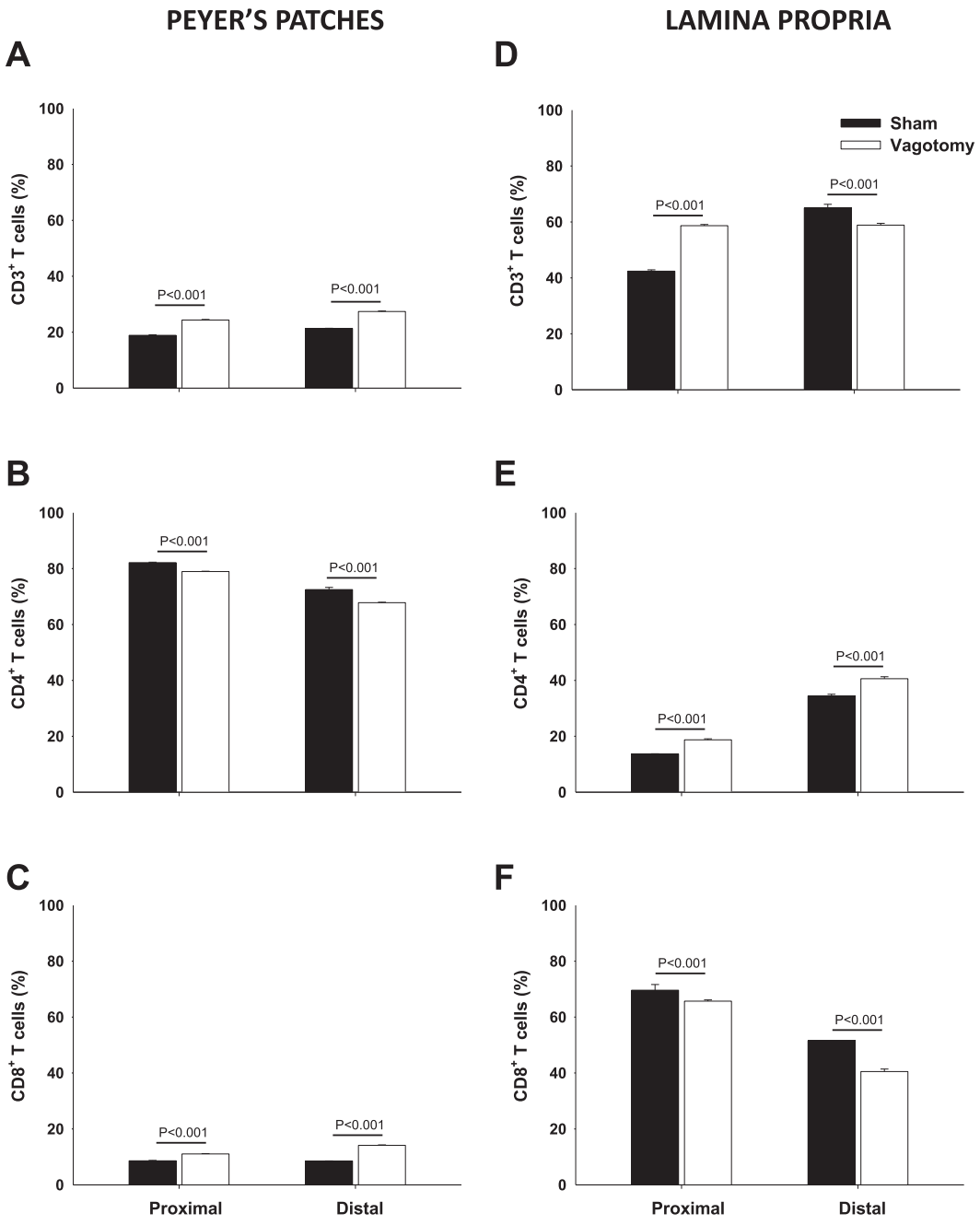

Fig. 3. Percentage (%) of T cell populations in the small intestine from the vagotomy and sham mice. The proximal and distal T cell percentages (%) in Peyer's patches and lamina propria in the vagotomy and sham mice: A, D) $CD3^+$ T; B, E) $CD4^+$ T and C, F) $CD8^+$ T cells. The in-line *p* value indicates comparisons versus the sham group in each region.

discrepancies may reflect a kinetic effect. Indeed, experiments in mice have shown that the jejunal levels of both the anti- and pro-inflammatory ILs either decrease after 14 days or increase after 20 days post-bilateral subdiaphragmatic vagotomy (Mitsui et al., 2014). In a murine model of DSS-induced colitis, the increased expression of inflammatory markers was reduced on days 21, 33 and 61 post-vagotomy (ventral or dorsal plus pyloroplasty) (Ghia et al., 2007). Thus, the findings herein may also result from both the vagotomy approach used and the time of parameter assessment after vagotomy. This assumption may partially underlie the modulatory properties of the anterior vagotomy found in the current study, unlike the lack of modulatory properties of the bilateral vagotomy itself (Ghia et al., 2006; Ghia et al., 2007).

Notably, the anterior vagotomy triggered an IgA^+ plasma cell response in the distal Peyer's patches and TNF-α expression by $CD4^+$ T cells in the proximal Peyer's patches and lamina propria; even though the IgA^+ plasma cells are the major source of IgA antibodies, they also play a presumable role in antibody-independent innate inflammatory responses, whereas TNF-α drives IgA^+ plasma cell generation (Gommerman et al., 2014).

In the context of intestinal regionalization, the differential effects of vagotomy on the proximal and distal segments may unveil the modulatory pathways of the posterior vagal trunk caused by the loss of anterior vagal trunk integrity. Coeliac branches from the posterior (right) vagal trunk innervate the entirety of the small intestine, while the anterior (left) trunk of the vagus nerve prominently innervates the stomach and the proximal duodenum (Berthoud and Neuhuber, 2000; Stakenborg et al., 2013).

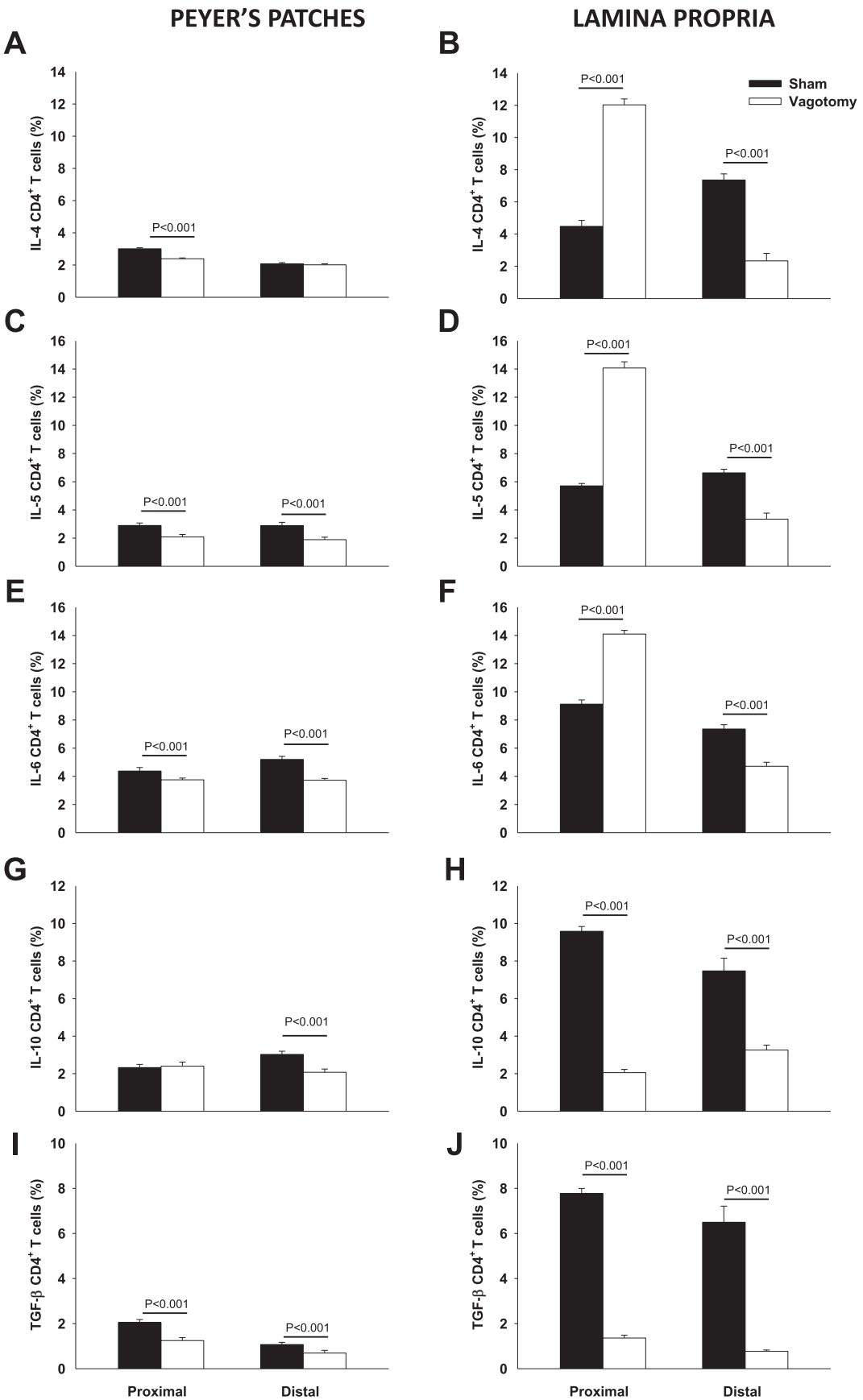

Fig. 4. Percentage (%) of $CD4^+$ T cells stained for IgA-producing interleukins (ILs). The proximal and distal % of $CD4^+$ T cells intracellularly stained for IgA-producing ILs in Peyer's patches and lamina propria in the vagotomy and sham mice: A, B) IL-4; C, D) IL-5; E, F) IL-6; G, H) IL-10 and I, J) TGF-β. The in-line *p* value indicates comparisons versus *the* sham group.

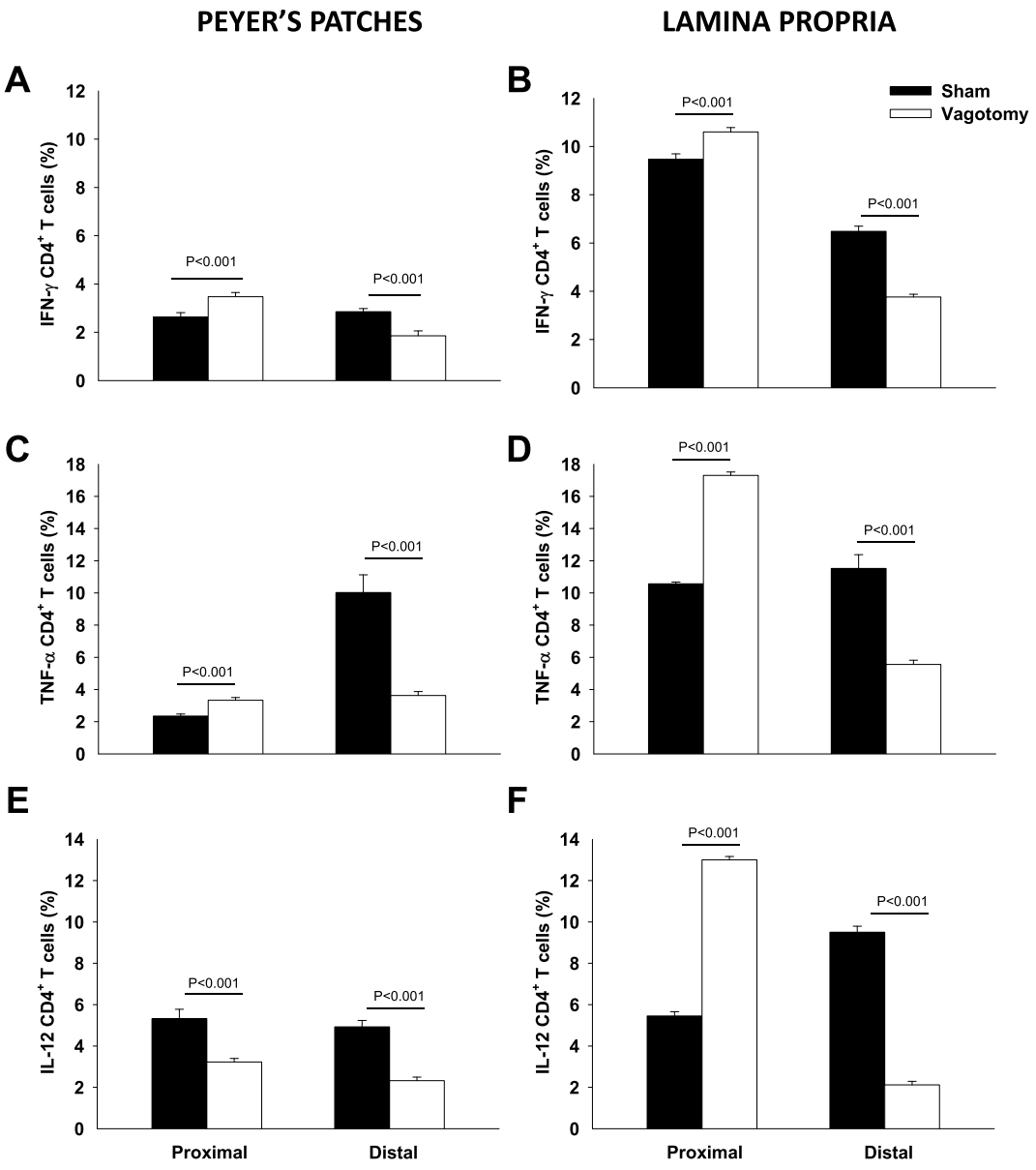

Fig. 5. Percentage (%) of $CD4^+$ T cells stained for pro-inflammatory cytokines. The proximal and distal % of Peyer's patch and lamina propria $CD4^+$ T cells intracellularly stained for pro-inflammatory cytokines in the vagotomy and sham mice: A, B) IFN-γ; C, D) TNF-α and E, F) IL-12. The in-line *p* value indicates comparisons versus sham group.

In addition, the divergent impact of vagotomy on the proximal and distal segments may reflect the modulatory effects of enteric peptide hormones such as cholecystokinin (CCK), which is secreted prominently in the proximal small intestine and increases the IgA response (Freier et al., 1987; Wilson et al., 1982; Svendsen et al., 2015; Egerod et al., 2012). Moreover, these findings may result from a very complex interplay among parasympathetic and enteric pathways. The crosstalk between the vagus nerve and intrinsic enteric fibres has been evidenced by the impact of right and left vagotomies on fluctuations in intestinal neuropeptide levels (El-Salhy et al., 2000). An anterior vagotomy reduces the duodenal levels of vasoactive intestinal peptide (VIP) 8 weeks post-vagotomy (El-Salhy et al., 2000). VIP is known to be involved in the modulation of IgA secretion and IgA^+ plasma cell responses (Shibata et al., 2008). In mice that underwent vagotomy, the levels of serotonin (5-hydroxytryptamine (5-HT)) were significantly decreased in the proximal small intestine (Gomes et al., 1985]. The expression of 5-HT_3 receptors is prominent in the proximal small intestine and is under parasympathetic control, as was found in rats that underwent vagotomy (Glatzle et al., 2002). Serotonin is a neurotransmitter, and its release from cholinergic submucosal neurons promotes the growth and turnover of the intestinal mucosal epithelium via the 5-HT_{2A} receptor (Gross et al., 2012); however, serotonin release from mucosal enterochromaffin cells promotes intestinal inflammation via 5-HT_3 receptors (Kato, 2013).

Neuroanatomic studies have shown that in addition to involving enteric pathways, vagal modulation of intestinal inflammation seems to involve sympathetic signals via β2 catecholamine receptors expressed by myeloid and lymphoid cell populations (Willemze et al., 2018, 2019). The levels of endogenous catecholamines, such as noradrenaline, are known to be higher in the duodenum than they are in the ileum (Taubin et al., 1972). Adrenergic fibres derived from the vagus nerve are quantitatively insignificant; however, they exert local control of the sympathetic stores of gastrointestinal catecholamines (Graffner et al., 1985). Catecholamines play a dual role in IgA production in the small intestine (Jarillo-Luna et al., 2007; Reyna-Garfias et al., 2010). Catecholamines also seem to control the distribution of immunocompetent

cells; as documented in mice, where sympathectomy decreased either IgA^+ plasma cell numbers in the duodenum or $CD4^+$ and $CD8^+$ T cell number in the ileum (Ke et al., 2011).

In this study, IgA transcytosis by the polymeric immunoglobulin receptor (pIgR) was not determined. Despite this limitation, the current study provides insights into the modulatory role of the parasympathetic system on the IgA response via the vagus nerve that have not been reported previously.

The graphical abstract depicts the most prominent effects of vagotomy in Peyer's patches and lamina propria in each intestinal region. We can conclude that anterior vagotomy induces common effects on parameters associated with antibody responses in the proximal and distal small intestinal segments; a divergent impact of vagotomy in the proximal and distal regions was prominently seen in $CD4^+$ T cells expressing pro-inflammatory cytokines in the lamina propria. The findings may in part reflect the modulatory impact of the prominent cholinergic innervation in the proximal rather than distal small intestine.

Consistent with the results described in clinical vagotomy trials in IgA-deficient patients who develop severe post-vagotomy diarrhoea (Bonaz et al., 2017; McLoughlin et al., 1976; McLoughlin et al., 1978), our findings support the hypothesis that the vagus nerve plays a role in intestinal homeostasis via IgA response modulation.

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Declaration of Competing Interest

None.

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