Disturbances in epithelial ionic secretion in different experimental models of colitis

Rubén Pérez-Navarro, Isabel Ballester, Antonio Zarzuelo, Fermín Sánchez de Medina*

Department of Pharmacology, School of Pharmacy, University of Granada, Campus de Cartuja s/n, 18071 Granada, Spain

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Abstract

This paper studies the disturbances in ionic secretion in the colon of rats with different models of acute and chronic colitis measured as changes in short-circuit current. The aim was to verify whether the reported inhibition of basal and stimulated secretion in the trinitrobenzene sulfonic acid and mytomicin C models are applicable to experimental colitis as such. All models showed remarkable similarity in ion transport as determined in Ussing chambers, with downregulated basal as well as carbachol evoked secretion. The EC50 of carbachol was unchanged in all cases. Iodoacetamide and oxazolone colitis models were notable exceptions in that the dose response curves for carbachol were unaltered compared to controls. The reason is unclear but seems to be unrelated to either interferon γ or interleukin 4 levels or to the severity of the inflammatory response.

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Keywords: Inflammatory bowel disease; Colitis models; Short-circuit current; Ionic secretion

Introduction

Inflammatory bowel disease (IBD), a term that comprises Crohn’s disease and ulcerative colitis, is a chronic condition characterized by intestinal inflammation. The etiology of IBD remains unclear, although it is assumed to result from an interplay of genetic, environmental and immunologic influences (Podolsky, 1991; Fiocchi, 1998). Both diseases follow a very similar course, i.e.
inflammation of the digestive tract which recurrent periods of exacerbation and remission of the symptoms; however, there are some important differences. Thus Crohn’s disease affects primarily the colon and small intestine with full thickness mural inflammation, whereas ulcerative colitis affects solely the colon at the mucosal level. A relatively new difference is the fact that Crohn’s disease is a type 1 T-helper cell (Th1)-mediated disease (Elson et al., 1996; Okamoto et al., 1999), whereas ulcerative colitis is essentially a type 2 T-helper cell (Th2)-mediated disease (Boirivant et al., 1998; Dohi et al., 1999). Therefore, Crohn’s disease is characterized by overproduction of interleukin 12 and interferon γ (IFN-γ), while interleukin 4 (IL-4) is the predominant cytokine in ulcerative colitis (Neurath et al., 1995; Mizoguchi et al., 1999).

One of the most notable characteristics of IBD is a profound alteration of ionic transport which results in diarrhoea (Musch and Chang, 1994). Despite the initial concept that inflammatory mediators, which are majoritarily prosecretory in nature (Wardle et al., 1993; Kachur et al., 1995; Ciancio and Chang, 1992; Stenson, 1990), would mediate the development of diarrhoea, it is clear now that the response of the inflamed intestine to secretagogues is in fact depressed (Sandle et al., 1990; Bell et al., 1995; Sánchez de Medina et al., 2002a; Sanchez de Medina et al., 2002b). The basis of hydroelectrolytic transport in the human intestine is well understood (Dawson, 1991; Kunzelmann and Mall, 2002), involving the secretory and absorptive movement of a number of ions, notably Cl−, Na+, K+, HCO3− and H+, across the epithelial layer. This process is subject to close regulation within the enterocyte as well as by external influences, namely mast cells, enterochromaffin cells, immunocompetent cells and the enteric nervous system (Kaunitz et al., 1995; Kunzelmann and Mall, 2002). We have previously shown that the disturbances in ionic (mostly chloride) secretion in these conditions are related to a defective production of cAMP within the enterocyte using the trinitrobenzene sulfonic acid (TNBS) model of chronic colitis (Sánchez de Medina et al., 2002a). The elucidation of the mechanisms responsible for the altered ionic transport in the context of intestinal inflammation is of evident clinical interest, since the quality of life of IBD patients is significantly impaired by diarrhoea. A number of models of intestinal inflammation have been developed in the past few years, which may be used to investigate this matter (Kim and Berstad, 1992; Blumberg et al., 1999). We and others have characterized the nature of the alterations in ionic transport using basically the TNBS model of colitis (Bell et al., 1995; Sánchez de Medina et al., 2002a; Sanchez de Medina et al., 2002b). Therefore it is not known to what extent these observations are applicable to colonic inflammation in general. Hence we designed the present study in which 9 different models of acute and chronic colonic inflammation are assessed in terms of basal and stimulated ionic secretion using the voltage clamp technique.

Materials and methods

Animals

Female Wistar rats (180–220 g) obtained from the Laboratory Animal Service of the University of Granada were used, except for HLA-B27/α2 transgenic rats and age matched Fischer control rats, which were provided by Taconic (Germantown, NY). Animals were housed in makrolon cages (3–4 rats per cage) and maintained in our laboratory in air conditioned animal quarters with a 12 h light-dark cycle. Animals were provided with free access to tap water and food (Panlab A.04). This study was carried out in accordance with the Directive for the Protection of Vertebrate Animals used for Experimental and
other Scientific Purposes of the European Union (86/609/EEC) and was approved by the Ethics Committee of the University of Granada.

Reagents

Dextran sulfate was obtained from ICN Biomedicals (Costa Mesa, CA), sodium hypochlorite (NaClO) was provided by Aldrich (Madrid, Spain), ammonium chloride (NH₄Cl) was supplied by Merck (Barcelona, Spain). Glutathione reductase was obtained from Boehringer Mannheim (Barcelona, Spain). Taq polymerase and the RNA retrotranscription kit were from Amersham Biosciences (Barcelona, Spain). Unless stated otherwise, all other reagents, including TNBS, were obtained from Sigma (Madrid, Spain).

Induction of colitis

TNBS model

Colitis was induced by the method originally described by Morris et al. (1989) with minor modifications. Animals were fasted overnight and anaesthetised with halothane. Under anaesthesia, animals were given 10 mg of TNBS dissolved in 0.25 ml of 50% ethanol (v/v) by means of a Teflon cannula inserted 8 cm through the anus. During and after TNBS administration animals were kept in a head-down position until they recovered from anaesthesia, and then returned to their cage. Rats from the non colitic (normal) group received 0.25 ml of phosphate buffered saline. Animals were sacrificed after 7 days.

Dextran sulfate model

The induction of colitis was adapted from a previously described work (Stucchi et al., 2000). Animals received 5% dextran sulfate sodium (DSS, 36–50 kD), administered via drinking water ad libitum during 7 days, after which they were sacrificed. This model is referred to as acute DSS. A separate group of rats were allowed to recover for 1 week with plain water after the initial DSS treatment and subjected to a second week of DSS (Vetuschi et al., 2002) in order to induce a more chronic type of colitis (chronic DSS model). In both cases control animals received water ad libitum.

Iodoacetamide model

Colitis was induced by method originally described by Rachmilewitz et al. (1995). Animals were treated as in the TNBS model except that 6.3 mg of iodoacetamide in distilled water were instilled. Animals were sacrificed after 1 wk. Control rats received a distilled water enema.

Acetic acid model

The induction of colitis was adapted from that originally described by MacPherson and Pfeiffer (1978). Animals were treated as in the TNBS model except that colitis was induced with an enema of 2 ml of 4% (v/v) acetic acid, which was neutralized after 10 s with 2 ml of phosphate-buffered saline (pH = 7.4), administered while holding the animals in a head-down position. Animals were sacrificed after 24 h. Control animals received only the phosphate-buffered saline enema.
Monochloramine model

Colitis was induced by means of a monochloramine enema (3.2 mg in 0.25 ml of distilled water). Monochloramine was obtained immediately before administration by reacting 0.5 M NaClO and 0.5 M NH₄Cl. The reaction was completed in less than 1 min, as followed by the absorbance at 260 nm. Rats from the non colitic (normal) group received 0.25 ml of phosphate buffered saline. A group of animals were sacrificed after 1 wk (chronic inflammation) and other group after 24 h (acute inflammation).

Oxazolone model

The method of Ekström with some modifications was used (Ekstrom, 1998). The animals were sensitized under halothane anesthesia 1 wk before colitis induction by applying 12 mg oxazolone dissolved in 3 ml of acetone/ethanol (1:4 v/v) on the shaved abdominal skin (\(\sim 8 \text{ cm}^2\)). Sensitization was repeated after 24 h in the same fashion. Control animals received the vehicle. Colitis was induced with an enema of 9 mg of oxazolone emulsion in a mixture of methylcelulose/olive oil (1:1 v/v). Control animals received the vehicle only. Control experiments confirmed that colitis was induced only in presensitized animals (data not shown). Animals were sacrificed after 4 days.

HLA-B27/\(\beta_2\) transgenic rats

HLA-B27/\(\beta_2\) rats were obtained commercially and examined at 22 wk of age, a time point when inflammation is first detected (Hammer et al., 1990). Fischer rats were used as controls.

Assessment of colonic inflammation

Animals were sacrificed by cervical dislocation and the colonic segments were extracted, placed on an ice cold plate and cleaned of fat and mesentery. Each specimen was weighed and its length measured under a constant load (2 g). Immediately a segment of 2 cm (approximately 3–4 cm from the anus) was separated and submerged in ice cold Ringer solution for voltage-clamp experiments. The composition of the Ringer solution was (in mM): 115 NaCl, 25 NaHCO₃, 1.2 CaCl₂, 1.2 MgCl₂, 2.4 K₂HPO₄, 0.4 KH₂PO₄, and 10 glucose. The rest of the colon (proximal colon and the remainder distal area) was subsequently opened and longitudinal samples of the colon were obtained. One fragment was kept at \(-30^\circ\text{C}\) for myeloperoxidase (MPO) activity determination, and another fragment was weighed and frozen in 1 ml of 5% (w/v) trichloroacetic acid for total glutathione content determination. All biochemical measurements were completed within 2 weeks from the time of sample collection and were performed in duplicate.

Myeloperoxidase assay

Myeloperoxidase (MPO) activity, an index of neutrophil infiltration, was measured spectrophotometrically according to the technique described by Krawisz et al. (1984). Samples were suspended in 1 ml of 50 mM sodium phosphate buffer incorporating 0.5% hexadecyltrimethylammonium bromide (pH = 6.0), and minced with scissors for 15 s on an ice cold plate. The resultant suspension was subsequently diluted to a final 1:20 w/v ratio and homogenized for 1 min with an automatic Heidolph homogenizer, sonicated for 10 s, and subjected to 3 freeze-thaw cycles. The homogenates were then centrifuged at 7000 g and 4°C for 10 min and the supernatants (50 \(\mu\)l) assayed for MPO activity using 0.0005% hydrogen peroxide as enzyme substrate and o-dianisidine dihydrochloride (0.169 mg/ml) as a
marker, in 150 μl of 50 mM phosphate buffer (pH = 6.0). The enzymatic activity was calculated from the slope of the curve at 460 nm. One unit of MPO activity was defined as that degrading 1 μmol/min of hydrogen peroxide at 25°C. The results are expressed as MPO units per gram of wet tissue.

Total glutathione content

Total glutathione content was quantitated spectrophotometrically with a recycling assay (Akerboom and Sies, 1981). Samples were thawed, minced, diluted 1:20 (w/v) in ice cold 5% (w/v) trichloroacetic acid and homogenized for 1 min with a Heidolph homogenizer. The homogenates were centrifuged at 7000 g for 15 min and 100 μl of the supernatants added to the assay mixture containing 143 mM phosphate buffer (pH = 7.5), 6.3 mM sodium EDTA, 0.33 mM NADPH and 6 mM 5,5’-dithio-bis(2-nitrobenzoic acid). This mixture was allowed to stand at 30°C for 5 min and glutathione reductase was added to a final concentration of 266 U/ml. The amount of glutathione was calculated from the slope of the curve at 412 nm. Results are expressed as nmol/g wet tissue.

Voltage clamp experiments

The large intestinal segment was gently flushed with ice-cold Ringer solution and the serosa and outer muscle layers separated by blunt dissection. The colonic fragment, composed of the mucosal and submucosal layers, was then mounted on Ussing chambers (exposed area: 0.64 cm²) and short-circuited with DVC-1000 voltage clamp devices (Word Precision Instruments, Aston, United Kingdom). Only one piece of tissue per colonic segment was used. Care was taken to avoid the areas of necrosis. A voltage step of +3 mV was briefly applied every 5 min to calculate tissue conductance by Ohm’s Law. The preparations were allowed to equilibrate for 20–30 min until stable basal readings of $I_{sc}$ ($I_0$) and conductance ($G_0$) could be obtained. A concentration response curve to the secretagogue agent carbachol, added from a water concentrated solution, was then obtained. The curves were individually fitted with a sigmoidal logistic equation using the Origin 5.0 computer software (Microcal Software, Northampton, MA), from which the EC$_{50}$ was calculated.

Cytokine determination

For the determination of IL-4 and IFN-γ fresh colonic samples devoid of the outer serosa and muscular layers (see above) were briefly minced and incubated for 20 min in phosphate-buffered saline (1:5 w/v) at 37°C with continual shaking. The supernatants obtained after centrifugation were frozen at −80°C until cytokine determination by enzyme linked immunoassay (Amersham Biosciences, Barcelona, Spain).

Statistical analysis

All results are expressed as mean ± S.E.M. Differences among means were tested for statistical significance using one way analysis of variance and a posteriori least significance tests. Differences between pairs of means were analysed by Student’s unpaired two-tailed t-test. Statistical significance was set at $P < 0.05$. All analyses were carried out with SigmaStat 2.0 (Jandel Corporation, San Rafael, CA).
Results

Colonic inflammation

We have studied 4 models of acute colonic inflammation, namely colitis induced by acetic acid, oxazolone, DSS and monochloramine. The former two models are well described in the literature and are characterized by a short, self-limiting course (1–4 days), while monochloramine colitis is a novel model developed by our research group which has both an acute and a chronic stage. DSS, which induces colonic inflammation as long as it is administered in drinking water, was given for 1 week to produce acute colitis or for 2 alternating weeks to produce chronic colitis (see below). Acetic acid administration resulted in haemorrhagic inflammation of the mucosa involving the proximal and distal colon; monochloramine led to similar but more localized and less severe lesions which were restricted to the distal portion of the large intestine. DSS induced mild inflammation with some ulcers throughout the colon, while oxazolone produced only slight macroscopic damage.

On the other hand, 5 models of chronic colonic inflammation have been also evaluated, i.e. colitis induced by TNBS, dextran sulfate sodium, iodoacetamide and monochloramine, plus spontaneous colitis in HLA-B27/β2 transgenic rats. Both TNBS and iodoacetamide produce severe, necrotic lesions that heal after several weeks and leave scars and fibrosis as sequelae. Dextran sulfate sodium led to generalized oedema with localized ulcers and haematochezia, while monochloramine chronic stage was characterized by mucosal necrosis and submucosal oedema. In all cases (except DSS, see Materials and methods) animals were studied at 1 wk after colitis induction. HLA-B27/β2 transgenic rats showed very slight evidence of inflammation to the naked eye at 22 wk of age, a time point where inflammation reportedly sets in.

The inflammatory status of the large intestine was characterized biochemically as well as morphologically by a number of markers, namely the weight:length ratio, MPO activity and total glutathione levels (Table 1). All models, except oxazolone, showed a significant increase in the intestinal

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Markers of inflammation in experimental acute or chronic rat colitis</th>
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<tr>
<td></td>
<td>Weight (mg/cm)</td>
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<tr>
<td></td>
<td>Control</td>
</tr>
<tr>
<td>Acute colitis</td>
<td></td>
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<tr>
<td>Acetic acid</td>
<td>82.1 ± 3.8</td>
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<tr>
<td>Monochloramine</td>
<td>83.9 ± 2.3</td>
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<tr>
<td>Oxazolone</td>
<td>91.3 ± 6.8</td>
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<tr>
<td>Dextran sulfate</td>
<td>76.2 ± 1.1</td>
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<tr>
<td>Chronic colitis</td>
<td></td>
</tr>
<tr>
<td>TNBS</td>
<td>76.4 ± 3.2</td>
</tr>
<tr>
<td>Dextran sulfate</td>
<td>64.2 ± 5.4</td>
</tr>
<tr>
<td>Iodoacetamide</td>
<td>83.9 ± 2.3</td>
</tr>
<tr>
<td>Monochloramine</td>
<td>83.9 ± 2.3</td>
</tr>
<tr>
<td>HLA-B27/β2</td>
<td>71.9 ± 2.3</td>
</tr>
</tbody>
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Data are mean ± S.E.M. (n ≥ 6). *P < 0.05 vs. control. Glutathione was not measured in HLA-B27/β2 rats.
weight/length ratio, which is indicative of tissue edema and/or fibrosis. Neutrophil infiltration, as evidenced by elevated MPO levels, was a feature of all models of intestinal inflammation. Glutathione depletion, which is an index of oxidative stress, was also detected in most but not all models. Please note that glutathione was not measured in the HLA-B27/β2 transgenic model. Thus the parameters studied confirm the presence of an inflammatory response in all of the models studied.

Ionic secretion

We used the voltage clamp technique to measure transepithelial ionic transport in the distal colon of control and colitic rats mounted in Ussing chambers (Fig. 1). We and others (Sánchez de Medina et al., 2002a; Andres et al., 1985) have previously established that in the rat distal colon short circuit current (Isc) represents mainly chloride secretion, with a significant but minor contribution of bicarbonate secretion. Basal ion transport (I0) in the colon was generally decreased both in acute and chronic

![Graph A](attachment:image1.png)

**Fig. 1.** Basal electrical parameters in experimental colonic inflammation. A. Basal conductance. B. Basal Isc. Open columns are controls, black columns are inflamed. Data are mean ± S.E.M. (n ≥ 6). *P < 0.05 vs. control.
experimental colitis. This is in sharp contrast with the basal conductance data, which show a significant increase in only two models, i.e. acetic acid and TNBS colitis.

In an attempt to continue exploring the colonic secretory ability, the secretagogue carbachol was used to stimulate ionic secretion (Figs. 2 and 3). The maximal response to carbachol, added to the basolateral side of the preparations, was reduced ($P < 0.05$) by 77.8% for the acetic acid model, 45.3% and 36.2% for the acute stage of monochloramine and DSS, 39.4% for the TNBS model, 71.5% for the chronic DSS model, 40% for the chronic stage of monochloramine and 82.4% for HLA-B27/β2 transgenic rats. However, the dose-response curve was not altered in iodoacetamide and oxazolone colitis. In all cases the EC$_{50}$ was unchanged by colonic inflammation. (data not shown).

**Cytokine profile of colitis models**

In order to correlate any discrepancies in the behaviour of the different models assayed, we characterized the pattern of cytokine expression in the inflamed intestine using enzyme linked
Fig. 3. Dose response curves to carbachol in chronic experimental colitis. A. TNBS. B. Iodoacetamide. C. Chronic DSS. D. Chronic monochloramine. E. HLA-B27/\beta_2 transgenic rats. Control: open squares; inflamed: solid circles. *P < 0.05 vs. control. Data are mean of each concentration of carbachol ± S.E.M. (n = 3–10).
immunoassay (Fig. 4). The HLA-B27/β2 model could not be analyzed for cytokine profile but it has been extensively characterized as developing a Th1 type of inflammatory response (Hata et al., 2001).

IL-4 colonic production was significantly reduced in the iodoacetamide, acetic acid and monochloramine models and increased in the rats treated with oxazolone. On the other hand, IFN-γ levels were significantly increased only in the TNBS group. However, when the IFN-γ/IL-4 ratio was calculated, a marked increase was observed in the monochloramine, TNBS, iodoacetamide and acetic acid models, whereas the oxazolone group displayed a significant reduction. No change was detected in the DSS rats.

Discussion

One of the cardinal signs of IBD is the occurrence of diarrhoea associated and correlated with the development of inflammation (Musch and Chang, 1994). Both motility and ionic transport abnormalities have been proposed to be involved in this symptom. Thus Jacobson et al. have described alterations in myoelectric activity in experimental colitis, which extend beyond the inflammatory sites (Jacobson et al., 1995). On the other hand, ionic transport changes have been reported for human IBD (Sandle et al., 1990) as well as some experimental models (Kachur et al., 1995; Sánchez de Medina et al., 2002a; Bell et al., 1995). These changes include not only diminished absorption (Sundaram and West, 1997; Sundaram et al., 1997; Sundaram et al., 1998), but also, paradoxically, reduced ionic secretion (Kachur et al., 1995; Sánchez de Medina et al., 2002a; Asfaha et al., 1999). In fact, the response to a number of secretagogues has been consistently shown to be significantly downregulated in the context of inflammation. This finding questions the hypothesis that inflammatory diarrhoea results from the activation of secretion by inflammatory mediators such as interleukin 1, hydrogen peroxide, prostaglandins, leukotriene B4, etc. We have studied extensively the ionic disturbances that take place in colonic inflammation using the TNBS model of chronic colitis (Sánchez de Medina et al., 2002a; Sánchez de Medina et al., 2002b). These studies showed that the submucosal nervous system plays an important role in the inhibition of stimulated secretion in chronic TNBS colitis via a reduction in the cAMP production by the enterocyte. However, it is important to establish that these findings are not
specific to the experimental model used but relevant to colonic inflammation in general. Thus we have presently characterized basal and carbachol stimulated ionic secretion in 9 models of acute and chronic colitis to verify this hypothesis. In addition, we tried to correlate any observed changes with the severity and type of inflammatory response.

Our results generally confirm that the basic findings reported for the TNBS model are applicable to almost all the other models examined, since colitis was associated with reduced basal and stimulated ionic secretion. In particular, basal ionic transport, which represents mostly chloride secretion (Andres et al., 1985; Sánchez de Medina et al., 2002a), was diminished in all 9 models. Tissue conductance, on the other hand, was only increased significantly in acetic acid (acute) and TNBS (chronic) colitis. Conductance was also higher, albeit nonsignificantly, in the short term acute models, namely oxazolone and acute monochloramine colitis, but generally not in the chronic models. These findings are consistent with the previously reported increase in conductance observed in the early stages (1–4 days) of TNBS colitis (Bell et al., 1995; Sanchez de Medina et al., 2002b). Our own previous observations suggest that the defect in conductance in TNBS colitis may be more specific than previously thought, since this parameter is normalized in the absence of chloride (Sanchez de Medina et al., 2002b).

The downregulation of stimulated transport in the colitic intestine has been reported to be even more striking than the effects on basal secretion (Sánchez de Medina et al., 2002a; Asfaha et al., 1999). We chose carbachol to test the effects in the different inflammatory models because its response is clearly affected in the TNBS model (Sánchez de Medina et al., 2002a; Sanchez de Medina et al., 2002b) and is also relatively fast, thus allowing a quicker completion of the experiments. The results obtained demonstrate that most colitis models share the same behaviour, i.e. inhibition of maximal secretion without affecting the EC50. This is similar to our own previous observations, suggesting that the same mechanisms are involved. Notable exceptions were oxazolone acute colitis and iodoacetamide chronic colitis, which displayed concentration-response curves to carbachol similar to those of the controls. Because the severity of the inflammatory response was radically different in these two models this cannot be considered a causative factor. Indeed, there is little correlation between these variables in all models considered; for instance, HLA-B27 transgenic rats and DSS chronic colitis show the greatest degree of inhibition while having a relatively mild colitis.

Next we attempted to find a relation with the quality of the inflammatory response by analyzing the pattern of cytokine expression. We have focused on the hallmark Th1 and Th2 cytokines, IFN-γ and IL-4. Of all the models studied, only oxazolone colitis was anticipated to mount a Th2 response, as shown previously in mice (Heller et al., 2002). In fact, this is one of the few models of intestinal inflammation that has a Th2 profile, since the vast majority of models of experimental colitis have been identified as Th1. Our results largely confirm these observations, since oxazolone treated rats had an increased production of IL-4. Conversely, IL-4 was reduced in all other models except TNBS and DSS colitis, suggesting a Th1 type of inflammation. This was directly confirmed by IFN-γ measurement in TNBS colitis, but not in the remaining models. Because the Th1 and Th2 types of inflammatory reaction have reciprocal inhibitory effects on each other, we calculated the IL-4/IFN-γ ratio, which proved to be a better indicator. Thus rats from the oxazolone group had a small but significant reduction in this parameter, whereas all other groups, with the sole exception of DSS rats, showed a significant increase, corresponding to the expected Th1 type of response. The reason why the IL-4/IFN-γ ratio was unchanged in DSS colitis is unknown. However, it is important to note that some authors have detected increased populations of CD4+ cells bearing IL-4 or IFN-γ in the chronic stage of DSS colitis in mice (Dieleman et al., 1998), suggesting that this particular model may not be purely Th1 in nature. At any rate, since the iodoacetamide and oxazolone models are
examples of both types of response, respectively, these cytokines are unlikely to account for the atypical behaviour, i.e. lack of inhibition of carbachol evoked secretion.

In conclusion, experimental models of colonic inflammation are almost invariably associated with impaired basal and stimulated ionic secretion, even in cases of mild involvement. DSS and oxazone colitis are notable exceptions to this rule for reasons unknown but unrelated to the nature of the immune response and to the severity of inflammation.

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