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Effect of chronic inflammation on intestinal peristalsis

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تأثير الالتهاب المزمن على التقلص الذاتي للامعاء

فايزه بكر عبده
جامعة الملك عبد العزيز- كلية العلوم- قسم علوم الأحياء

الملخص العربي

تستخدم الاصابة بالبلهارسيا لدراسة الالتهابات المسببة للتغيرات في الوظائف الحركية للامعاء. دراستنا السابقة لخلل الوظائف الحركية للامعاء والناتجة عن الاصابة الحادة (٨ اسابيع) للبلهارسيا قادت الى بحث وظيفة وسائط الالتهابات (Inflammatory mediators) التي تفرز خلال فترة الإلتهاب وكذلك دراسة الميكانيكيه التي تعمل بها هذه الوسائط اثناء التغيرات خلال فترة الاصابة المزمنة (١٦ اسبوع).

أجريت التجارب على مجموعه من الفئران السويسرية السليمة وكذلك مجموعة من الفئران المصابة بالبلهارسيا (*Schistosoma mansoni*) لمدة ستة عشر أسبوع ثم بنيت النتائج على أساس مقارنه الفئران المصابة بالفئران غير المصابة (السليمة).
تم إحداث الحركة الانقباضية لكل من الصائم والقولون للقناة الهضمية باستخدام طريقة (Trendelenburg).

الالتهاب المزمن للامعاء احدث تأثيرًا عميقا في الحركة الانقباضية للصائم والقولون حيث احدث زيادة معنوية في ارتفاع قمم الانقباضات (Amplitudes) مصحوبًا بزيادة معنوية في ترددها والذي انعكس في صورة نقص في الوقت (Intervals) بين الانقباض والاخر.
مثبط السيكلواكسيجينيز (نابروكسن) (Cyclo-oxygenase inhibitor naproxen, 10μM) سبب زيادة معنوية في ارتفاع قمم الانقباضات ونقص في المسافات الزمنية بين الانقباضه والاخرى في كلاً من صائم الفئران السليمة والمصابة وذلك خلال فترة الالتهاب الحاد فقط.
اما في القولون فإن النابروكسن سبب نقصًا في ارتفاع القمم في كلا المجموعتين منذ بداية التجربة وحتى نهاية الاسبوع الاخيرمنها، لكنه سبب زيادة في الفترات الزمنية بين الانقباضات أثناء الالتهاب الحاد فقط.
مضاد المستقبل الثالث 5-HT_3 (Y-25130, 1μM) لم يؤثر على الفترات الزمنية بين الانقباضات طول فترة التجربة ولكنه ادى الى تثبيط قمم الانقباضات في المجموعتين اثناء الالتهاب الحاد فقط.

نستخلص من هذه النتائج وجود اختلافات في حساسية كلاً من الصائم والقولون نتيجة للاصابه بالبلهارسيا. البروستانويد (Prostanoid) وكذلك خامس هيدروكسي التربتامين (5-HT) يلعابان دورًا هامًا في تنظيم وظيفة الحركة المعوية في حالة الصحة والمرض ولكن تغير الحساسية في الطور المبكر و النهائي للاصابة قد يشير الى المرونة في الميكانيكية المسؤولة عن إحداث الخلل الوظيفي للامعاء.

EFFECT OF CHRONIC INFLAMMATION ON INTESTINAL PERISTALSIS

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Key words: Motility, Naproxen, Inflammation, 5-HT, *S. mansoni*

ABSTRACT

Schistosomiasis have been used to investigate inflammation induced changes in intestinal motor function. Our previous study on intestinal motor dysfunction during Schistosoma mansoni (*S. mansoni*) infection led to this investigation on role of inflammatory mediators and the mechanisms underlying post-inflammatory changes during chronic inflammation. Experiments were performed on male Swiss mice 8-, 12- and 16-wk following infection with *S. mansoni* compared to unifected controls. Jejunal and colonic motility were assessed using a Trendelenburg type preparation to study aboral directed motor complexes (MCs).

Chronic infection had profound effects on jejunal and colonic motility where there was a significant increase in MCs amplitude and an increase in frequency reflected by a decrease in the intervals between MCs. Cyclo-oxygenase (COX) Naproxen (10μM) caused significant increase in the amplitude concomitant with a reduction in the MCs intervals in the jejunum of control and 8-wk infected animals only. In the colon, although Naproxen decreased MCs amplitude in control animals and throughout the post-infection period, it increased the MCs interval in uninfected mice and during early periods of infection only. The 5-HT_3 antagonist Y-25130 (1μM) had no effect on MCs interval in control and infected animals, but in both jejunum and colon it caused a significant decrease in MCs amplitude in control and 8-wk infected animals but not in 12- and 16-wk.

In conclusion, these data demonstrated temporal differences in the sensitivity of jejunal and colonic motor function following infection with *S mansoni.* Prostanoids and 5-HT_3 play an important role in the regulation of motor function in both control and infected animals but altered sensitivity in the early and late post-infection period may point to plasticity in the mechanisms responsible for intestinal dysmotility.

INTRODUCTION

Intestinal inflammation may induce functional and structural changes of the smooth muscle cells leading to alterations in smooth muscle contractility (Moreels *et al.*, 2001). Although the mechanism of these alterations is still unknown, the activation of mast cells and the enteric neurons that release neurogenic mediators disturb the normal activity of gastrointestinal (GI) smooth muscle (Galligan, 2004; Boeckxstaens, 2006). These mediators also play an important role in the maintenance of intestinal inflammation (Linden *et al.*, 2003).

Schistosomiasis can lead to several chronic syndromes, after 7-wk of the infection, when eggs production start and penetrate the vessel wall to reach the terminal ileum and the colon leading to inflammation (Moreels *et al.*, 2001). Fifty percent of the eggs remain entrapped within the gut wall inducing chronic inflammation which characterized by severe motility disturbance (De Man *et al.*, 2002; De Jonge *et al.*, 2003).

Previously, we have shown the role of the inflammatory mediators, COX inhibitor and 5-HT_3 receptor antagonist on intestinal motor dysfunction in Schistosoma *mansoni* (*S. mansoni*) infection (Abdu, 2007). The current study was designed to investigate the role of these mediators in the mechanisms underlying post-inflammatory changes of GI tract motility during chronic inflammation.

During the inflammatory process, the neurochemical mediators are released and have actions on various cell types, including enteric neurons (Spiller, 2002). A common feature of intestinal inflammation is the upregulation of the COX enzyme, leading to increased synthesis of several eicosanoids including prostaglandins (Eberhart *et al.*, 1994; Roberts *et al.*, 2001). The mechanism of action of nonsteroidal anti-inflammatory drugs (NSAIDs); such as naproxen, is the inhibition of COX which exists in two isoforms, COX-1 and COX-2 (Vane *et al.*, 1998; Warner *et al.*, 1999). The GI tract expresses high levels of COX-1 which functions as a house-keeping enzyme (Vane *et al.*, 1998) but, under physiological conditions, the GI contains only low levels of COX-2 (Ferraz *et al.*, 1997; Maricic *et al.*, 1999). Most studies of the GI function of COX isoforms related to mucosal homeostasis, given that both COX-1 and COX-2 inhibition carries a

risk of intestinal inflammation (Warner *et al.*, 1999; Wallace *et al.*, 2000).

Dysmotility of both large and small bowel of IBS (Irratable bowel syndrome) patients has been described (Bush *et al.*, 2001). Hyper secretory activity is a feature of IBS (Bearcroft *et al.*, 1998). However, visceral hypersensitivity has been also implicated in IBS (Drossman, 1999). Current therapies for IBS, including dietary fiber; opioids for diarrhea, smooth muscle relaxants, and psychotropic and psychological agents, were not selective and do not give consistent relief of symptoms (Camilleri, 1999). 5-HT is belived to be a critical step in the sensory transduction of chemical and mechanical information from the lumen of the gut to the intrinsic and extrinsic sensory neurons that innervate the small and large intestine. In pathological GI function, the process of sensory transduction may be disturbed and compounds that modulate 5-HT_3 receptors are therapeutic (Bertrand, 2004). Several lines of evidence support the use of serotonin subtype 3 (5-HT_3) receptor antagonists for the treatment of IBS. Y-25130 possesses potent and selective antagonistic property for 5-HT_3. (Odani *et al.*, 1993; Ooe *et al.*, 1993; Kelley and Hodge, 2003). 5-HT_3 receptor antagonists attenuate 5-HT_3 induced signalling in visceral afferents (Gregory and Ettinger, 1998). Intestinal distension in animals leads to activation of reflex behaviour that was used to model visceral inflammation. 5-HT_3 antagonists potently suppress these reflexes (Mayer and Gebhart, 1994). These compounds also suppress gut motility in IBS patients that occurred in the absence of effect on rectal tone (Prior and Read, 1993).

Therefore, this study aimed to (1) evaluate the role of inflammatory mediators such as prostanoid and 5-HT_3 in the mechanisms underlying post-inflammatory changes in smooth muscle motility during chronic inflammation; and (2) investigate the relationship between active inflammation and altered motility in order to understand how inflammation leads to motor abnormalities which may contribute to the development of new treatments for patients with IBS.

MATERIAL AND METHODS

Schistosoma mansoni Infection

The maintenance of the *S. mansoni* life cycle and the transcutaneous infection of mice with *S. mansoni* have been previously described (Bogers *et al.*, 2000; Moreels *et al.*, 2001) male Swiss mice (age 7-wk) were transcutaneously infected with about 100 *S. mansoni* cercariae as described by the same authors using treated water containing 100 infectious cercariae of a *Biomphalaria alexandrina* strain of *S. mansoni*. The cercariae were allowed to penetrate during 30 min after which the water was removed and checked for remaining cercariae. Control and infected mice were sacrificed after 8-, 12-, and 16-wk, then the contractile activity of isolated segments from jejunum and colon were investigated. All experiments were approved by animal research Ethic Committee of King Fahad Medical Research Centre (KFMRC).

Tissue Preparation

Control and infected animals were scarified by cervical dislocation. A mid-line laparotomy was performed and a segment of proximal jejunum and colon was rapidly excised and placed in gassed (95% O_2 and 5%CO_2) Krebs bicarbonate buffer solution (composition in mM: NaCl 117, KCl 4.7, $NaHCO_3$ 25, $CaCl_2$ 2.5, $MgCl_2$ 1.2, $NaH_2PO_4.2H_2O$ 1.2 and D-glucose 11). Segments were cleared of any mesenteric connective tissue and the lumen flushed with Krebs solution. Tissues were prepared according to the method described by Abdu *et al.*, 2002. Two jejunal and colon segments approximately 5 cm in length were prepared from each animal and four in total were mounted horizontally in separate 20ml perfusion chambers. Tissues were maintained at 37C°, perfused with Krebs solution at a rate of 5ml min^{-1} and allowed to equilibrate for at least 30 min before recording. Motor complex of jejunuam and colon of infected and uninfected mice were monitored and analyzed by using (Neurolog\NL 900D, Digitimer Ltd, Hertfordshire, England) to compare regional differences and their responsiveness to blockade of inflammatory mediators including prostanoids and 5-HT.

Experimental Protocol

Isolated jejunal and colon segments were distended to 2-3.5 cmH_2O and 4-5 cmH_2O, respectively to evoke MCs. Only preparations in which regular MCs were maintained were used for subsequent experiments. Drugs (naproxen and 5-HT_3 receptor antagonist Y-25130) or the appropriate vehicle were added to the chambers 15 min after stopping perfusion and recording continued for a further 20 min before washing out the drugs and re-instating perfusion.

Drugs

All the peptides were dissolved in distilled water unless otherwise stated. 5-HT_3 receptor antagonist (Y-25130) was dissolved in saline (0.9% NaCl). All drugs were stored at –20°C. Freshly diluted aliquots were maintained on ice during the course of the experiments and added to the bath in microlitre volumes.

Data Analysis

MCs were quantified in terms of their peak amplitude above baseline and expressed as cmH_2O, while duration and interval between them were expressed in seconds (s). Baseline values were taken during the 15 min before drug application and the response effect was recorded in

the 15 min following application. Responses are expressed as absolute values ± S.E.M with N = number of animals. Paired data were compared using Student's *t*-test or Wilcoxon rank-sum test as appropriate. Probability of ($P<0.05$) was considered as significant.

RESULTS

Jejunal MCs of control animals had a maximum pressure of 2.65 ± 0.3 cmH_2O, separated by intervals of 39 ± 10s (Fig. 1A & B). Colonic MCs had a maximum pressure of 34 ± 4 cmH_2O and intervals of 85 ± 8s (Fig. 4A & B).

MCs in the Jejunum

The amplitude of 8-wk infected jejunum had increased significantly (from 2.66 ± 0.26 to 8.58 ± 1.36). This elevation had diminished in 12- and 16-wk post-infected animals (6.06 ± 1.06, $P < 0.01$ and 5.72 ± 1.79, $P > 0.05$, respectively) compared to the control (Fig. 1B).

The intervals in the jejunum were also increased in 8-, 12- and 16-wk (from 39 ± 10 to 52.57 ± 5, $P > 0.05$; 75.71 ± 10, $P < 0.05$; and 48.73 ± 9, $P > 0.05$, respectively) compared to the control. However, this increase was only significant in 12-wk infected jejunum (Fig. 1B).

Effect of COX Inhibitor in the Jejunum

COX inhibitor naproxen had different effect on the jejunum regarding the post infection periods of inflammation (Fig. 2A). COX inhibitor naproxen (10μM) significantly increased the amplitude in control (2.64 *vs* 4.93 ± 0.1) and 8-wk infected jejunum (8.96 ± 0.5 *vs* 12.36 ± 0.15,); whereas, the intervals were decreased significantly in control (39.58 ± 5 *vs* 24.10 ± 2) and after 8-wk of infection (49.06 ± 3 *vs* 19.01 ± 0.6); an effect that was relatively obvious in infected tissue compared to controls ($P < 0.05$, Fig. 2B). In contrast, in 12- and 16-wk infected jejunum, naproxen (10μM) slightly attenuated the amplitude (4.9 ± 1.5 *vs* 4.55 ± 2, $P > 0.05$ and 7.96 ± 5 *vs* 5.27 ± 3.5, $P > 0.05$, respectively) but had no clear effect on MCs intervals (Fig. 2B).

Effect of 5-HT_3 Receptor Antagonist Y-25130 in the Jejunum

The effect of 5-HT_3 receptor antagonist Y-25130 (1μM) was shown in Fig. 3A. It inhibited MCs amplitude significantly in both control and 8-wk infected tissues only (Fig. 3B). Whereas in 12-wk post-infection the response to Y-25130 was slightly reduced (7.89 ± 2.5 *vs* 5.93 ± 5, $P > 0.05$) and almost disappeared in 16-wk infected animals (5.08 ± 1 *vs* 5.05 ± 2, $P > 0.05$, Fig. 3B). Although Y-25130 inhibited the frequency of MCs in 8 and 16-wk post infection, this effect did not reach the significancy.

MCs in the Colon

The response to infection in the colon differs from jejunum (Fig. 4A), there were no significant increase of amplitude in 8-wk infected tissues (Fig. 4B). The significant increase of amplitude was observed at 12-wk (from 34 ± 4 to 59.15 ± 6,) and 16-wk post infection (from 34 ± 4 to 226.99 ± 36, $P < 0.001$) compared to the control (Fig. 4B). The intervals between MCs in the colon had increased significantly in 8- and 12-wk post infected animals (from 85 ± 8 to 128.56 ± 17, and to 183.88 ± 19, respectively). However, after 16-wk there was no significant changes in intervals compared to the control (Fig. 4B).

Effect of COX Inhibitor in the Colon

In the colon, naproxen (10μM) had an opposite effect to the jejunum (Fig. 2A & 5A). The amplitude of MCs decreased significantly in control (27.19 ± 5.5 *vs* 18.5 ± 4) and 8-wk (36.77 ± 10 *vs* 28.32 ± 10) infected tissue. This effect was maintained during 12-wk (37.5 ± 20 *vs* 31.38 ± 18) and 16-wk (257.06 ± 43 *vs* 192.38 ± 25) post-infection (Fig. 5B). In terms of intervals, naproxen (10μM) induced significant increase in control (81.09 ± 14 *vs* 105.31 ± 14) and 8-wk infected colon (137.29 ± 37 *vs* 245.27 ± 49); such an effect was greater in infected tissue compared to control ($P < 0.01$). Whereas, in 12-wk infected animals the response to naproxen (10μM) was less and non-significant (169.9 ± 41 *vs* 228.38 ± 69) and nearly disappeared in 16-wk (123.09 ± 24 *vs* 127.04 ± 31) compared to the control (Fig. 5B).

Effect of 5-HT_3 Receptor Antagonist Y-25130 in the Colon

The 5-HT receptor antagonist Y-25130 (1μM) significantly decreased MCs amplitude in control (37.39 ± 3 *vs* 21.38 ± 2.5) and 8-wk infected colon only (39.72 ± 3 *vs* 20.55 ± 2.5). This effect (Fig. 6A & B) was disappeared in 12- (58.68 ± 3 *vs* 59.04 ± 9.5) and 16-wk (305.05 ± 76 *vs* 302.51 ± 76). The used receptor antagonist had no effect on MCs intervals during 8-wk, 12- and 16-wk infected jejunum and colon compared to the control (Fig. 6B). Although the drug elongated MCs intervals of control and 8-wk infected colon as well as reduced these values in 12- and 16-wk infected tissues, these effects were statistically non-significant.

DISCUSSION

Intestinal *schistosomiasis* induces acute and chronic inflammatory changes of the small and large intestine and its the major cause of inflammation associated with motor dysfunction (De Man *et al.*, 2002; De Jonge *et al.*, 2003).

The present study confirmed that intestinal motor function is considerably altered in infected jejunum at the early stage (8-wk), while in the colon the late phase (12-wk) of inflammation lead to substantial alterations.

These observations are consistent with Moreels *et al.*, (2001). They found that *S. mansoni* infection were associated with hyper contractile

activity in small and large intestine. This observation resulted from the chronic granulomotus inflammatory response to the accumulation of Schistosoma eggs in the gut wall.

Our previous observations (Abdu, 2007) revealed that COX inhibitor naproxen affect the production of prostaglandins release and led to abnormal contractile activity in early period of *schistosomiasis*.

In this study, we investigated the effect of COX inhibitor on prostaglandins release in response to chronic inflammation in order to reveal whether prostaglandins induce changes in neuronal activity could contribute to alterations in smooth muscle motility that associated with parasitic inflammation.

In the guinea pig colon, submucos plexus neurons, prostaglandins application has been shown to lead to membrane depolarization and increased frequency (Frieling *et al.*, 1997). Prostaglandins also activate myenteric plexus neurons in the guinea pig ileum (Dekkers *et al.*, 1997) and augment acetylcholine release from myenteric neurons of the small intestine (Das and Ganguly, 1984) and colon (Mulholland & SIMEONE 1993). These effects were consistent with the effect of Trichinella induced chronic inflammation in the small intestine (Palmer *et al.*, 1998).

We previously described (Abdu, 2007) that naproxen (10μM) increases the frequency of MCs in the jejunum while inhibits MCs in the colon in early phase of inflammation, implying to the role of endogenous prostaglandins on the activation of different receptor subtypes in different region of GI tract. The major observation of this study was that the COX inhibitor naproxen (10μM) inhibited MCs amplitude in chronic infected colon while having no effect on the amplitude in jejunum. This result was similar to Moreels *et al.*, (2001) findings where COX inhibitor was not able to reverse the increased contractile activity induced by the different receptor agonists or KCl in the small intestine during chronic inflammation in the jejunum. On the other hand, in normal jejunum and colon , both COX act at the neuronal level to modulate the contractile activity driven by excitatory cholinergic pathways (De Man *et al.*, 2002). In the presence of chronic inflammation, deferential role of COX-1 and COX-2 isoforms in the modulation of neuromuscular activity is hampered by oxidative stress (Fornai *et al.*, 2006). One of two isoforms seems to play a predominant role in control of colonic neuromuscular function. Such explanation may reflect the variability of mediators involved in the different inflammatory condition as well as the differences in the sensitivity of muscle layers to these mediators in different region of intestinal tract (Morimoto *et al.*, 1997).

The inhibition of prostaglandins production caused by none selective COX inhibitor naproxen may refer to an inhibition of both cyclo-oxygenase isoforms (COX-1 and COX-2). Recently, a number of studies (Gretzer *et al.*, 2001; Tanaka *et al.*, 2001) demonstrated that the inflammatory properties of NSAIDs are not only described by the inhibition of COX-1 but also of COX-2, implicating both isoforms in maintaining the integrity of the GI mucosa (Tanaka *et al.*, 2002).

The result that naproxen had a significant effect on motility in chronic phase of infection in the colon while it was not in the jejunum suggests that the colon might has higher chronic inflammatory response to infection than jejunum. This could be due to the accumulation of more Schistosome eggs in the wall of the colon which lead to hyper contractility and severe inflammation in chronic infection (Moreels *et al.*, 2001).

Another aim of the present study was conducted to understand whether chronic inflammation leads to changes in the availability of 5-HT_3 from entrochromaffin cell (EC) cells since 5-HT_3 was a critical mediator in regulating peristalsis during 8-wk post infection. The involvement of 5-HT_3 receptors -mediated initiation of peristalsis in chronic inflammation was assessed with 5-HT_3 receptor selective antagonist Y-25130.

We previously reported that 5-HT_3 receptor antagonist Y-25130 inhibited MCs in mouse jejunum and colon in 8-wk post infection (Abdu, 2007)suggesting that Y-25130 possess a potent and selective 5-HT_3 receptor antagonistic property (Odani *et al.*, 1993; Ooe *et al.*, 1993). However, in this study, the antagonist had no effect chronic infection may be due to reduction of synthesis and reuptake of 5-HT_3 and to inappropriate release of some neurogenic mediators in severe inflammation (Spiller, 2002).

In the present study, although 5-HT_3 receptor antagonist affected the amplitude of both jejunum and colon in 8-wk *schistosomiasis*, it had no effect on the intervals during the time course of the infection suggesting that 5-HT_3 released from motor neuron and implying to the involvement of neuromuscular apparatus (Galligan, 2004).

These results suggest that alterations in motor activity in *S.mansoni* infected animals are mediated, in part, by different COX receptor mechanisms which lead to alterations in both jejunal and colonic on jejunum and colon motility in chronic *schistosomiasis* which may indicate that chronic infection with *S. mansoni* disturbs the release of 5-HT_3 in the enteric neural circuits that contributed to the intestinal motor dysfunction in chronic inflammation in both jejunum and colon. This motor dysfunction in both jejunum and colon in motility. The conflicting data in the effect of naproxen on MCs during 8-wk inflammation in jejunum and colon indicated that motility disturbance in *S. mansoni* infected mice may intervene by different prostanoid receptors.

In conclusion, Prostanoids is an essential component for the maintenance of regular motor activity in the small intestine. Chronic infection with *S. mansoni* disturbs the release of 5-HT in the enteric neural circutes which contribute to the intestinal motor dysfunction in both jejunum and colon in normal and altered function triggered by inflammation.

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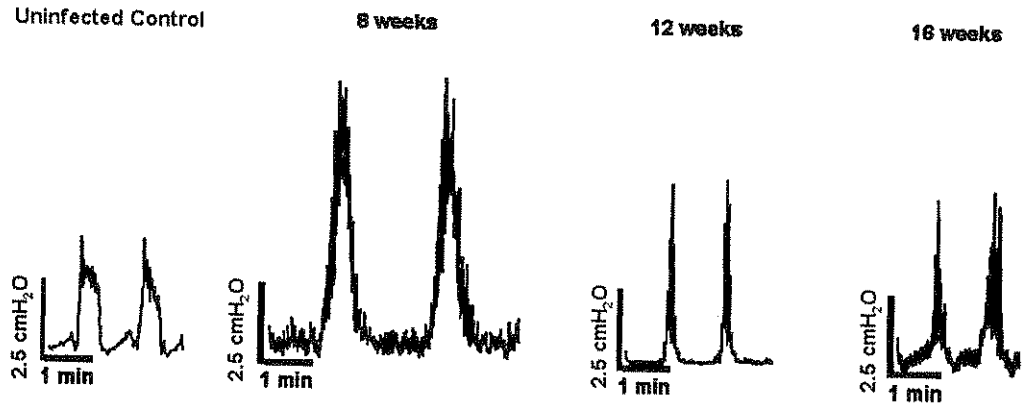
EXPLANATION OF FIGURES



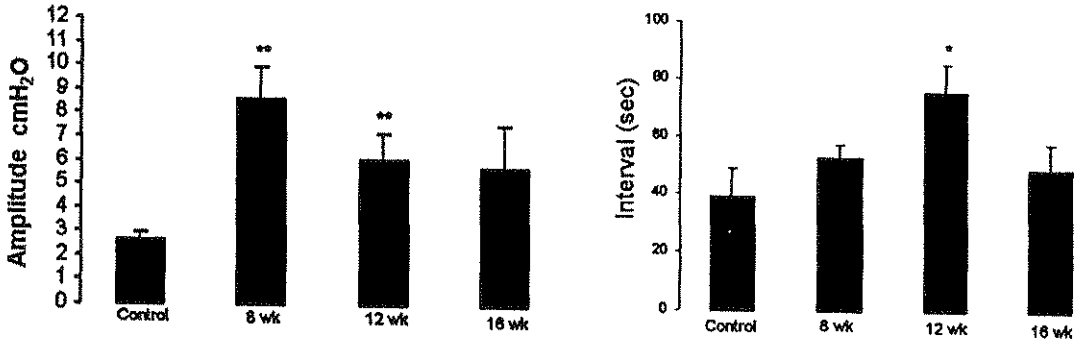


Fig. 1: Motor Complex (MCs) in the Jejunum

(A) Expanded pressure trace showing the pattern of contractile activity observed in control and 8-, 12- and 16-wk infected jejunum at a distending pressure of 2-3.5 cmH_2O. **(B)** Are histograms showing the effect of intraluminal distension on MCs interval (on the right) and amplitude (on the left) in tissues from 8-, 12- and 16-wk infected jejunum compared to control, (n = 8).

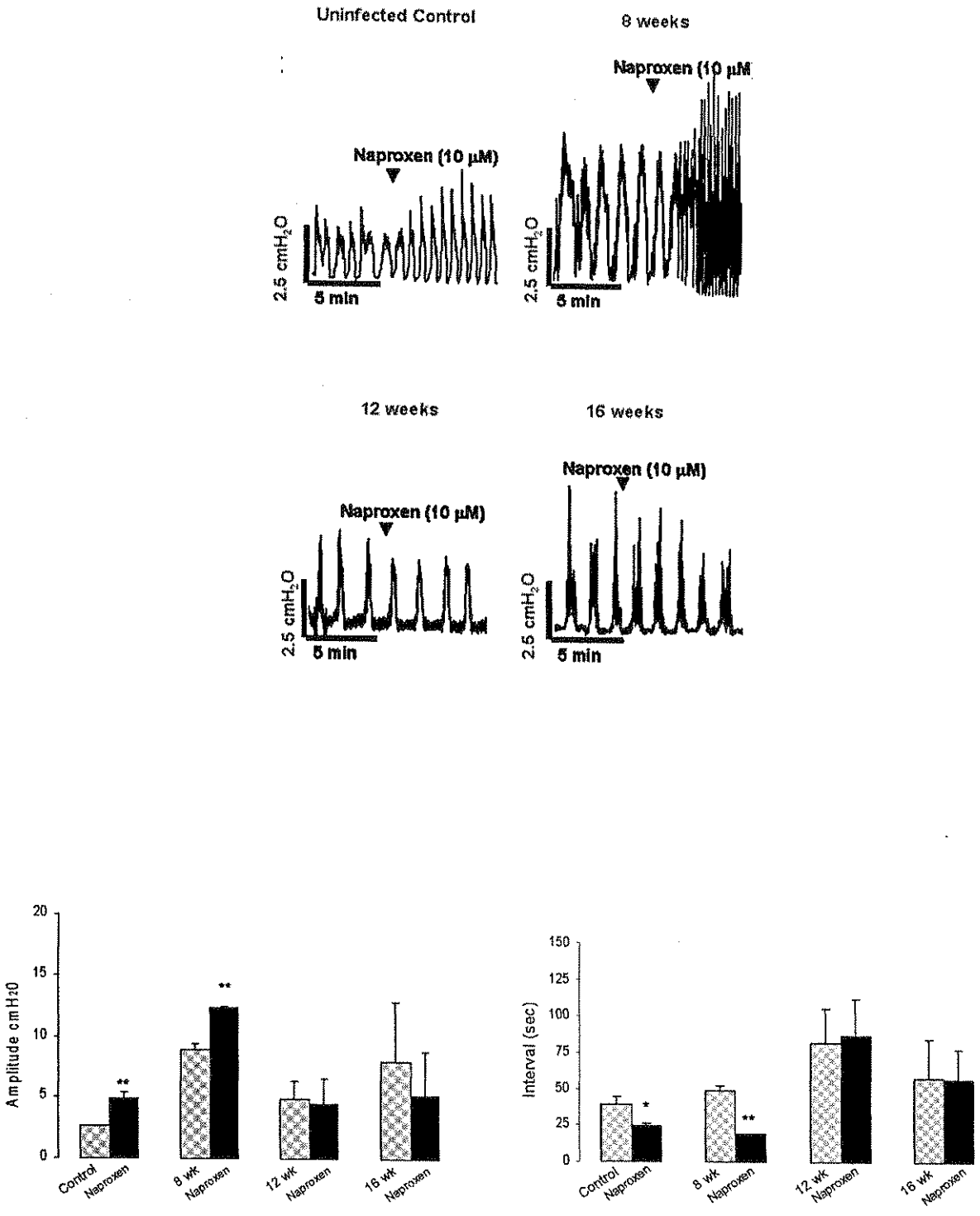


Fig. 2: Effect of COX Inhibitor (Naproxen) on MCs in Jejunum

(A) Pressure recording showing MCs amplitude and interval in control and 8-wk (upper trace), 12- and 16-wk (lower trace) infected jejunum. **(B)** Histograms depicting the amplitude (on the left) in control and 8-, 12- and 16-wk infected jejunum and interval (on the right) of MCs evoked by naproxen during the time course of experiments, (n = 6).

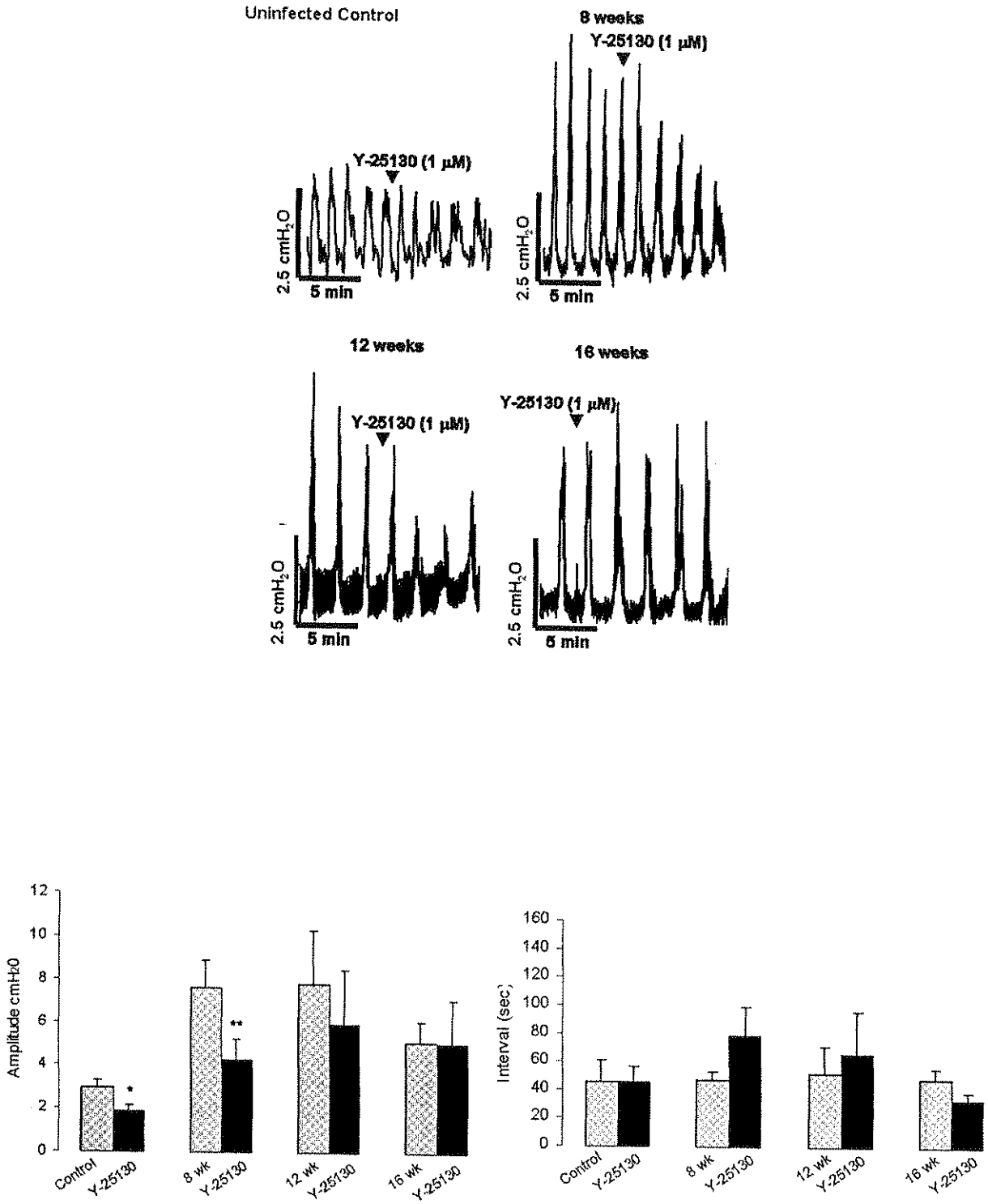


Fig. 3: Effect of 5-HT$_3$ Receptor Antagonist Y-25130 on MCs in Jejunum

(A) The effect of Y-25130 on MCs in an isolated control and 8-, 12- and 16-wk infected jejunum. **(B)** Y-25130 significantly inhibited MCs amplitude (on the left) in control and 8-wk infected jejunum only but had no significant effect on MCs interval (on the right), (n = 6).

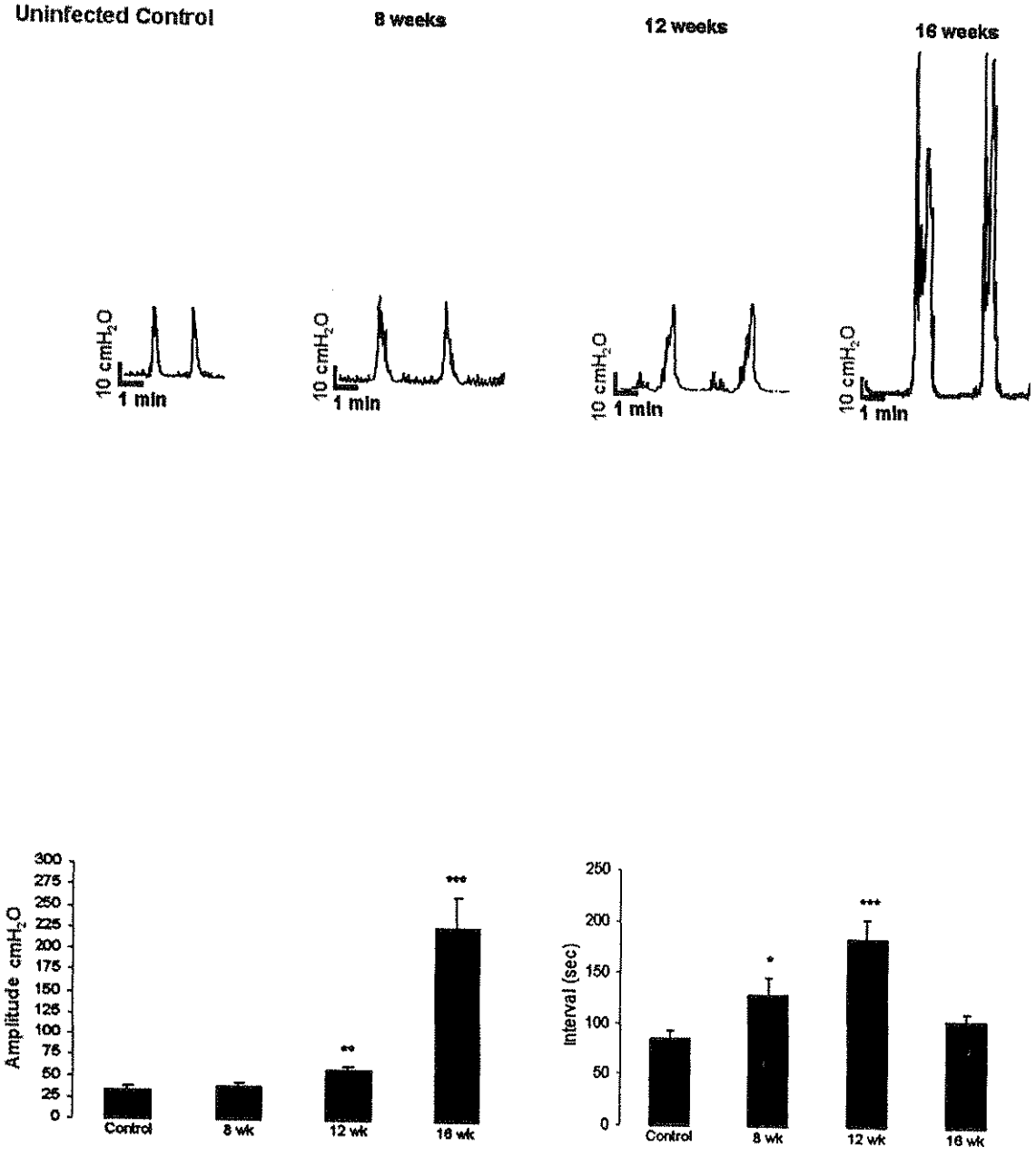


Fig. 4: Motor Complex (MCs) in the Colon

(A) Expanded pressure trace showing the pattern of contractile activity observed in control and 8-, 12- and 16-wk infected colon at a distending pressure of 4-5 cmH_2O. **(B)** Are histograms showing the effect of intraluminal distension on MCs interval (on the right) and amplitude (on the left) in tissues from 8-, 12- and 16-wk infected colon compared to control, (n = 8).

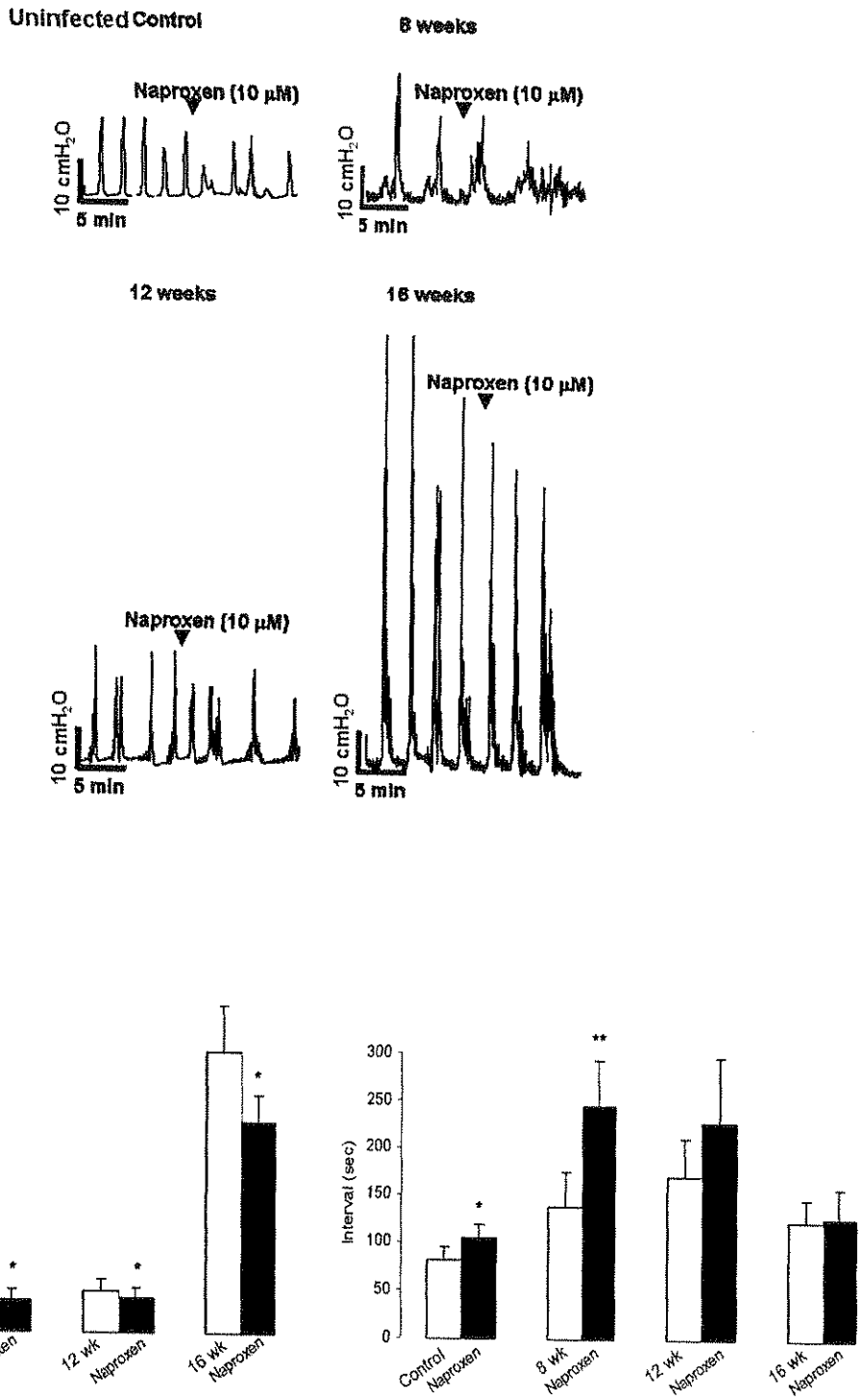


Fig. 5: Effect of COX Inhibitor Naproxen on MCs in Colon

(A) Pressure traces of isolated control and infected colon showing the reverse effect of naproxen on MCs in the colon. **(B)** In contrast to the findings in the jejunum (Fig. 2 B) naproxen significantly attenuated MCs amplitude (on the left) over the time course of the experiment and increased MCs interval (on the right) in control and 8-wk only, (n = 6).

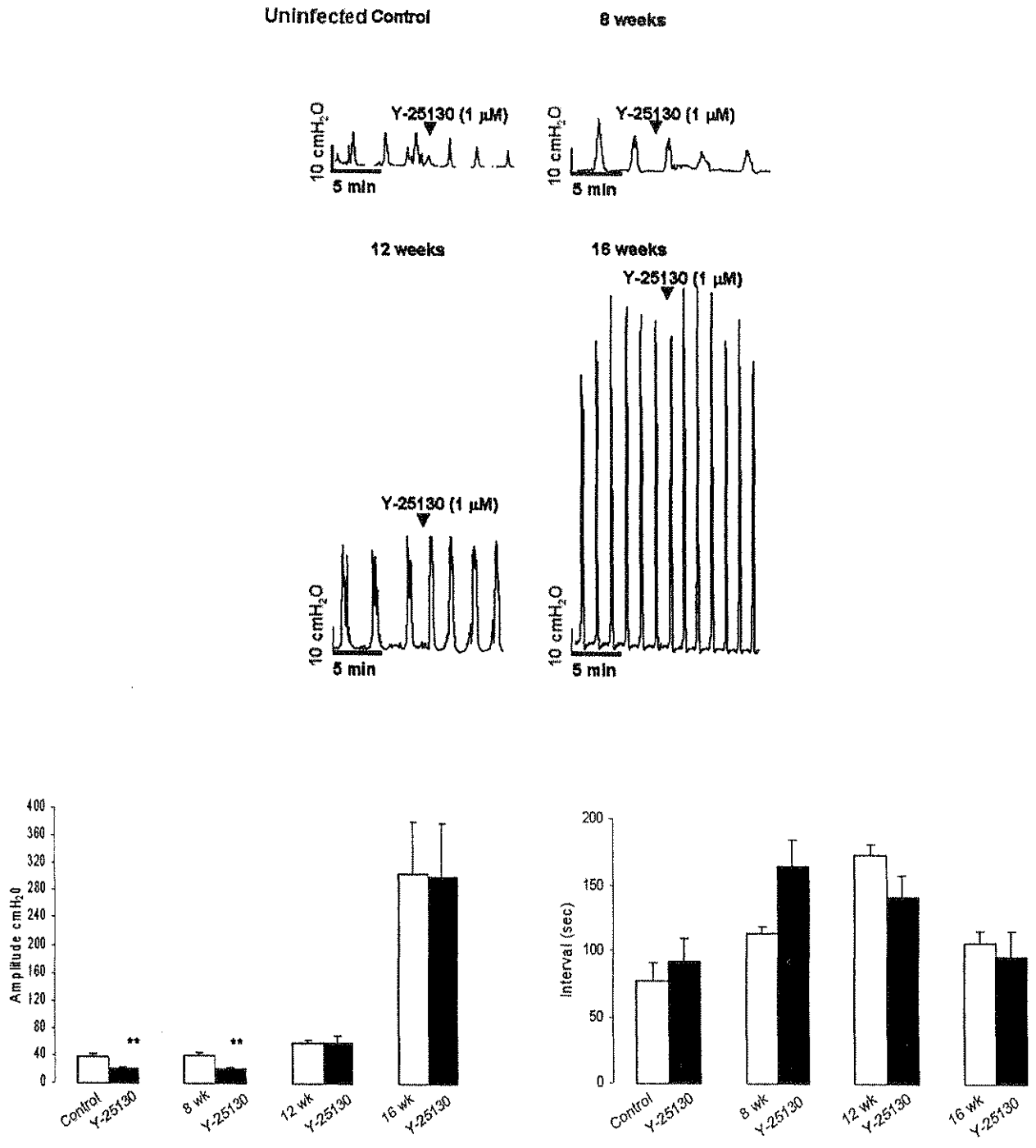


Fig. 6: Effect of 5-HT$_3$ Receptor Antagonist Y-25130 (1μM) on MCs in the Colon

(A) Pressure recording showing the effect of Y-25130 on MCs amplitude and interval in an isolated control and 8- (upper trace), 12- and 16-wk (lower trace) infected colon. (B) Y-25130 significantly inhibited MCs amplitude (on the left) in control and 8-wk only but had no significant effect on MCs interval (on the right) during the time course of the experiments (n = 6).

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