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أما مضاد المستقبل 5-HT4 (Y-25130, 1μM) فقد ثبط قمم الانقباضات في كل من الفئران السليمة والمصابة في جزئي القناة الهضمية، الصائم والقولون، إلا أنه لم يؤثر معنويا على الفترات الزمنية بين جميع هذه الانقباضات.

نستخلص من هذه النتائج أن (Prostanoid وَ 5-HT) يؤثران وظيفيا على تنظيم الحركة الانقباضية للأمعاء سواءً في الحالات السليمة، او في حالة الالتهابات الناتجة من الإصابة الطفيلية.

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العدد السابع والعشرون (A) علم الحيوان

تأثير الإصابة بالبلهارسيا على الوظائف الحركية في صائم وقولون الفئران

فايزه عبده

جامعة الملك عبد العزيز – كلية العلوم– قسم علوم الأحياء

تعزى الحركة غير الطبيعية للأمعاء خلال الالتهابات إلى توزيع وإفراز بعض الوسائط الكيميائية مثل البروستانويد Prostanoid وكذلك خامس هيدروكسي التربتامين 5-HT، كما تعزى أيضاً إلى انجذاب وتفاعل هذه الوسائط مع المستقبلات المخصصة لها، ولكن ميكانيكية عمل هذه الوسائط والمستقبلات المشاركة أثناء حدوث الالتهاب لا تزال غير معروفة.

أجريت التجارب على مجموعه من الفئران الذكور السويسرية السليمة وكذلك مجموعة من الفئران المصابة بالبلهارسيا (*Schistosoma mansoni*) لمدة ثمانية أسابيع وبنيت النتائج على أساس مقارنتها بالفئران السليمة. تم إحداث الحركة الانقباضية للقناة الهضمية باستخدام طريقة (Trendelenburg) ، كما حُسبت نتائج متوسط القيم وحللت باستخدام البرامج الإحصائية (paired or un-paired t-tests).

لوحظ زيادة ارتفاعات الانقباضات(Amplitudes) زيادة معنوية في أنسجة الصائم المصابة مقارنة بالسليمة، بينما كان هناك فرقاً معنوياً في الفترات الزمنية (Intervals) بين الانقباضة والأخرى في القولون.

زاد مثبط إنزيمات السيكلواكسيجينيز (نابروكسن) (Cyclo-oxygenase inhibitor (naproxen, 10µM من ارتفاع قمم الانقباضات وقلل الفترات الزمنية بينها في كل من صائم الحيوانات السليمة والمصابة، وقد كان هذا التأثير أكثر وضوحًا في الفئران المصابة مقارنة بالسليمة. لكن النابروكسن في القولون قلل من ارتفاع قمم الانقباضات وزاد من الفترات الزمنية بين هذه الانقباضات، وقد كان هذا التأثير أكثر وضوحًا في الفئران المصابة مقارنة بالسليمة.

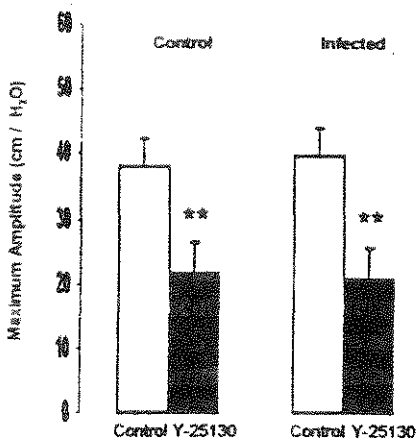

Figure 7A: Effect of 5-HT_3 Receptor Antagonist Y-25130 on MCs in Colon:
Y-25130 significantly inhibited MCs amplitude in both control and infected colon ($P<0.01$ and $P<0.01$).

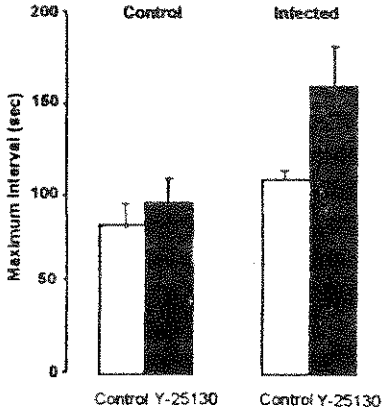

Figure 7B: 5-HT_3 Receptor Antagonist Y-25130 had no effect on MCs intervals.

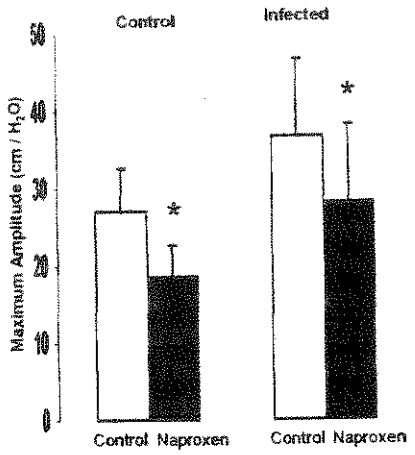

Figure 6A: Effect of COX Inhibitor Naproxen on MCs in the Colon:

In contrast to the findings in the jejunum (Fig. 2A) naproxen significantly attenuated MCs amplitude ($P<0.03$ and $P<0.02$).

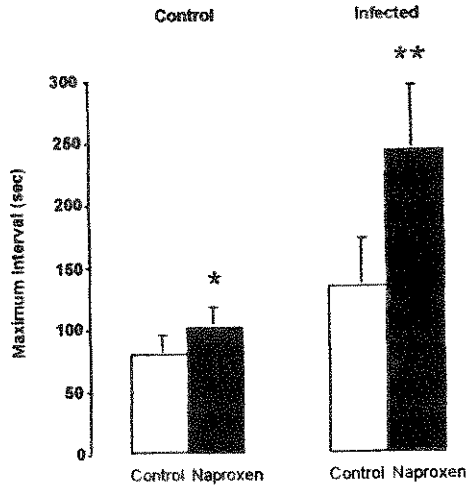

Figure 6B: COX Inhibitor Naproxen increased MCs interval ($P<0.02$ and $P<0.01$) in control compared to infected tissue..

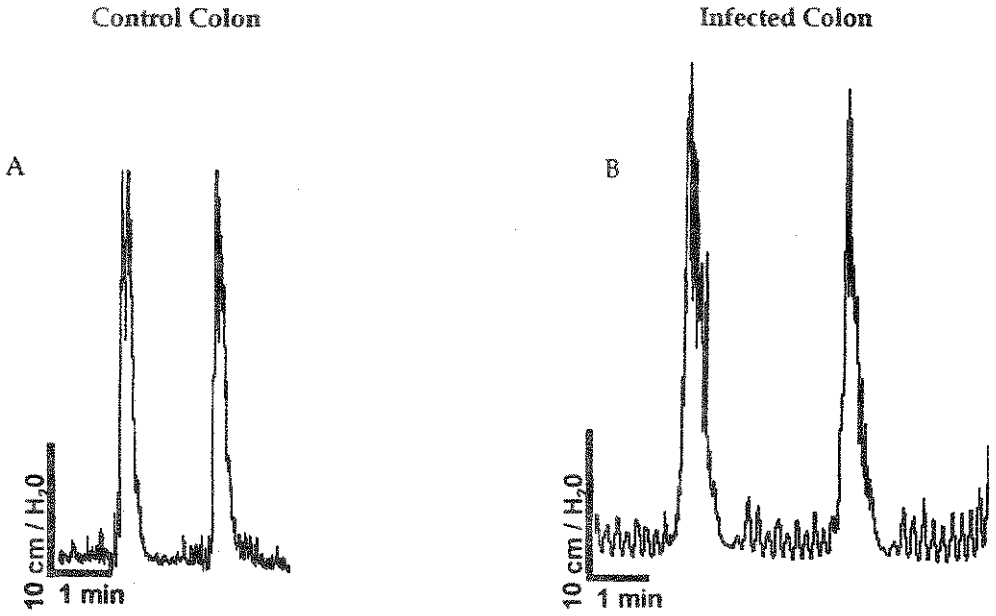

Figure 5: Motor Complex (MCs) in the Colon:

Expanded pressure trace showing the pattern of contractile activity observed in control (A) and infected (B) colon at a distending pressure of 4-5 cm/H_2O.

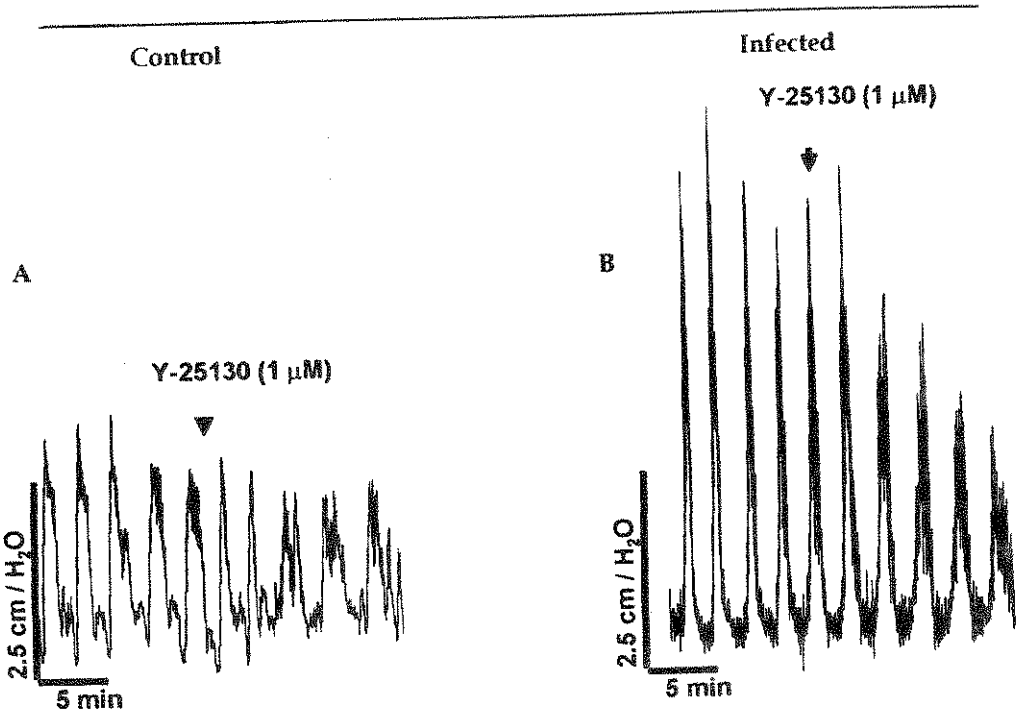

Figure 4 (A+B): Effect of 5-HT_3 Receptor Antagonist Y-25130 on MCs in the jejunum:

(A) Y-25130 significantly inhibited amplitude on MCs in an isolated control jejunum ($P<0.05$). (B) Y-25130 significantly inhibited MCs amplitude in infected jejunum ($P<0.005$).

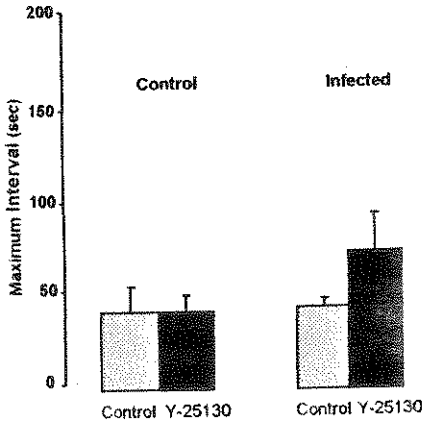

Figure 4C: 5-HT_3 Receptor Antagonist Y-25130 had no significant effect on MCs interval

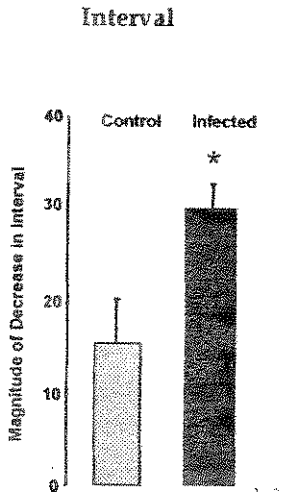

Figure 3: Effect of Naproxen in the Jejunum:
Histogram showing the magnitude of decrease of interval in infected animals ($P<0.05$).

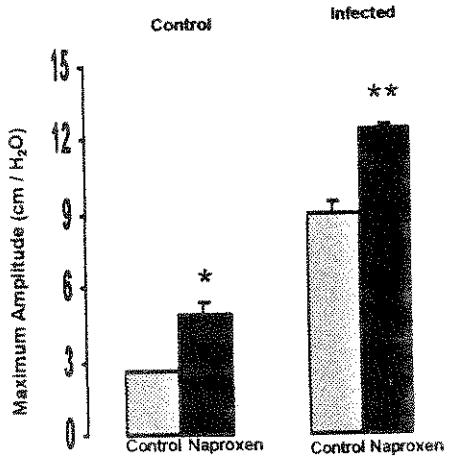

Figure 2A: Effect of COX-2 Inhibitor (Naproxen) on MCs in the jejunum: Histogram depicting the increase of MCs amplitude in control and infected ($P<0.05$ and $P<0.01$) jejunum.

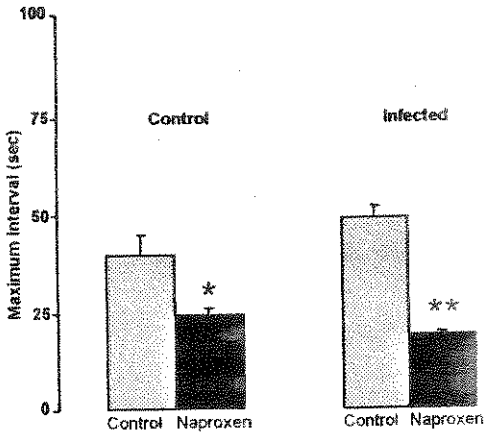

Figure 2B: Effect of COX inhibitor (Naproxen) on MCs in the jejunum
Histogram depicting the decreased of MCs interval evoked by naproxen in control and infected tissues ($P< 0.02$ and $P<0.01$, respectively).

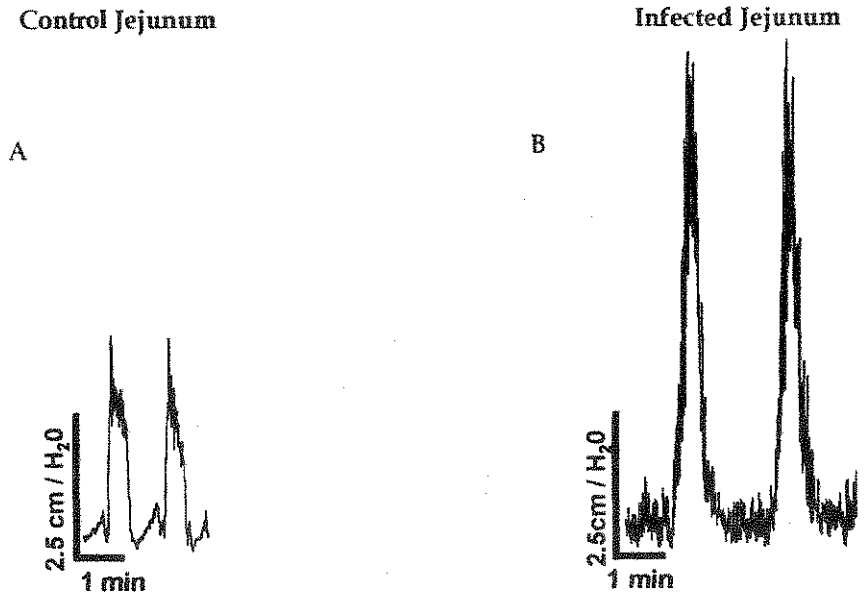

Figure 1: Motor Complexes in the Jejunum:
Expanded pressure trace showing the pattern of contractile activity observed in control and infected jejunum at a distending pressure of 2.5-3 cm/H2O.

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terminals of primary afferent nerves intrinsic to the enteric nervous system which then activate downstream interneuron's and motoneurons in enteric neural circuits mediating peristalsis.

The inhibitory effect of Y-25130 on MCs amplitude was also supported by studies of (Bush *et al.*, 2001; Spiller, 2006) who observed that drugs that alter 5-HT signaling have some therapeutic benefit in the treatment of patients with Irritable bowel syndrome (IBS). However, our results which shows that the effect of 5-HT_3 receptor antagonist was less pronounced in the colon when compared to the jejunum are consistent with the recent findings of Berthoud *et al.*, (2004); Grundy and Schemann, (2004) who showed that the mucosal 5-HT synthesis and reuptake were significantly reduced in pathological conditions such as ulcerative colitis and IBS.

In conclusion, the present study suggests that infection with *S. mansoni* leads to disturbance of GI motility. The different effect of infection on amplitude and interval of MCs possibly reflects different actions on the neuromuscular apparatus and the enteric reflex circuits that control the pattern of contractile activity.

ACKNOWLEDGMENT

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the involvement of COX inhibitor displayed different action of this inhibitor on jejunum and colon.

Pattern of contractile activity in both control and infected jejunum and colon indicated that intraluminal distension in 8-wk post infection produced an increase of jejunual amplitude and colonic MCs intervals. Thus, obviously different receptors-mediated contractions were involved during inflammation. This was consistent with De Man *et al.*, (2001) results who found that infection with *S mansoni* disturbed the cholinergic enteric neurotransmission and may contributed to the intestinal motility disturbances. The outcome of the study were also supported by the hypothesis which declares that the clinical symptoms of intestinal *Schistosomiasis* may be mediated by a dysfunction of GI motor function (De Jonge *et al.*, 2003; El Zawawy *et al.*, 2006).

In the present work, Cyclo-oxygenase inhibitor naproxen (10μM) increased the frequency of MCs in the jejunum and inhibited MCs in the colon of control and infected mice that implied to the role of endogenous PG on the activation of different receptor subtypes in various regions of GI tract. This conclusion was similar to Narumiya *et al.*, (1999); Grasa *et al.*, (2006); Santos *et al.*, (2007) whom demonstrated that PG receptors were found in different regions of GI tract and functionally divided into contractile and relaxant receptors that mediate diverse effect of PG. Again ,this assumption was supported by Dekkers *et al.*, (1997) who reported that PG evoked contraction in longitudinal muscle and relaxation in circular muscle entail to the involvement of different PG receptors and may indicate that endogenous PG were an essential component for the maintenance of regular contractile activity in inflammation and under normal conditions.

It is important to mention that the effect of naproxen on MCs activity were greater in infected animals compared to control suggesting that the inhibition of cyclo-oxygenase by COX inhibitors may affect the production of PG release during infection. Our result was similar to the findings of De Man *et al.*, (2002)., They stated that infection with *S.mansoni* disturbs the release of neurotransmitters and mediated modulation of cholinergic enteric neurotransmission.

5-HT_3 -receptor antagonist Y-25130 used in this investigation inhibited MCs amplitude of mouse jejunum and colon during basal conditions. These results were supported by the hypothesis of Galligan, (2004) who suggested that modulation of 5-HT release from EC cells is critical to normal and abnormal GI function because EC cell are sensory transducers that respond to mechanical stimuli applied to the mucosa causing 5-HT release. The release of 5-HT from EC cells can then act at 5-HT_3 and 5-HT_4 receptors localized on the

P<0.05). At the mean time there was no effect on MCs amplitude (34±4 *vs* 39±4.5, P>0.05, Fig. 5 A+B).

Effect of Naproxen on MCs in the Colon

The effect of COX inhibitor naproxen (10μM) on the colon produced opposite effect to the jejunum. In control and infected colon naproxen repressed MCs frequency. MCs amplitude was decreased significantly in both control (27.19±5.5 *vs* 18.5±4, P<0.05, Fig. 6A) and infected (36.77±10 *vs* 28.32±10, P<0.05) tissue compared to the observation in jejunum in which naproxen had a higher effect on MCs amplitude. Naproxen in the colon had a pronounced effect on MCs intervals. Such an effect was greater in infected tissue compared to control. (137.29±37s *vs* 245.27±49s, P<0.01 and 81.09±14s *vs* 105.31±14s, P<0.05 respectively, Fig. 6B).

Effect of 5-HT$_3$ in the Colon

5-HT$_3$ receptor antagonist (1μM) inhibited the amplitude in both control (39.93±4.5 *vs* 21.387±2.5, P<0.01) and 8-wk infected colon (39.72±4.5 *vs* 20.55±2.5, P<0.01, Fig. 7A). However, the magnitude of the inhibition was less marked in the colon (P>0.05) when compared to the jejunum (P<0.05). MCs intervals were not affected by Y-25130 in both control (77.71±13s *vs* 92.15±17s, P<0.09) and infected (113.35±5s *vs* 164.93±20s, P<0.06) tissues. Although there was an increase in MCs intervals in infected tissue, this increase did not reach the significant value (Fig. 7B).

DISCUSSION

Intestinal inflammation with *S.mansoni* leads to alteration in GI motility. However, the mechanisms underlying these alterations and the receptor involved in the inflammatory response were not fully determined (De Jonge *et al.*, 2003).

In this study, the pattern of contractile activity in response to intraluminal distension in 8-wk infected mice differs from the response in control mice in both jejunum and colon. In the jejunum, *Schistosomiasis* induced significant increased in MCs amplitude while it triggered increased in MCs intervals in 8-wk infected colon. These observations were in agreement with De Man *et al.*, (2002); El Zawawy *et al.*, (2006), since *S. mansonai* infection induced smooth muscle hyper contractility of the small intestine.

Although the pathogenesis of *Schistosomiasis* have been extensively studied, little investigations have been focused on the role of inflammatory mediators such as 5-HT and PG on motor patterns of contractile activity in the small and large bowel wall during infection. Moreover, this study on

compared to control. The activity consisted of periodic increases in intraluminal pressure separated by periods of relative quiescent.

The increase in intraluminal pressure coincided with wave of contraction seen as parallel line propagates from oral to aboral. Base line pressure was about the same in control and infected animals. However, in control jejunum, MCs had a maximum pressure of 2.65±0.25 cmH_2O, separated by intervals of 38.8±10 seconds (Fig. 1A). While in infected jejunum MCs had a maximum pressure of 8.58±1 cmH_2O and intervals of 52.57±6 seconds (Fig. 1B). The amplitude of jejunal MCs was increased significantly in tissues from infected jejunum compared to control, whereas there was no significant effect of on MCs intervals.

Effect of COX-1 Inhibitor on MCs of the Jejunum

In control jejunum the COX inhibitor naproxen (10μM) increased the amplitude (2.46±0.01 *vs* 4.93±0.5 cmH_2O, $P<0.05$) and decrease the intervals of MCs (39.58±5s *vs* 24.1±2s, $P<0.05$, Fig. 2B). In infected jejunum, naproxen amplified the amplitude (8.96±0.5 *vs* 12.36±0.1 cmH_2O, $P<0.01$, Fig. 2A) and reduced the MCs intervals (49.06±3s *vs* 19.01±0.6s, $P<0.01$, Fig. 2B). Such an effect that was greater in infected tissue compared to controls ($P<0.05$, Fig. 3).

Effect of 5-HT_3 Receptor Antagonist in the Jejunum

In control jejunum 5-HT_3 receptor antagonist (Y-25130, 1μM) induced significant inhibition of amplitude (2.93±0.3 *vs* 1.84±0.03 cmH_2O, $P<0.05$, Fig. 4A). Such an effect was greater in infected tissue compared to control (7.57±1 *vs* 4.26±1 cmH_2O, $P<0.01$, Fig. 4B).

The effect of 5-HT_3 receptor antagonist on MCs intervals was different. Although the intervals in control tissue remain unchanged (45.67±15s *vs* 45.19±11s, $P>0.05$) there was a tendency for the interval to increase in infected tissue (47.60±5s *vs* 78.74±20s, $P<0.06$ Fig., 4C). However, this increase was not significant.

Motor Complex in Colon

Intraluminal distension of mouse colon revealed a similar pattern of contractile activity in mouse jejunum, whereas the parameters of peristaltic reflex between jejunum and colon were different. In control and infected colon, the intraluminal pressure required to initiate the peristaltic reflex was higher when compared with jejunum. In control tissue, base line pressure was 4-5 cmH_2O, while maximum pressure was 34±4 cmH_2O and the interval was 85±8s. Although infected jejunum revealed significant increase in MCs amplitude compared to control ($P<0.05$, Fig. 1B), infected colon showed significant increase in intervals (84.4±8.3s *vs* 128.55±17s,

(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). Tissues were prepared as 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 20 ml perfusion chambers. Tissues were maintained at 37°C, perfused with Krebs solution at a rate of 5ml/min, and allowed to equilibrate for at least 30 min before experiments started. Motor complex (MCs) of jejunual and colon in infected and uninfected mice were monitored and analyzed by using (Neurolog/NL 900D, Digitimer Ltd, Hertfordshire, England) to record contractile activity as changes in intraluminal pressure under volumetric conditions 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) were added to the chambers 15 minutes after stopping perfusion and recording continued for a further 20 minutes before washing out the drugs and re-instating perfusion.

Drugs

All the peptides were purchased from Sigma Chemical (USA) and were dissolved in distilled water unless otherwise stated. 5-HT_3 receptor antagonist (Y-25130) was dissolved in saline (0.9% Na Cl). 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 measured in terms of their peak amplitude above baseline (cmH_2O), while duration and interval between them were expressed in seconds (s). Pretreatment values were taken during the 15 minutes before drug application and the response effect was monitored in the 15 minutes following application. Results are expressed as absolute values ± standard error of mean (S.E.M). Paired data were compared using Student's t-test. Probability of $P<0.05$ was considered significant.

RESULTS

MCs in Jejunum

Luminal distension of isolated segments of mouse jejunum evoked a regular pattern of motor activity. There was no difference between the patterns of activity in infected jejunum

The COX-1 enzyme is the major isoform expressed in GI tract (Tanaka *et al.*, 2002; Warner and Mitchell, 2004). It is believed that the adverse effect of nonsteroidal anti-inflammatory drugs (NSAIDs) result from the inhibition of this isoform (Northey *et al.*, 2000).

Naproxen is antagonist with some selectivity at COX-1 isoform. It has been shown to control the formation of PG and reduce the inflammation by inhibiting COX-1 isoform (Warner and Mitchell, 2004).

5-HT is a critical mediator of the peristaltic reflex released from EC cells that respond to mechanical stimuli applied to the mucosa. 5-HT is also implicated in the pathogenesis of intestinal peristalsis since locally released 5-HT contributes to the initiation of motor reflexes and the transduction of nociceptive stimuli (Delvaux *et al.*, 1998). 5-HT_3 and 5-HT_4 receptor ligands have proved to be effective in the treatment of visceral hypersensitivity and motility disorders (Grundy and Schemann, 2004). Pharmacological blockade of 5-HT_3 receptor diminishes propulsive motor activity, and reduces peristaltic reflex activity (Wade *et al.*, 1996; Tuladhar *et al.*, 1997).

Therefore, the rational of the present study was to compare the patterns of contractile activity in control animals with other animals that have been subjected to an inflammatory insult and to examine the role of 5-HT and prostanoids by using 5-HT_3 selective receptor antagonists (Y-25130) and COX inhibitor naproxen on the generation of abnormal motor patterns.

MATERIAL AND METHODS

Schistosoma mansoni Infection

The maintenance of the *S. mansoni* life cycle and the transcutaneous infection of mice with S. mansoni were carried out according to the methods of Bogers *et al.*, (2000); Moreels *et al.*, (2001). Swiss male mice (age 7-wk) were transcutaneously infected with about 100 *S. mansoni* cercariae, then loaded with treated water containing 100 infectious cercariae of a *Biomphalaria Alexandriana* 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 by cervical dislocation after 8-wk of infection and the contractile activity of isolated segments from jejunum and colon were investigated. All experiments were approved by the Ethic Committee of King Fahad medical research centre (KFMRC).

Tissue Preparation

Control and infected animals were stunned by a blow on the head. 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

considerable attention on studying the mechanisms which generate these symptoms particularly the role of enteric neural circuits that contribute to the intestinal inflammation (Kiyosue *et al.*, 2006). *Schistosomiasis* are useful in studying inflammation-induced changes in intestinal sensory motor function. It is characterized by gastrointestinal (GI) motility-related disorders (De Jonge *et al.*, 2003) due to the distribution or release of chemical mediators such as prostanoids and 5-HT and to the affinity of their specific receptors.

5-hydroxytryptamine (5-HT, serotonin) and **cyclo-oxygenase** (COX) are known to act as neurogenic mediators within the enteric neural circutes during inflammation (Silva *et al.*, 1998; Neves *et al.*, 1999; Moreels *et al.*, 2001). They exert their effects through interactions with different receptor subtypes on nerves and muscle cells in the small intestine (Lordal and Hellstrom, 1999; Miranda *et al.*, 2006). 5-HT has been found in the enterochromaffin cells (EC) of the mucosa of GI tract (Berthoud *et al.*, 2004; Bertrand, 2006). It is also localized in the cell bodies of neurones in the myenteric plexus (Bertrand *et al.*, 2000), nerve fibres distributed in both myenteric and submucous plexuses (Spiller, 2002) as well as in the lamina propria (Bertrand *et al.*, 2000).

COX is the most common therapeutic drug target in GI tract (Warner and Mitchell, 2004; Fornai *et al.*, 2006). The two COX enzymes, COX-1 and COX-2, were responsible for the production of prostanoids such as PGE2, PGF2 alfa, Prostacycyclin and thrompoxane (Fornai *et al.*, 2006).

Endogenous prostaglandin (PG) have been shown to be important mediators of GI motility in control conditions (Tanaka *et al.*, 2002). As a result, the COX inhibitor naproxen was used to study the role of PG in the *S. mansoni* infection-induced alterations of contractile activity.

PG are also known to modify GI motility during inflammation (Manning *et al.*, 2002), but the cell surface receptors mediating these prostanoid actions have not been fully characterized. PGE receptors of the EP1, EP2, EP3 and EP4 type, were expressed in the gut of several species including man (Wu, 1995; Northey *et al.*, 2000). Cellular localization studies indicate that the external muscle layers display EP1, EP2 and EP3 receptors and that some EP3 receptors are also associated with enteric neurons of the rat and mouse intestine (Whelton *et al.*, 2002).

Pharmacological investigations have shown that circular muscle cells of the guinea-pig's ileum exhibit EP1 and EP3 receptors, which mediate contraction on activation by agonists, whereas EP2 receptors bring about relaxation (Northey *et al.*, 2000).

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EFFECT OF INTESTINAL *SCHISTOSOMIASIS* ON MOTOR FUNCTION IN THE MOUSE JEJUNUM AND COLON

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Key words: ***Schistosoma mansoni,*** Prostanoids, 5 Hydroxy Tryptamine, Motility, Jejunum and Colon.

ABSTRACT

Motor abnormalities during inflammation are related to distribution and/or release of chemical mediators such as prostanoids and 5-Hydroxy Tryptamine (5-HT) in addition to the affinity of their specific receptors. However, the mechanisms of these mediators and the receptors involved are unknown. Experiments were performed on Swiss male mice 8-wk following infection with *Schistosoma mansoni* compared to uninfected controls. Jejunal and colonic motility was assessed using a Trendelenburg type preparation to study aborally directed motor complexes (MCs). Results showed that the amplitude of jejunal MCs was increased in tissues of infected jejunum compared to control ($P<0.05$), while in the colon, there was a significant increase in MCs intervals in infected tissue compared to uninfected animals. The cyclo-oxygenase (COX) inhibitor naproxen (10μM) increased the amplitude and shortened the intervals of MCs in both control and infected jejunum; an effect that was greater in infected tissue compared to controls ($P<0.05$). In contrast, in the colon, naproxen lowered the amplitude and augmented the intervals of MCs. This effect was also higher in tissue of infected animals compared to uninfected control ($P<0.01$). Although the 5-HT_3 receptor antagonist, Y-25130 (1μM), inhibited MCs amplitude in both control and infected colon and jejunum, Y-25130 had no effect on MCs intervals.

In conclusion, the present results suggested that infection with *Schistosoma mansoni* lead to alterations in both jejunal and colonic motility. Prostanoids and 5-HT are implicated in both normal motility and in altered function triggered by infection.

INTRODUCTION

Post-inflammatory changes in intestinal sensory-motor function are thought to play a major role in the aetiology of irritable bowl symptoms. Currently, there is

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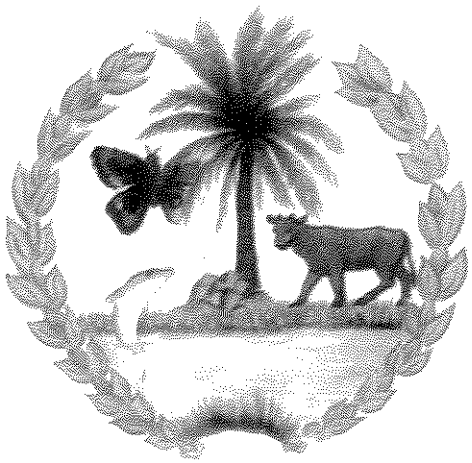

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