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ScienceDirect
Phytomedicine 13 (2006) SV 100–106
Phytomedicine
www.elsevier.de/phymed

STW 5 (Iberogast®) reduces afferent sensitivity in the rat small intestine

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Abstract

Introduction: A limited number of drugs are available for the treatment of functional dyspepsia and irritable bowel syndrome. The efficacy of STW 5 (Iberogast®) was previously shown in clinical trials. Since visceral hypersensitivity seems to be the prime pathomechanism of functional gastro-intestinal disorders, the aim of this study was to explore whether STW 5 reduces intestinal afferent sensitivity in the upper gastrointestinal tract.

Methods: Two groups of male Wistar rats were pretreated with either the herbal preparation STW 5 or its vehicle (30.8% ethanol). Then, after 2 h, general anesthesia was induced by pentobarbitone (60 mg kg^{-1} i.p.) and extracellular multi-unit afferent recordings were obtained from mesenteric afferents innervating the proximal jejunum. The intestinal afferent nerve response to increasing doses of 5-HT and bradykinin were quantified as well as afferent discharge following a ramp distension of the adjacent intestinal loop from 0 to 60 cm H_2O.

Results: Afferent discharge to 5-HT and bradykinin increased dose-dependently. Following the different doses of 5-HT, the peak in afferent nerve discharge was always reduced after pretreatment with STW 5 compared to controls with a response of 110 ± 5 imp s^{-1} after STW 5 and 128 ± 3 in vehicle controls at the maximum dose (40 μg kg^{-1}; $p < 0.05$; mean ± SEM). For bradykinin, afferent responses were reduced following STW 5 at the 20 and 40 μg kg^{-1} dose but not at 10 μg kg^{-1} (40 μg kg^{-1}: 176 ± 7 imp s^{-1} following STW 5 versus 200 ± 6 imp s^{-1} in controls; $p < 0.05$). The ramp distension of the intestinal loop stimulated a rise in intestinal afferent nerve discharge that was always lower in the STW 5 pretreated group compared to vehicle controls with the exception of the discharge rate at the pressure level of 0 and 20 cm H_2O (all other pressures up to 60 cm H_2O $p < 0.05$).

Conclusions: Sensitivity of intestinal afferents to mechanical and chemical stimuli is reduced following treatment with the herbal preparation STW 5. This mechanism may help to explain why STW 5 relieves dyspeptic and bowel symptoms in patients.

Keywords: Afferents; Functional dyspepsia (FD); Irritable bowel syndrome (IBS); Hypersensitivity; STW 5; Iberogast; *Iberis amara*; Visceral sensitivity

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doi:10.1016/j.phymed.2006.03.014

Introduction

The pathophysiology of functional gastro-intestinal disorders is not completely understood and its diagnosis is based on the patient's clinical impression as standard diagnostic procedures of the upper gastrointestinal tract do not show abnormalities (Talley et al., 1999). Among other contributing factors, visceral hypersensitivity is considered a principal mechanism for symptom generation in irritable bowel syndrome (Ritchie, 1973) and functional dyspepsia (Tack et al., 1998, 2001).

The herbal preparation STW 5 (Iberogast®) has been used for almost 50 years in the treatment of functional gastro-intestinal disorders. The preparation consists of nine different extracts that were originally combined from single extracts that were known from clinical experience rather than from formal studies. For a long time the usefulness of STW 5 to improve symptoms in patients suffering from functional dyspepsia has been acknowledged by many physicians before its efficacy became evidence-based by a clinical studies (Rösch et al., 2006). The results of these clinical studies are remarkable in two ways. First, STW 5 is very well tolerated and, therefore, is a medication that may be made available to basically all patients including children without restrictions. Second, there are virtually no other pharmacological treatment options that specifically address functional dyspepsia and irritable bowel syndrome.

The mechanism responsible for the clinical efficacy of STW 5 is not known. Several reports suggest that visceral hypersensitivity is the predominant pathomechanism for functional bowel disorders (Camilleri et al., 2001; Mayer and Gebhart, 1994). Thus, we hypothesized that STW 5 may reduce visceral sensitivity in the upper gastrointestinal tract and, thereby, improve symptoms in dyspeptic patients. The aim of this study (Liu et al., 2004) was to investigate whether STW 5 reduces intestinal afferent sensitivity to chemical and mechanical stimuli in the rat small intestine.

Methods

Male Wistar rats (300–400 g) received oral STW 5 (a solution containing 30.8% ethanol) or vehicle (30.8% ethanol) at a volume of $10\,ml\,kg^{-1}$. The substance or vehicle was injected into the rat's stomach with a metal cannula which was introduced via the animal's esophagus (gavage). The group given STW 5 and the group given vehicle consisted of four animals each. The dose was chosen as the highest dose that is still practicable to be applied in rats in order to explore the potential of this herbal preparation. STW 5 is commercially available (Iberogast®, Steigerwald Arzneimittelwerk GmbH, Darmstadt, Germany) and contains nine different extracts of bitter candytuft, Angelica root, milk thistle fruit, caraway fruit, celandine herb, liquorice root, Chamomile flower, lemon balm leaf and peppermint leaf. Two hours after oral administration, a laparotomy was performed following deep anesthesia with pentobarbitone (dose $60\,mg\,kg^{-1}$ i.p.; stock solution at $160\,mg\,ml^{-1}$ Nembutal®, Sanofi Santé Animale, Libourne-Cedex, France; diluted 1:3 with normal saline for injection; injected volume $1.125\,ml\,kg^{-1}$). Then, a neurovascular bundle from the mesentery of the proximal jejunum was dissected on a black perspex platform and multi-unit mesenteric afferent nerve recordings were obtained from a mesenteric nerve. The actual afferent recording started approximately 4 h following STW 5 or vehicle administration, since the preparation required 1–1.5 h and an additional 30 min period was required for signal stabilization. The institutional guides for the use and care of animals were followed throughout the study.

Mesenteric afferent nerve recordings

The details of this preparation have been described previously (Kreis et al., 2002). In brief, following anesthesia, the left carotid artery was cannulated to monitor arterial blood pressure (Transducer: DT-XX, Ohmeda Pvt Ltd., Singapore. Amplifier: Neurolog Pressure Amplifier NL108, Digitimer Ltd., Welwyn Garden City, UK). A small tube was inserted into the trachea to facilitate breathing and the right jugular vein was equipped with i.v. lines for the administration of mediators. After celiotomy, the borders of the abdominal wall were sutured to a metal ring to create a well. A 10 cm loop of jejunum beginning at the ligament of Treitz was cannulated at both ends for luminal ramp distension. The loop was drained open before and after distensions, in order to minimize intraluminal pressure changes subsequent to motor events triggered by the mediators administered. Thus, changes in intestinal luminal pressure or motor events were not recorded during administration of 5-HT and bradykinin. The abdominal cavity was filled with light liquid paraffin, prewarmed to 37 °C (Sigma, Munich, Germany). About 5 cm distal to the ligament of Treitz, a mesenteric nerve was dissected from a single neurovascular bundle in the mesentery of the proximal jejunum under a microscope (Wild, M3Z, Heerburg, Switzerland). The proximal end of the nerve was cut at a distance of 10–15 mm from the jejunal wall and placed on one arm of a bipolar platinum electrode, while a small strip of connective tissue was wrapped around the second arm – serving as indifferent electrode. Thus, multi-unit afferent recordings were obtained from the mesenteric nerve. The electrophysiological signal was transmitted to a Neurolog Headstage (Neurolog NL 100, Digitimer Ltd., Welwyn Garden City, UK), the signal amplified (Neurolog NL 104) and filtered with a band width between 100 and 1000 Hz (Neurolog NL 125). Impulses were displayed on an oscilloscope

(TDS 310, Tektronix, Cologne, Germany) and simultaneously digitized by a CED 1401+ unit in order to allow storage on the hard drive of a personal computer and later on a CD-ROM for off-line computer analysis (CED1401+ interface board and Spike2 software, Cambridge Electronic Design, Cambridge, UK).

Protocol

At the beginning of the protocol, the preparation for afferent nerve recordings was kept running for a 30 min period without manipulations for signal stabilization. Then, intestinal afferent nerve discharge to 5, 10, 20 and 40 $\mu g\,kg^{-1}$ 5-HT i.v. was recorded. This was followed by a mechanical ramp distension of the intestinal loop from 0 to 60 cm H_2O which was performed with continuous infusion of normal saline into the previously closed loop at a constant rate of 1 $ml\,min^{-1}$. Ramp distensions were repeated three times. Finally, bradykinin was administered i.v. at 10, 20 and 40 $\mu g\,kg^{-1}$. Afferent discharge was recorded and saved on-line approximately 30 s before each stimulus was administered and continued for at least 1 min after blood pressure and afferent discharge frequency had come back to the prestimulus baseline level. Stimuli were administered at a minimum interval of 5 min. 5-HT and bradykinin were purchased from Sigma chemicals, Munich, Germany. Solution were prepared and diluted in normal saline. Identical volumes (0.1 $ml\,kg^{-1}$) were injected i.v. independent of the dose administered.

Data analysis and statistics

Afferent nerve recordings were evaluated blinded. During ramp distension, responses were determined by quantifying the firing frequency over a 3 s period at 10 cm H_2O increments of intrajejunal pressure. Mean afferent discharge at baseline during the 30 s period prior to distension was subtracted. Afferent responses to 5-HT and bradykinin were also obtained from the peak firing rate during a 3 s period minus baseline discharge. All data were normally distributed which was determined by Kolmogorov–Smirnov test and were quantified as mean ± SEM. Statistical analysis was performed by two-way ANOVA with the different doses/pressures as one variable and vehicle/STW 5 as the other variable. Student–Newman–Keuls test was run for subsequent comparison of subgroups. $P<0.05$ was considered statistically significant.

Results

Afferent sensitivity to 5-HT and bradykinin

Afferent discharge at baseline was $24.1\pm0.6\,imp\,s^{-1}$ in animals receiving STW 5 ($n=4$) which was not different from $23.7\pm0.6\,imp\,s^{-1}$ in controls ($n=4$). A dose-dependent increase in afferent firing was recorded following the administration of 5-HT i.v. which was always smaller in animals that had received STW 5 pretreatment compared to vehicle controls (30.8% ethanol). Afferent discharge peaked at $110\pm5\,imp\,s^{-1}$ at the maximum dose of 5-HT (40 $\mu g\,kg^{-1}$) following STW 5 pretreatment and $128\pm3\,imp\,s^{-1}$ following vehicle ($p<0.05$, Fig. 1). A similar dose-dependent increase in afferent nerve discharge was present following bradykinin i.v. (Fig. 2). In contrast to the 10 $\mu g\,kg^{-1}$ dose, peak afferent discharge was reduced at 20 and 40 $\mu g\,kg^{-1}$ following STW 5 compared to vehicle (both $p<0.05$). At 40 $\mu g\,kg^{-1}$ of systemic bradykinin, afferent nerve discharge was $176\pm7\,imp\,s^{-1}$ following STW 5 and $200\pm6\,imp\,s^{-1}$ following vehicle ($p<0.05$).

Afferent sensitivity to mechanical ramp distension

A pressure-dependent increase in afferent nerve discharge was observed subsequent to mechanical ramp distension of the intestinal loop from 10 to 60 cm H_2O which involves the sensitization of low- and high-threshold afferents. Following STW 5, this increase in afferent firing was decreased at all pressures above baseline compared to vehicle except at 20 cm H_2O ($p<0.05$; Fig. 3). Afferent nerve discharge was $147\pm8\,imp\,s^{-1}$ at the maximum pressure of 60 cm H_2O following STW 5 and $171\pm5\,imp\,s^{-1}$ in vehicle controls ($p<0.05$).

Discussion

This study demonstrates that baseline discharge was unchanged following STW 5 compared to controls. However, the afferent nerve response was decreased in the STW 5 group compared to vehicle controls by 13% for systemic 5-HT compared to the control response and by 12% for the high dose of bradykinin. Furthermore, a reduction of afferent discharge was seen by approximately 14% at the maximum pressure during mechanical distension of the intestinal loop. On one hand, these are comparatively modest changes, given the high dose of STW 5. On the other hand, this reduction in afferent sensitivity was shown in a small number of animals in each group which demonstrates the consistent nature of the STW 5 action.

Multi-unit afferent nerve recordings at the level of the mesentery involve three subpopulations of intestinal afferents that contribute to the afferent nerve response. These are vagal and splanchnic afferents together with intestinofugal fibers projecting to the prevertebral ganglia (Grundy, 2002). 5-HT has been characterized previously to trigger a biphasic intestinal afferent nerve

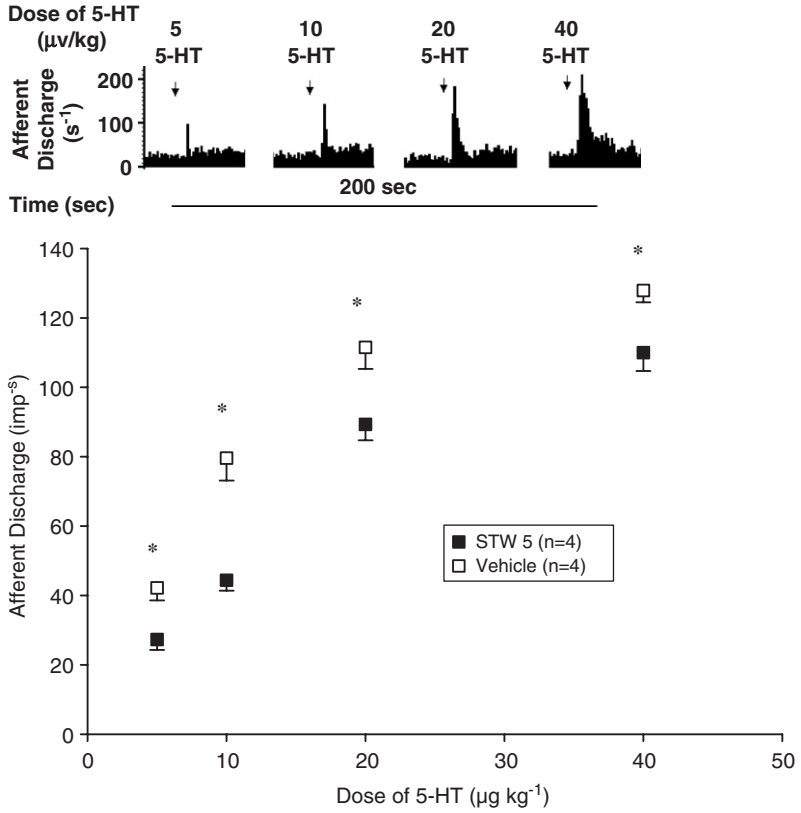

Fig. 1. Upper panel: The upper trace shows representative sequential rate histograms of mesenteric multi-unit afferent nerve discharge to increasing doses of 5-HT in a vehicle pretreated animal. Lower panel: The graph summarizes the afferent nerve response to the different doses of systemic 5-HT following vehicle (30.8% ethanol) or STW 5 pretreatment. At all doses, the response was reduced following STW 5 pretreatment ($\sharp p < 0.05$).

response (Hillsley et al., 1998; Hillsley and Grundy, 1998). The first component which was quantified in the present study by the peak discharge frequency was shown to stimulate mucosal afferent vagal nerve fibers via the 5-HT_3 receptor (Hillsley and Grundy, 1998), while the second response component is probably indirect, related to the intestinal motor response and mediated via 5-HT_{2a} receptors (Hillsley et al., 1998). Thus, the afferent vagus, the mucosa and the 5-HT_3 receptor are all potential targets for STW 5 considering the observations for 5-HT in the present study. While no data of STW 5 on afferent vagal and mucosal nerve fibers are available, binding of components of the preparation to the 5-HT_3 receptor has been described which involves the potential of an antagonistic effect (Simmen et al., 2003, 2006).

5-HT appears to play a pivotal role for visceral afferent sensitivity not only because 5-HT has been shown to stimulate intestinal afferents in animal experiments (Hillsley et al., 1998) but also since drugs acting on the 5-HT_3 or 5-HT_4 receptors improved symptoms in patients suffering from IBS (Lacy, 2004; Bergmann, 2003). However, pharmacological modulation of 5-HT receptors has also caused severe side effects which limit its widespread usage (Cole et al., 2004).

Afferent nerve discharge was reduced at the higher doses of bradykinin when animals were pretreated with STW 5. Bradykinin is an inflammatory mediator that plays a central role for nociception (Wood and Docherty, 1997). It stimulates intestinal afferents via the bradykinin BII receptor (Maubach and Grundy, 1999). As a mediator that is involved in pain perception, it has been suggested that bradykinin acts mainly on spinal afferents which have been shown to be involved in the perception of noxious distension in the intestine (Grundy, 2002). Considering these previous studies and the results of the present investigation, it appears, that STW 5 not only desensitizes vagal afferents but also spinal afferent sensitivity.

The hypothesis that vagal afferents are involved in the desensitizing action of STW 5 is further supported by the observation that the afferent nerve response to low levels of distension was also reduced (< 20 cm H_2O). It is generally agreed that at this level of distension, which creates intraluminal pressures in the range of physiological motor events, low-threshold mechanoreceptors are activated that have been described to activate

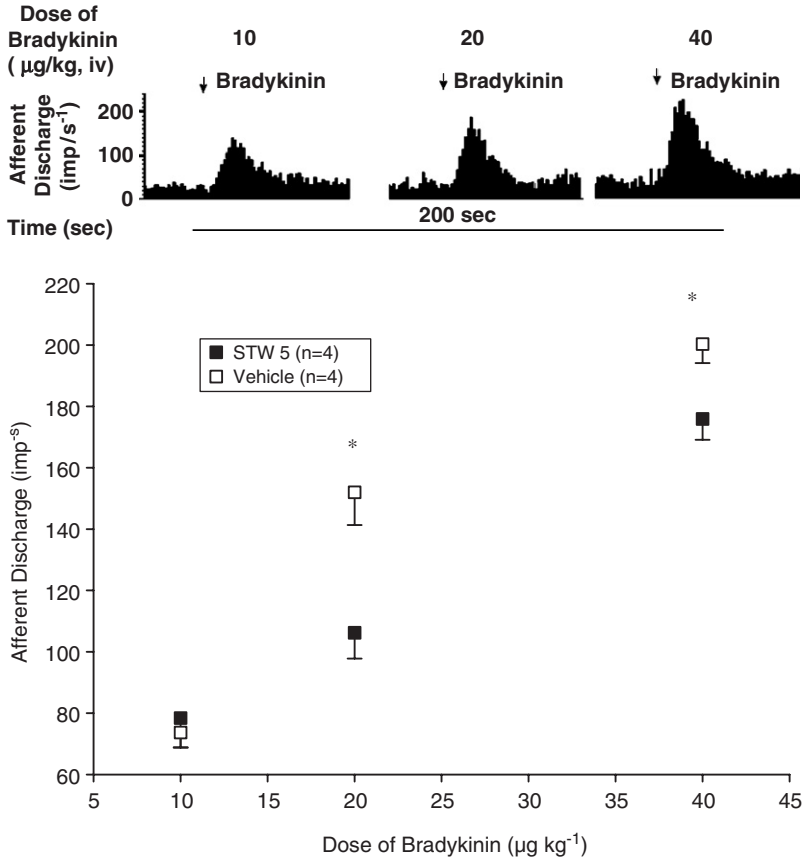

Fig. 2. Upper panel: The upper trace shows representative sequential rate histograms of mesenteric multi-unit afferent nerve discharge to increasing doses of bradykinin in a vehicle pretreated animal. Lower panel: The graph summarizes the afferent nerve response to the different doses of systemic bradykinin following vehicle (30.8% ethanol) or STW 5 pretreatment. The response was reduced at 20 and 40 µg kg^{-1} following STW 5 pretreatment compared to vehicle (30.8% ethanol; ♯$p<0.05$) but not at the 10 µg kg^{-1} dose.

predominantly vagal afferents (Sengupta et al., 1990). It is of note that the desensitizing action of STW 5 did not only affect low-threshold mechanoreceptors but also high-threshold mechanosensitive afferent units. At this level of distension which normally does not occur during physiological motor activity, intestinal nociceptors are activated that trigger intestinal afferent nerve discharge mainly on spinal afferent nerve fibers (Grundy, 2002; Sengupta et al., 1990). A different possible explanation is that the reduced intestinal afferent nerve discharge during intraluminal distension following STW 5 may be secondary to the desensitization of wide dynamic range mechanosensitive afferents or intestinofugal fibers projecting from the enteric nervous system to the prevertebral ganglia. In our opinion, this is rather unlikely since these types of nerve fibers only represent a rather small population in the mesenteric bundle and seem to be second-order neurons (Sharkey et al., 1998) which are predominantly activated during intestinal adaptation to luminal volume increases (Miller and Szurszewski, 2002).

5-HT and bradykinin trigger intestinal motor events that subsequently give rise to intestinal afferent nerve discharge by mechanosensitive afferents. These secondary effects of 5-HT and bradykinin are known to form a second response component of intestinal afferent nerve discharge that occurs after the initial response which has a direct stimulatory effect on intestinal afferents (Hillsley et al., 1998; Maubach and Grundy, 1999). A potentially attenuating effect of STW 5 on the motor response to 5-HT and bradykinin needs to be considered as STW 5 was reported to have an effect on the smooth muscle of the intestinal wall by other investigators (Heinle et al., 2006; Schemann et al., 2006; Okpanyi et al., 1993; Ammon et al., 2006). However, during the present study, the intestinal loop was drained open, so that the pressure could not build up in the lumen, avoiding a major mechanical stimulus on the intestinal wall following the administration of 5-HT and bradykinin. In order to further prevent undesired quantification of mechano-motor activity following these inflammatory mediators, only the initial response

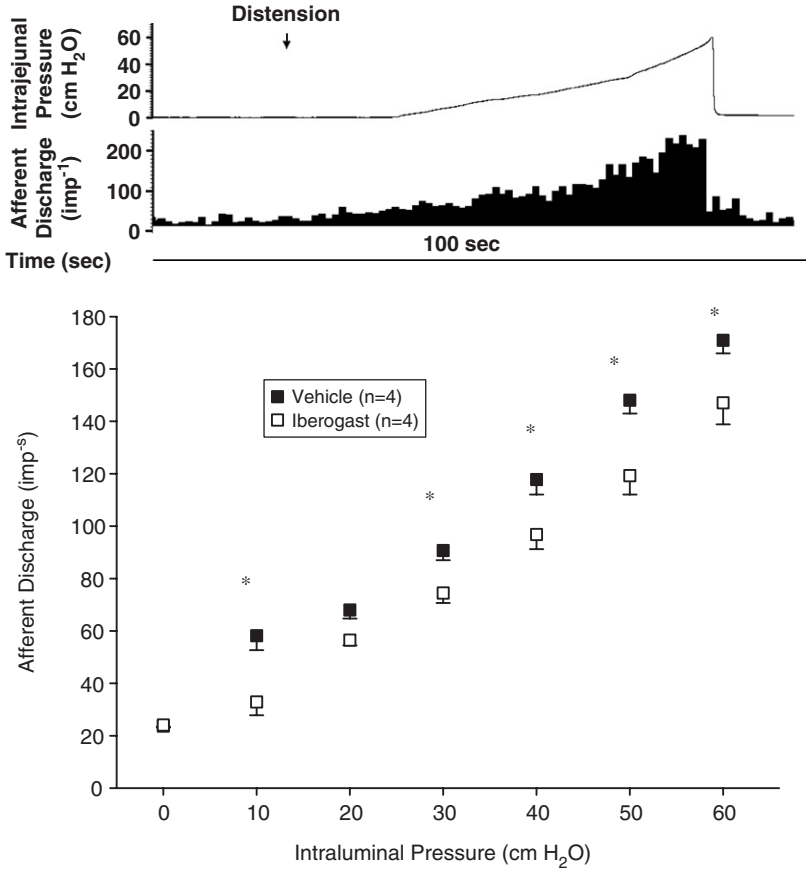

Fig. 3. Upper panel: Representative recording of a ramp distension of the intestinal loop in a vehicle pretreated animal. The upper trace shows the increasing pressure in the intestinal loop. The lower trace displays the corresponding sequential rate histograms of mesenteric afferent nerve discharge as imp s^{-1}. Lower panel: The graph summarizes the afferent nerve response at the different levels of luminal distension. Afferent discharge was reduced at all distension pressures except 20 cm H_2O following STW 5 pretreatment compared to vehicle (30.8% ethanol; $\sharp p < 0.05$).

component that contains the peak afferent nerve response was evaluated. Thus, it seems unlikely that the STW 5 effect is merely explained by an action on the muscle wall in the small intestine. However, this remains to be determined in subsequent, more detailed experimental setups.

STW 5 is a preparation that consists of nine different herbal extracts that have been investigated as a combination in the present study. With the present study design, it is not possible to determine, which of the components of STW 5 are responsible for the observed decrease in intestinal afferent sensitivity and whether interactions among the different extracts are relevant for its pharmacological action. In order to identify these extracts and their specific effects, more detailed investigations are warranted.

We conclude that STW 5 decreases afferent sensitivity in the proximal small intestine of rats to certain chemical and mechanical stimuli. This potential of STW 5 to modulate visceral afferent sensitivity may be the underlying mechanism by which STW 5 relieves symptoms in patients suffering from functional dyspepsia and irritable bowel syndrome. Nevertheless, the precise mechanism involved and the relative contribution of the different components of STW 5 await further study.

Acknowledgements

This investigation was funded by the Steigerwald Arzneimittelwerk GmbH, Darmstadt, Germany.

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