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The herbal preparation STW 5 (Iberogast®) desensitizes intestinal afferents in the rat small intestine[1]

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Abstract *Introduction: Visceral hypersensitivity in the upper gastrointestinal tract is a potential pathomechanism of functional dyspepsia. The herbal preparation STW 5 (Iberogast®) provides symptomatic relief for this condition. We aimed to investigate whether STW 5 modulates intestinal afferent sensitivity.*

Methods: The herbal preparation STW 5 or vehicle (30.8% ethanol) were administered orally in male Wister rats. After 2 h animals were anaesthetized and extracellular multi-unit intestinal afferent nerve recordings were secured from the neurovascular bundle of the mesentery in the proximal jejunum. Afferent discharge to ramp distension of the intestinal loop (0–60 cm H_2O) and dose–response curves for i.v. bradykinin (10, 20 and 40 μg kg^{-1}) and 5-HT (5, 10, 20 and 40 μg kg^{-1}) were recorded.

Results: Baseline discharge was not different between the vehicle and treatment group. Ramp distension was followed by a pressure dependent increase in afferent nerve discharge that was decreased following STW 5 pretreatment for all distending pressures reaching 147 ± 8 impulses s^{-1} (imp s^{-1}) following STW 5 vs 171 ± 5 imp s^{-1} following vehicle at 60 cm H_2O (mean ± SEM; $P < 0.05$). A dose-dependent increase in afferent discharge was observed for 5-HT and bradykinin. Following STW 5 pretreatment, afferent discharge was reduced at all doses of 5-HT to 110 ± 5 at the maximum dose after STW 5 and 128 ± 3 imp s^{-1} in controls (all $P < 0.05$). Afferent discharge to bradykinin was similarly reduced at 20 and 40 μg kg^{-1} but not at 10 μg kg^{-1} of bradykinin with a discharge rate of 176 ± 7 imp s^{-1} following STW 5 and 200 ± 6 imp s^{-1} in controls at 40 μg kg^{-1} ($P < 0.05$).

Conclusions: The preparation STW 5 reduces intestinal afferent nerve discharge following chemical and mechanical stimuli, while baseline discharge is not affected. This effect of STW 5 on afferent sensitivity may contribute to its therapeutic relief of dyspeptic symptoms.

Keywords *afferents, functional dyspepsia, hypersensitivity, STW 5, visceral sensitivity.*

INTRODUCTION

Functional dyspepsia and irritable bowel syndrome are the two most commonly seen functional gastrointestinal disorders. While functional dyspepsia involves upper gastrointestinal symptoms, patients with irritable bowel syndrome present with symptoms that have been attributed to the colon.[1,2] Functional bowel disorders are characterized by the absence of morphological or histological alterations in the gastrointestinal tract. Thus, the diagnosis of functional dyspepsia and irritable bowel syndrome are based on patients' symptoms and the clinical impression rather than on objective findings.[3,4]

The early observation that patients who suffer from irritable bowel syndrome are more sensitive to rectal distension than healthy controls [5,6] was more recently confirmed in a large number of patients with more sophisticated technology.[7] Thus, it appears that in patients with irritable bowel syndrome mechanical stimuli from the gastrointestinal tract cause painful sensations that are not perceived as painful in healthy individuals. This led to the conclusion that these patients are characterized by rectal hypersensitivity.

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Based on these considerations, medical strategies were developed in experimental and clinical studies to dampen intestinal afferent sensitivity with the aim to improve the symptoms of patients suffering from functional bowel disorders. Particularly, the inflammatory mediator and nerve transmitter 5-HT appears to play a pivotal role for visceral afferent sensitivity as 5-HT has been shown to stimulate intestinal afferents in animal experiments [8] and drugs acting on the 5-HT_3 or 5-HT_4 receptor improved symptoms in patients suffering from IBS.[9,10] However, pharmacological modulation of 5-HT receptors has also been associated with side effects which limit its widespread usage.[11]

The herbal preparation STW 5 (Iberogast®) which consists of nine different herbal extracts was shown to improve symptoms in patients suffering from functional dyspepsia without any side effects.[12] The precise mechanism of its therapeutic effect, however, is unknown. We hypothesized that STW 5 may reduce intestinal afferent nerve sensitivity since visceral hypersensitivity is assumed to be a prime pathophysiological mechanism for functional bowel disorders.[1,7]

We, therefore, aimed to investigate whether STW 5 desensitizes intestinal afferents of the proximal small intestine in the rat.

METHODS

Male Wister rats (300–400 g) underwent oral administration of either STW 5 (a solution containing 30.8% ethanol) or vehicle (30.8% ethanol) at a volume of 10 mL kg^{-1}. Each group consisted of four animals. STW 5 is a commercially available herbal preparation (Iberogast®, Steigerwald Arzneimittelwerk GmbH, Darmstadt, Germany) that contains nine different extracts, i.e. bitter candytuft (*Iberis amara*), angelica roots (*Anglicae radix*), milk thistle fruits (*Cardui mariae fructus*), caraway fruits (*Carvi fructus*), celandine herb (*Chelidonii herba*), liquorice roots (*Liquiritiae radix*), camomile flowers (*Matricariae flos*), melissa leaves (*Melissae folium*) and peppermint leaves (*Menthae piperitae folium*). In order to explore the drug in a 'proof of concept' fashion, the single dose of 10 mL kg^{-1} was chosen, which is higher than the dose recommended for humans. The oral administration was performed by injecting STW 5 or vehicle into the rat's stomach through a metal cannula, which was introduced via the animal's oesophagus (gavage). Two hours later, a laparotomy was performed after animals had been deeply anaesthetized 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}) and multi-unit mesenteric afferent nerve recordings were obtained from the mesentery of the proximal jejunum. As the preparation required 1–1.5 h and an additional 30-min period was required for signal stabilization, the actual afferent recording started approximately 4 h following STW 5 or vehicle administration. Thus, as adults rats quickly absorb and metabolize oral ethanol, [13] only minor plasma concentrations of ethanol were assumed to be present in the control (vehicle) and STW 5 group during recordings. The institutional guides for the use and care of animals were followed throughout the study (license number: C 4/00).

Mesenteric afferent nerve recordings

The details of this preparation have been described previously [14] In brief, following anaesthesia, a tracheal cannula was inserted to facilitate breathing and the right jugular vein was cannulated for the administration of mediators. The left carotid artery was cannulated to monitor arterial blood pressure (Transducer: DT-XX, Ohmeda Pte Ltd., Singapore; Amplifier: Neurolog Pressure Amplifier NL108, Digitimer Ltd., Welwyn Garden City, UK). After laparotomy, a 10-cm loop of jejunum beginning at the ligament of Treitz was cannulated at both ends for luminal ramp distension of the intestinal loop. Before and after distension, the loop was drained open in order to minimize intraluminal pressure changes subsequent to motor events triggered by the mediators administered. Thus, no differences in intestinal luminal pressure or motor events were recorded during administration of 5-HT and bradykinin. About 5 cm distal to the ligament of Treitz, a mesenteric nerve was isolated under a microscope (Wild, M3Z, Heerburg, Switzerland) from a single neurovascular bundle in the mesentery of the proximal jejunum. 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 relayed to a Neurolog Headstage (Neurolog NL 100, Digitimer Ltd, Welwyn Garden City, UK) and the signal was amplified (Neurolog NL 104, Digitimer Ltd) and filtered with a bandwidth between 100 and 1000 Hz (Neurolog NL 125, Digitimer Ltd). Signals were displayed on an oscilloscope (TDS 310, Tektronix, Cologne, Germany) and simultaneously digitized by a CED1401+ 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

Following a 30-min recording period for signal stabilisation, intestinal afferent nerve discharge to 5, 10, 20 and 40 μg kg^{-1} 5-HT i.v. was recorded. Then, a mechanical ramp distension of the intestinal loop was performed from 0 to 60 cm H_2O by 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. The duration of a ramp distension was typically 60–65 s and no difference was observed between the first and third distension. At the end of the protocol, bradykinin was administered i.v. at 10, 20 and 40 μg kg^{-1}. All doses of bradykinin and 5-HT were given as a 'single-shot' injection. Each recording was started approximately 30 s before the 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 an interval of 5 min. 5-HT and bradykinin were purchased from Sigma chemicals, Munich, Germany. Solution were prepared and diluted in normal saline such as that identical volumes (0.1 mL kg^{-1}) were injected i.v. independent of the dose administered.

Data analysis

Data were evaluated blinded which means that the scientist who evaluated the afferent nerve responses did not know whether the experiments were done with vehicle or STW 5. During ramp distension, responses were determined by quantifying the firing frequency over a 3-s period at 10 cm H_2O increments in intrajejunal pressure. The middle of this 3-s period was precisely defined by the corresponding pressure level in the intestinal loop. Afferent discharge at baseline prior to distension was subtracted in order to evaluate the increase in discharge in response to distension. Baseline discharge was defined as the mean discharge per second during the 30 s before the stimulus was applied. Afferent responses to 5-HT and bradykinin were similarly obtained from the peak-firing rate during a 3-s period minus baseline discharge. All data were normally distributed as determined by Kolmogorov–Smirnov test and were quantified as mean ± SEM and 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 used for subsequent pairwise comparison of subgroups. A $P < 0.05$ was considered as statistically significant.

RESULTS

Baseline afferent nerve discharge was 23.7 ± 0.6 impulses s^{-1} (imp s^{-1}) in controls ($n = 4$) which was not different from 24.1 ± 0.6 imp s^{-1} in animals receiving STW 5 ($n = 4$). Following systemic 5-HT, a dose-dependent increase in afferent nerve discharge was observed that was reduced in STW 5 pretreated animals compared with vehicle (30.8% ethanol) controls. At the maximum dose of 5-HT (40 μg kg^{-1}) afferent discharge was 110 ± 5 imp s^{-1} following STW 5 and 128 ± 3 imp s^{-1} following vehicle ($P < 0.05$, Fig. 1).

Mechanical ramp distension of the intestinal loop gave rise to a pressure-dependent increase in afferent

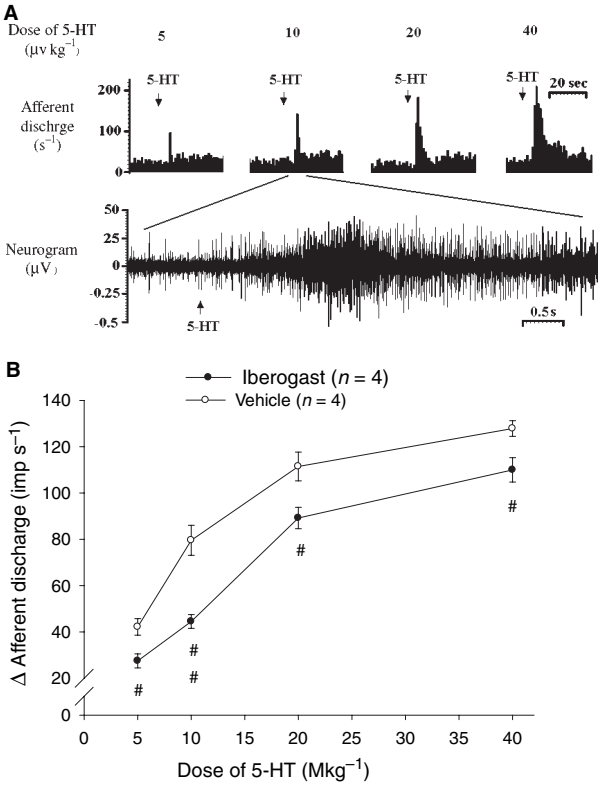

Figure 1 (A) The upper trace shows representative sequential rate histograms of mesenteric multi-unit afferent nerve discharge to increasing doses of 5-HT in a vehicle pretreated animal. In the lower trace, a raw nerve recording of a response to 10 μg kg^{-1} 5-HT i.v. is displayed. (B) The graph summarizes 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 (the symbol # represents $P < 0.05$).

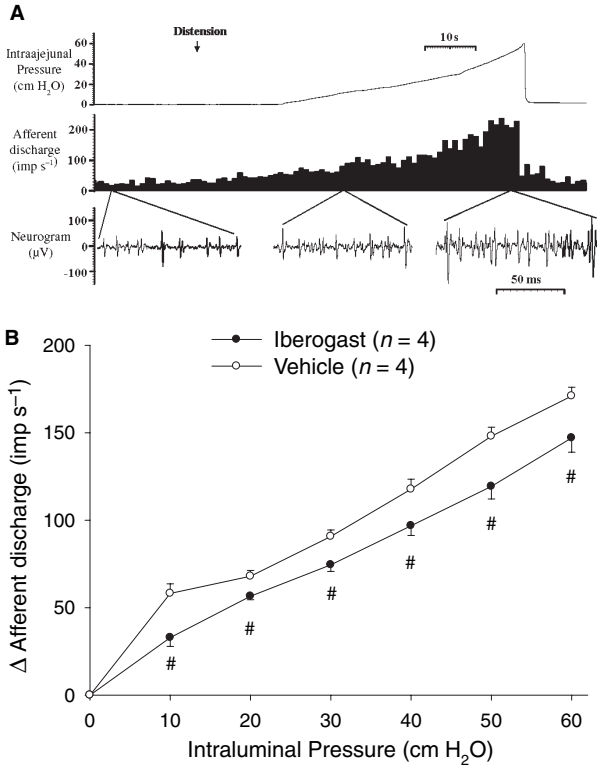

Figure 2 (A) Representative recording of a ramp distension of the intestinal loop in a vehicle pretreated animal. The upper trace shows the increasing pressure in the intestinal loop. The middle trace displays the corresponding sequential rate histograms of mesenteric afferent nerve discharge as impulses s^{-1}. The lower trace shows snap shots of raw nerve recordings at different levels of distension. (B) 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; the symbol # represents $P < 0.05$).

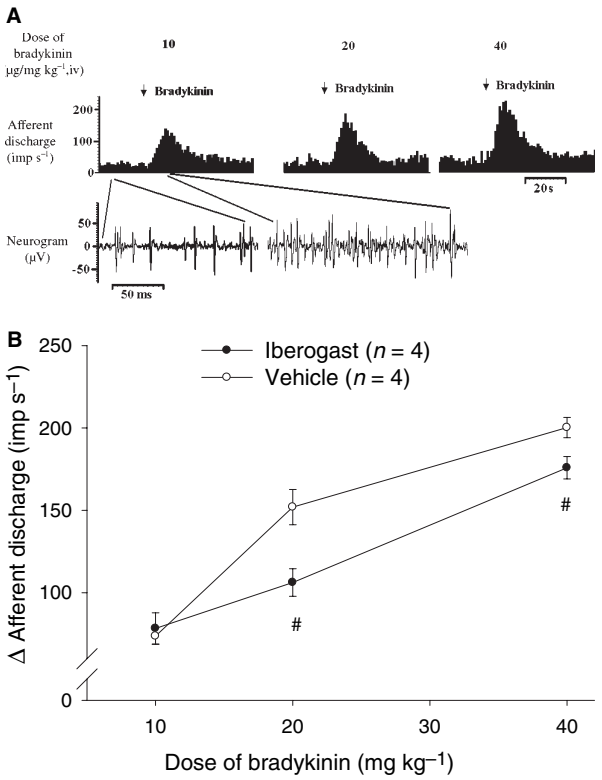

Figure 3 (A) The upper trace shows representative sequential rate histograms of mesenteric multi-unit afferent nerve discharge to increasing doses of bradykinin in a vehicle pretreated animal. In the lower trace, snap shots of a raw nerve recording of a response to 10 μg kg^{-1} bradykinin i.v. is displayed. (B) 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; the symbol # represents $P < 0.05$) but not at the 10 μg kg^{-1} dose.

nerve discharge that was decreased at all pressures above baseline except 20 cm H_2O following STW 5 administration compared to vehicle ($P < 0.05$; Fig. 2) which involves the sensitisation of low- and high-threshold afferents. At the maximum pressure of 60 cm H_2O, afferent nerve discharge was 147 ± 8 imp s^{-1} following STW 5 and 171 ± 5 imp s^{-1} in vehicle controls ($P < 0.05$).

Bradykinin stimulated a dose-dependent increase in afferent nerve discharge (Fig. 3). While maximum afferent nerve discharge was reduced at 20 and 40 μg kg^{-1} following STW 5 compared to vehicle (both $P < 0.05$), no difference was observed at the 10 μg kg^{-1} dose. At 40 μg kg^{-1} afferent nerve discharge was 176 ± 7 imp s^{-1} following STW 5 and 200 ± 6 imp s^{-1} following vehicle ($P < 0.05$).

DISCUSSION

In the present study, mesenteric afferent nerve discharge in the proximal jejunum was reduced to different afferent stimuli following pretreatment with the herbal preparation STW 5 (Iberogast®) compared to vehicle (30.8% ethanol). The afferent nerve response was decreased in the STW 5 group by more than 15% for all doses of systemic 5-HT compared to the control response and by 10 to 30% for the high doses of bradykinin. Similarly, a reduction of afferent discharge by approximately 15–20% was recorded during the whole pressure range of mechanical distension of the intestinal loop. Baseline discharge was unchanged following STW 5 compared to controls.

The preparation STW 5 is a herbal medication that requires a 30.8% ethanol solution as a solvent.

However, the decrease in intestinal afferent sensitivity that was observed in this study following STW 5 is clearly to be attributed to the ingredients of the herbal preparation and not to ethanol as the treatment and the control group received the identical volume and concentration of ethanol.

Multi-unit afferent nerve recordings at the level of the mesentery involve that three distinct subpopulations of intestinal afferents contribute to the afferent nerve response, namely vagal and splanchnic afferents together with intestinofugal fibres projecting to the prevertebral ganglia.[15] Among the different stimuli administered, systemic 5-HT has been characterized previously to trigger a biphasic intestinal afferent nerve response.[8,16] The first component which was quantified in the present study by the peak discharge frequency was shown to stimulate mucosal afferent vagal nerve fibres via the 5-HT_3 receptor,[16] while the second response component is probably indirect, related to the intestinal motor response and mediated via 5-HT_{2a} receptors.[8] 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 fibres 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.[17,18]

When testing the afferent nerve response to systemic bradykinin, afferent nerve discharge was reduced at the higher doses of bradykinin when animals were pretreated with STW 5. Bradykinin is an inflammatory mediator that has a prime role for nociception.[19] It stimulates intestinal afferents via the bradykinin BII receptor.[20] 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.[15] This would imply that STW 5 not only desensitizes the vagal afferent nerve response but also spinal afferent sensitivity.

The concept that vagal afferents are involved in the desensitizing action of STW 5 is supported by the observation that the afferent nerve response to low levels of distension (<20 cm H_2O) was also reduced. 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 predominantly vagal afferents.[21] Interestingly, 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 afferents.[15,21] Alternatively, the reduced intestinal afferent nerve discharge during intraluminal distension following STW 5 may be explained by desensitisation of wide dynamic range mechanosensitive afferents or intestinofugal fibres projecting from the enteric nervous system to the prevertebral ganglia by STW 5.[22] However, these types of nerve fibres only represent a rather small population in the mesenteric bundle and seem to be second order neurons [20] which are predominantly activated during intestinal adaptation to luminal volume increases.[23] Thus, this interpretation of the observations in the present study appears rather unlikely, however, may not be completely ruled out by the available data.

5-HT and bradykinin trigger intestinal motor events that subsequently give rise to intestinal afferent nerve discharge via mechanosensitive afferents. These secondary effects of 5-HT and bradykinin have previously been shown 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.[8,20] A potential 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 others.[24,25] During the experiments for 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 component that contains the peak afferent nerve response was evaluated in this study. Thus, it appears 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 approaches.

STW 5 is a preparation, which consists of nine different herbal extracts that have been investigated as a combination in the present study. It is not possible to determine from the present investigation, 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. Further studies are required, to identify these extracts and their specific effects by more detailed investigations.

In conclusion, STW 5 has been shown to decrease afferent sensitivity in the proximal small intestine of rats to certain chemical and mechanical stimuli. This modulatory potential of STW 5 on visceral sensitivity may play a role for its beneficial effect in patients suffering from functional dyspepsia. However, the precise mechanisms involved and the relative contribution of the different components of STW 5 await further study.

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