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The herbal preparation STW5 (Iberogast®) has potent and region-specific effects on gastric motility

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Abstract *Functional dyspepsia (FD) is amongst the most common functional gastrointestinal disorders. Symptomatic treatment includes the use of herbal preparations whose effects on gastric motility are unclear. The present study aimed at investigating the effects of STW 5 (Iberogast®), a fixed combination of hydroethanolic herbal extracts, on gastric motility in vitro. Muscle strips from guinea-pig gastric fundus, corpus and antrum were set up in organ baths either in circular or longitudinal orientation. Addition of ethanol-free STW 5 to the organ baths (32–512 μg mL^{-1}) dose-dependently evoked a sustained and reversible relaxation of circular and longitudinal fundus and corpus muscle strips without changes in phasic activity. In contrast, antral muscle strips responded to STW 5 with a significant increase in the contractile force of phasic contractions without changes in tone. All effects were resistant to tetrodotoxin (0.5 μmol L^{-1}), atropine (1 μmol L^{-1}), ω-conotoxin GVIA (0.5 μmol L^{-1}), capsaicin (1 μmol L^{-1}) or* L*-NAME (100 μmol L^{-1}), suggesting that neither nerves nor nitric oxide pathways were involved. These data demonstrate that STW 5 profoundly alters gastric motility in a region-specific but not layer-specific manner and thus implicates Iberogast® in the treatment of FD patients suffering from motility disorders with impaired fundus accommodation and/or antral hypomotility.*

Keywords *functional dyspepsia, gastric motility, guinea-pig, smooth muscle contractility.*

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INTRODUCTION

Dyspeptic symptoms are highly prevalent within the general population, but structural lesions to explain symptoms including fullness in the upper abdomen, early satiety, bloating, epigastric pain, or nausea and vomiting are only found in a minority of patients.[1,2] Dyspepsia in the absence of a clinically identifiable structural lesion despite appropriate investigation is referred to as functional dyspepsia (FD).[2,3] The pathophysiology of FD and the origin of symptoms remain relatively poorly defined, but disturbed gastrointestinal function – namely sensory and motor disorders of the stomach and duodenum – appear to play a central role in the development of symptoms in at least a subset of cases.[4–6]

The optimum treatment of FD is uncertain. For the management of dyspepsia, empirical therapy has been recommended, usually without prior diagnostic procedures.[3] Acid-suppressive substances such as histamine H_2-receptor antagonists and, more recently, proton pump inhibitors as well as gastroprokinetics have been suggested as first line, empirical therapy,[3,7] and these substances have been shown to be significantly more effective than placebo in randomized, controlled clinical trials.[2,8] Overall, the beneficial effect of these drugs in FD is relatively small and many patients need to take them on a long-term basis.[8] Hence, the economic impact of pharmacological therapy for patients with FD is considerable[8,9] and cost-effective management strategies and treatments are urgently required.

Because the available pharmacological therapy for patients with FD is overall mainly unsatisfactory, over-the-counter remedies and herbal preparations for symptomatic relief are widely used by FD patients. While patients commonly perceive herbal drugs as safe and effective as well as relatively inexpensive 'natural' compounds,[10] most doctors tend to believe that if symptomatic efficacy of such preparations is reported,

this most likely reflects a placebo response or may be attributed to the high ethanol contents of the herbal extracts. However, recent randomized, placebo-controlled clinical trials of several herbal drug preparations with alleged anti-dyspeptic properties have reported significant superiority of the herbal drugs over placebo.[11–15] In addition, one of these studies could even demonstrate equivalent efficacy to ameliorate dyspepsia-specific gastrointestinal symptoms in FD patients for the herbal compound STW 5 (Iberogast®; Steigerwald Arzneimittelwerk GmbH, Darmstadt, Germany) in comparison with the well-characterized prokinetic synthetic mono-compound cisapride.[12,16] STW 5 is a multi-compound drug containing extracts from bitter candy tuft, chamomile flower, peppermint leaves, caraway fruit, liquorice root, lemon balm leaves, angelica root, greater celandine herbs and milk thistle fruit, each of which is reported to have multiple pharmacological properties relevant for gastrointestinal pathophysiology.[17] In the past, antibacterial, antisecretory, cytoprotective and anti-ulcerogenic as well as spasmolytic effects have been claimed for STW 5 based on pharmacological *in vitro* and *in vivo* studies (reviewed in 17–19). However, effects on STW 5 on gastric motility have not yet been investigated.

Therefore, the aim of this study was to assess the effects of the herbal preparation STW 5 on gastric motility *in vitro* employing guinea-pig stomach preparations.

MATERIAL AND METHODS

Animals

For this study 114 BFA guinea-pigs of either sex, weighing 320–780 g were used. Animals were obtained from Charles River Wiga (Sulzfeld, Germany) and maintained in isolated airflow units (Ehret, Emmendingen, Germany) at a temperature of 20–24 °C and a 14 : 10 h light/dark cycle. Drinking water and standard laboratory food pellets were provided *ad libitum*. All procedures used throughout this study were conducted according to the German Guidelines for Animal Care and approved by the Institutional Review Board of Animal Care Committee.

Tissue preparation

Guinea-pigs were killed by concussion and exsanguination from their cervical vessels. The entire stomach was removed and immediately placed in ice-cold oxygenated (95% O_2/5% CO_2) Krebs solution (pH 7.4) containing (in mmol L^{-1}): 117 NaCl, 4.7 KCl, 2.5 $CaCl_2$ ($2H_2O$), 1.5 $MgCl_2$ ($6H_2O$), 25 $NaHCO_3$, 1.2 NaH_2PO_4 and 11.0 Glucose. Subsequently, the stomach was opened along the greater curvature, thoroughly washed and pinned mucosal side up in Sylgard-coated Petri dishes. The mucosa was carefully dissected away under an Olympus SZ30 stereomicroscope (Olympus, Hamburg, Germany). Muscle strips (1.5 cm^2) were cut along both the circular and longitudinal muscle axis of gastric fundus, corpus and antrum, mounted in individual 25-mL organ baths and maintained in oxygenated Krebs solution at 37 °C.

One end of each tissue was attached to an isometric tension transducer connected with a Quad Bridge and a MacLab/4S analog/digital converter (MacLab, AD Instruments, Spechbach, Germany). Responses were recorded and analysed employing Chart 4.2 software (MacLab, AD Instruments) on a Windows XP-based computer.

In vitro motility studies

After mounting in the organ baths, tissues were equilibrated with a preload set at 15 mN for 45 min. To ascertain tissue viability, electrical field stimulation (EFS) was performed using a Grass SD9 stimulator set at a constant supramaximal voltage of 100 V, 10 Hz with a pulse width of 0.6 ms for 10 s. All tissues used in our experiments were vital and responded to EFS with an initial contraction followed by an inhibition of muscle contractility. Fundus muscle strips predominantly displayed the inhibitor response consisting of a pronounced relaxation while antral muscle strips showed almost exclusively contractile responses. After each EFS response, tissues were thoroughly rinsed and allowed to equilibrate for approximately 25 min.

Application of drugs

*STW 5*STW 5, a fixed combination of hydroethanolic herbal extracts, was used in the form of an ethanol-free lyophilisate (kindly provided by Steigerwald Arzneimittelwerk GmbH). It could readily be dissolved in Krebs buffer and was added to the organ baths in final concentrations ranging from 32 to 512 $\mu g\ mL^{-1}$. This concentration range is well below the amount of 51.3 mg of STW 5 provided by one therapeutic serving of 20 drops, equivalent to 1 mL STW 5. Concentration–response studies were performed in each individual tissue in a non-cumulative manner. Twenty minutes after each STW 5 application the tissues were rinsed three times with fresh Krebs buffer and allowed to recover for approximately 30 min until the tissues had reached previous tone.

Inhibitors To determine the mechanisms underlying the STW 5 effects, tissues were incubated with either the neurotoxins tetrodotoxin (TTX; 5×10^{-7} mol L^{-1}; purchased from Biotium, Hayward, CA, USA), ω-conotoxin GVIA (ω-CTX; 5×10^{-7} mol L^{-1}; Alomone Labs, Jerusalem, Israel), capsaicin (CAP; 10^{-6} mol L^{-1}; Sigma-Aldrich, Deisenhofen, Germany) or atropine (ATR; 10^{-6} mol L^{-1}; Sigma-Aldrich), or the nitric oxide synthase inhibitor N^{ω}-nitro-L-arginine methyl ester (L-NAME; 10^{-4} mol L^{-1}; Sigma-Aldrich). All drugs were added to the organ baths in volumes of less or equal than 1% of the bath volume. In all series of experiments, tissues were twice pretreated with STW 5 at a concentration of 256 μg mL^{-1} to ensure reproducibility of the response. Subsequently, the thoroughly rinsed tissues were incubated with the respective inhibitor for a further 20 min. Then, TTX, ω-CTX, ATR and L-NAME-treated tissues were electrically stimulated while CAP-treated tissues were re-exposed to CAP to validate the efficacy of the inhibitor. After confirmation that the EFS-response was abolished in TTX and ω-CTX pre-treated tissues, STW 5 was once again added to the organ baths. L-NAME and ATR pre-treated tissues displayed the well-known loss of the inhibitory or excitatory component of their EFS-response, respectively, while the successful defunctionalization of capsaicin-sensitive primary afferents in CAP-treated tissues could be documented by the subsequent failure of CAP to reinduce the typical relaxatory responses.[20] STW 5 effects in the presence of the respective inhibitor were directly compared with the preceding effects in the absence of the inhibitor in each tissue.

Data expression and statistical analysis

STW 5-induced changes in muscle tension were calculated in comparison with pretreatment baseline tension and expressed as ΔmN.

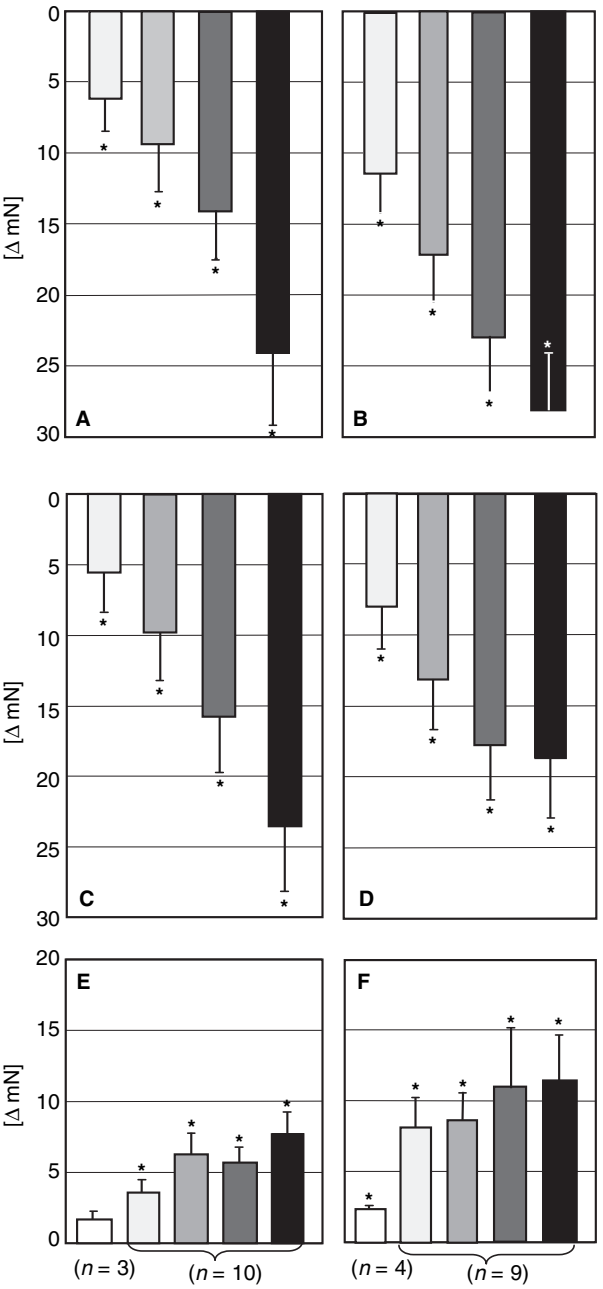

Figure 1 STW 5 effects on gastric smooth muscle tone are concentration-dependent and region-specific. Muscle strips from circular or longitudinal muscle layers of guinea-pig gastric fundus, corpus or antrum were mounted in organ baths and isometric muscle tension was recorded. Dose–response studies were performed by adding different concentrations of STW 5 to the organ baths and comparing pre- and post-treatment muscle tension in each individual tissue [ΔmN]. Each panel represents a series of STW 5 dose–response studies in one layer of one gastric region. STW 5 concentrations are coded by bar colour: :32 μg mL^{-1}; □: 64 μg mL^{-1}; ▩: 128 μg mL^{-1}; ▩: 256 μg mL^{-1}; ■: 512 μg mL^{-1}. Each bar represents mean ± SEM of n tissues. A: STW 5 induces a dose-dependent relaxation of gastric fundus circular muscle strips ($n = 7$). B: STW 5 induces a dose-dependent relaxation of gastric fundus longitudinal muscle strips ($n = 7$). C: STW 5 induces a dose-dependent relaxation of gastric corpus circular muscle strips ($n = 9$). D: STW 5 induces a dose-dependent relaxation of gastric corpus longitudinal muscle strips ($n = 9$). E: STW 5 dose-dependently enhances contraction amplitudes of the ongoing phasic activity in gastric antrum circular muscle strips (n is indicated under each individual bar). F: STW 5 dose-dependently enhances contraction amplitudes of the ongoing phasic activity in gastric antrum longitudinal muscle strips (n is indicated under each individual bar). *Statistically significant difference between pre- and post-treatment muscle tension ($P < 0.05$).

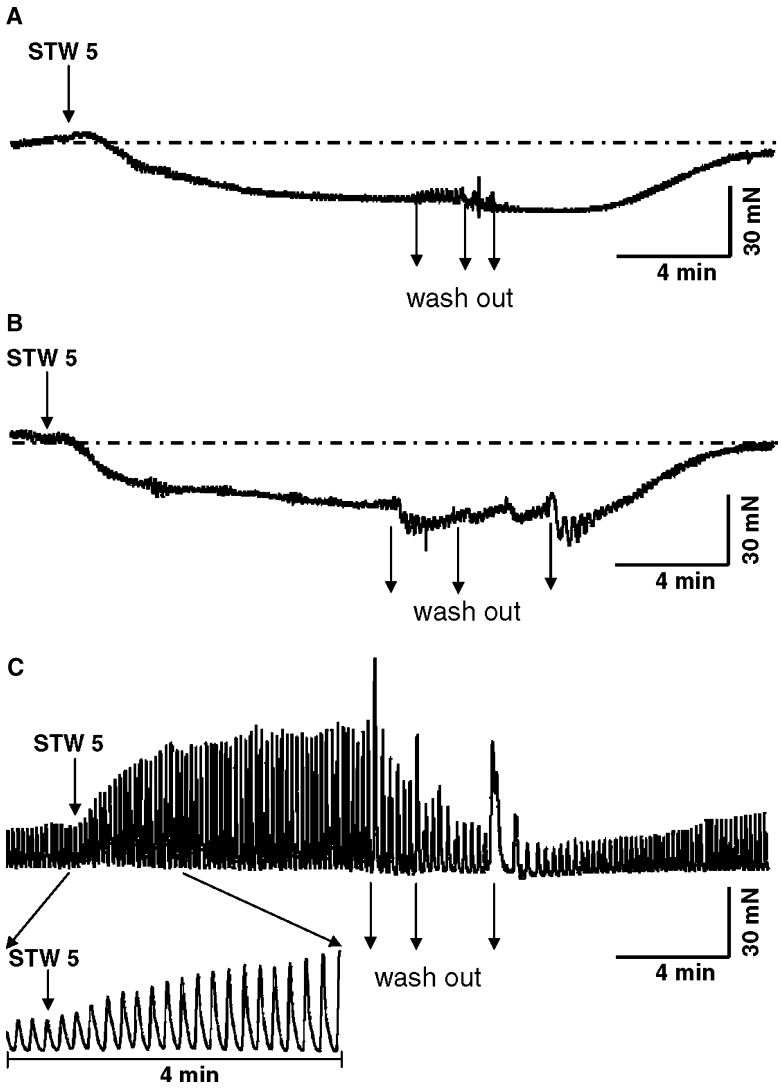

Figure 2 In gastric fundus and corpus, STW 5 evokes an initial transient increase in muscle tone followed by a long-lasting muscle relaxation while in antrum, STW 5 augments contraction amplitudes of ongoing phasic activity Shown are examples from gastric fundus longitudinal muscle (A), corpus circular muscle (B) and antrum longitudinal muscle (C), respectively. Muscle strips were mounted in organ baths and attached to isometric tension transducers. The arrows labelled 'STW 5' indicate when STW 5 (final concentration 256 μg mL^{-1}) was added to the organ baths; the arrows labelled 'wash out' indicate the three wash-outs after each drug application followed by re-equilibration of the tissues. A: In the gastric fundus muscle strip, basal muscle tension prior to application of STW 5 was 39 mN. Immediately after addition of STW 5 this tone rose to 46 mN. In the further course of the experiment muscle tension fell to 13 mN; the maximum relaxation by 26 mN was established after 14.5 min. Basal tone returned to pre-STW 5 values after wash-out. B: In the gastric corpus muscle strip, basal muscle tension prior to application of STW 5 was 50 mN. Immediately after addition of STW 5 this tone rose to 52 mN. In the further course of the experiment muscle tension fell to 21 mN; the maximum relaxation by 29 mN was established after 12 min. Basal tone returned to pre-STW 5 values after wash-out. C: In the gastric antrum muscle strip, mean contraction amplitude of phasic activity prior to application of STW 5 was 17 mN. Within 6.5 min after addition of STW 5 this contraction amplitude rose to 60 mN. Inset: Higher magnification of the first 4 min after application of STW 5. Note that there were no significant effects on contraction frequency.

Treatment groups were compared using paired Student's *t*-tests and statistical significance was assumed if $P < 0.05$. For intergroup comparisons (basal tone and duration to maximum relaxation) one-way ANOVA followed by post hoc testing using the Bonferroni correction (SigmaStat; SPSS, Erkrath, Germany) were used where appropriate. Statistical significance was assumed if $P < 0.05$.

RESULTS

Effects of STW 5 on gastric fundus and corpus

STW 5 consistently evoked a sustained and reversible relaxation of both circular and longitudinal gastric fundus and corpus muscle strips (Fig. 1A–D). The significant decreases in muscle tone were concentration-dependent with a delayed onset that was slightly longer in longitudinal muscle strips (Table 1), and they were not paralleled by changes in phasic activity in these regions (Fig. 2A,B). The tissue relaxation was fully reversible because after wash-out the basal tone of the muscle strips returned to baseline (Fig. 2A,B). There were no residual stimulatory effects of STW 5 on basal muscle tone after wash-out of the compound (Fig. 2 and Table 2). In addition to its robust inhibitory effect, STW 5 evoked an immediate but small and transient contractile response which was not concentration-dependent and could only be observed in a fraction of the tissues with a higher incidence in longitudinal muscle strips (Fig. 2A,B and Table 3).

Effects of STW 5 on antral contractility

Both circular and longitudinal muscle strips from gastric antrum responded to STW 5 with an immediate and long lasting, significant increase in contractile force even at the lowest concentration used (Figs 1E,F and 2C). In all experiments, STW 5 augmented contraction amplitudes of the ongoing phasic activity without significantly affecting contraction frequency. The mean contraction frequency in longitudinal muscle strips was 5.79 ± 0.75 contractions per minute, the mean contraction frequency in circular muscle strips was 5.43 ± 0.77 contractions per minute. This frequency was not significantly altered by any of the STW 5 concentrations applied to the tissues.

The STW 5-effects on contraction amplitudes were concentration-dependent (Fig. 1E,F) and fully reversible after wash-out. In addition, STW 5 induced an initial small and transient increase in antral muscle tone in a fraction of the tissues with a higher incidence in longitudinal muscle strips (Table 3). As in fundus and corpus muscle strips this increase in muscle tone was not concentration-dependent.

Table 1 Duration to maximum relaxation of fundus and corpus muscle strips to maximum increase in contraction amplitudes of antrum muscle strips after addition of different concentrations of STW 5

	64 μg mL^{-1}	128 μg mL^{-1}	256 μg mL^{-1}	512 μg mL^{-1}
Fundus circular	9.13 ± 2.65 min ($n = 4$)	9.42 ± 5.09 min ($n = 6$)	9.75 ± 2.85 min ($n = 6$)	10.33 ± 3.14 min ($n = 6$)
Fundus longitudinal	10.83 ± 2.36 min ($n = 6$)	12.33 ± 2.98 min ($n = 6$)	14.17 ± 1.03 min ($n = 6$)*†	13.25 ± 2.04 min ($n = 6$)
Corpus circular	6.75 ± 3.46 min ($n = 8$)	8.67 ± 4.78 min ($n = 9$)	9.28 ± 4.16 min ($n = 9$)	8.83 ± 3.77 min ($n = 9$)
Corpus longitudinal	11.50 ± 2.49 min ($n = 8$)†	11.13 ± 3.38 min ($n = 8$)	13.19 ± 2.11 min ($n = 8$)†	13.25 ± 1.17 min ($n = 8$)†
Antrum circular	105 ± 80.78 s ($n = 10$)	74.44 ± 54.39 s ($n = 9$)	106.00 ± 157.62 s ($n = 10$)	161.82 ± 188.19 s ($n = 11$)
Antrum longitudinal	35.71 ± 22.59 s ($n = 7$)	112.86 ± 93.31 s ($n = 7$)	75.00 ± 34.17 s ($n = 6$)	61.43 ± 38.33 s ($n = 7$)

Results are expressed as mean ± SEM (number of tissues per group). *Significantly different from duration to maximum relaxation using 64 μg mL^{-1} STW 5 in identical region ($P < 0.05$). †Significantly different from duration to maximum relaxation using identical STW 5 concentrations in circular muscle ($P < 0.05$).

Table 2 Effects of multiple STW 5 applications followed by wash-out on basal tone of fundus and corpus muscle strips. Muscle tone of the respective muscle strips was assessed immediately prior to the next STW 5 application and is referred to as the STW 5 concentration that was subsequently added to the tissues

	64 μg mL^{-1}	128 μg mL^{-1}	256 μg mL^{-1}	512 μg mL^{-1}
Fundus circular	45.76 ± 4.94 mN ($n = 6$)	50.34 ± 6.08 mN ($n = 6$)	49.48 ± 8.84 mN ($n = 6$)	47.57 ± 8.89 mN ($n = 6$)
Fundus longitudinal	42.91 ± 9.29 mN ($n = 7$)	41.69 ± 10.15 mN ($n = 7$)	41.57 ± 12.35 mN ($n = 7$)	41.50 ± 11.38 mN ($n = 7$)
Corpus circular	45.26 ± 13.36 mN ($n = 9$)	52.88 ± 10.87 mN ($n = 9$)*	54.17 ± 11.33 mN ($n = 9$)*	52.73 ± 12.89 mN ($n = 9$)
Corpus longitudinal	29.30 ± 11.06 mN ($n = 9$)	29.78 ± 12.71 mN ($n = 9$)	28.64 ± 13.21 mN ($n = 9$)	26.40 ± 13.82 mN ($n = 9$)

Results are expressed as mean ± SEM (number of tissues per group). *Significantly different from basal tone before application of 64 μg mL^{-1} STW 5 in the same region ($P < 0.05$).

	64 μg mL^{-1}	128 μg mL^{-1}	256 μg mL^{-1}	512 μg mL^{-1}
Fundus circular	2/6 (33)	4/6 (67)	4/6 (67)	2/6 (33)
Fundus longitudinal	5/6 (83)	6/6 (100)	5/6 (83)	5/6 (83)
Corpus circular	5/8 (63)	6/8 (75)	6/8 (75)	5/8 (63)
Corpus longitudinal	6/8 (75)	6/8 (75)	7/8 (88)	8/8 (100)
Antrum circular	1/7 (14)	1/6 (17)	1/7 (14)	3/7 (43)
Antrum longitudinal	3/8 (38)	1/8 (13)	3/8 (38)	2/8 (25)

Values within parentheses are expressed as percentage.

Table 3 Numbers of gastric fundus, corpus and antrum muscle strips displaying a transient increase in muscle tone upon STW 5 exposure

STW 5 effects are not nerve-mediated and do not involve nitric oxide

To determine the mechanisms underlying the observed STW 5 effects, tissues were incubated with several inhibitors of well-established enteric neural pathways and changes in STW 5 responses were recorded and analysed. An exception was made for the transient increase in muscle tone following STW 5 application because of the unsteady nature of this phenomenon. All other effects of STW 5 were resistant to pretreatment of the tissues with the fast sodium channel blocker tetrodotoxin (Fig. 3A), the synaptic transmission blocker ω-conotoxin GVIA (Fig. 3B), and defunctionalization of unmyelinated C-type fibres by long-term application of capsaicin (Fig. 3C), suggesting that these effects were non-neural in origin. In addition, the STW 5-induced significant increase in the contractile force of antral phasic contractions could not be blocked by the muscarinergic antagonist atropine (mean increase in contraction amplitude after STW 5 in the absence *vs* presence of atropine: antrum circular muscle Δ 5.43 ± 0.86 mN *vs* Δ 4.92 ± 0.53 mN ($n = 3$, n.s.); antrum longitudinal muscle Δ 6.95 ± 0.35 mN *vs* Δ 6.16 ± 0.25 mN ($n = 3$, n.s.). Finally, blockade of NO synthesis by the nitric oxide synthase inhibitor L-NAME could not block the STW 5-induced muscle relaxation (Fig. 3D), indicating that nitric oxide pathways are not involved in this response.

DISCUSSION

The present study provides evidence that the research formulation STW 5 profoundly alters gastric motility in a dose-dependent and region-specific manner. STW 5 was applied in the form of an ethanol-free lyophilisate of a fixed herbal combination of hydroethanolic extracts from bitter candy tuft, chamomile flower, peppermint leaves, caraway fruit, liquorice root, lemon balm leaves, angelica root, greater celandine herbs and milk thistle fruit.

In our experimental set-up, STW 5 evoked an immediate but small and transient increase in muscle tone in a fraction of all tissues followed by a robust and sustained relaxation of fundus and corpus circular and longitudinal muscle strips. The dramatic STW 5-induced decreases in fundus and corpus muscle tone were not paralleled by changes in phasic activity in these regions. Furthermore, there were no residual stimulatory effects of STW 5 on basal muscle tone after wash-out of the compound.

In contrast to the findings in the proximal stomach, antral muscle strips responded to STW 5 with a significant increase in the contractile force, indicating that the observed effects of STW 5 on gastric motility are highly region-specific. STW 5 effects on antral muscle strips occurred even if very low concentrations of the compound were added to the organ baths. In all experiments, STW 5 augmented antral contraction amplitudes of the ongoing phasic activity, and this effect was not paralleled by changes in contractile frequency. The effects of STW 5 on antral muscle strips were long lasting and reversible upon wash-out.

To our knowledge, this is the first report directly demonstrating an effect of plant extracts on gastric motility. In the past, antibacterial, antisecretory, cytoprotective and anti-ulcerogenic as well as spasmolytic effects have been claimed for STW 5 based on pharmacological *in vitro* and *in vivo* studies.[17–19,21,22] Because ethanol in itself has been shown to exert a profound dual effect on gastrointestinal motility in a dose-dependent manner,[23] the current studies have been conducted with ethanol-free extracts.

Several studies employing hydroethanolic STW 5 extracts have shown a stimulating effect of STW 5 in relaxed ileal smooth muscle preparations.[19] In contrast, we have not seen any significant STW 5-induced increase in basal muscle tone in gastric smooth muscle strips. Therefore, rather than having a general 'tonicizing' effect on the gastrointestinal tract,[19] STW 5 appears to exert region-specific effects not only in the stomach but in all segments of the gastrointestinal tract.

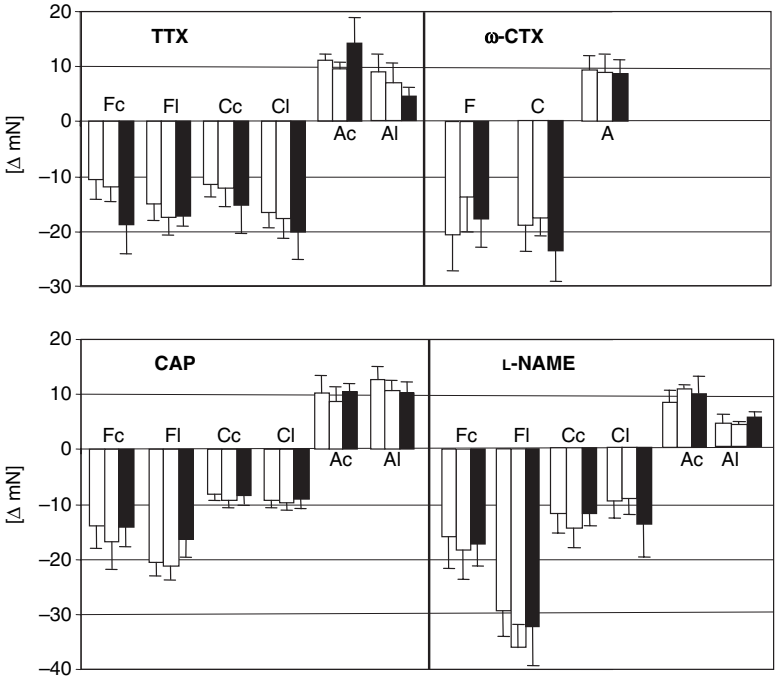

Figure 3 STW 5 effects on gastric motility are resistant to tetrodotoxin (TTX), ω-conotoxin GVIA (ω-CTX), capsaicin (CAP) or N^{ω}-nitro-L-arginine methyl ester (L-NAME). Muscle strips from circular or longitudinal muscle layers of guinea-pig gastric fundus, corpus or antrum were mounted in organ baths and isometric muscle tension was recorded. In each individual tissue changes in muscle tension [ΔmN] in response to STW 5 (final concentration 256 μg mL^{-1}) were recorded twice (open bars) before tissues were treated with the respective inhibitor. Subsequently, tissues were re-exposed to STW 5 (256 μg mL^{-1}) which induced equivalent responses as in the absence of the respective inhibitor (black bars). The upper left panel (TTX) summarizes the results from a series of experiments with the fast sodium channel blocker TTX. TTX was used in a concentration of 0.5 μmol L^{-1}. The upper right panel (ω-CTX) summarizes the results from a series of experiments with the N-type Ca_V-channel blocker ω-CTX. ω-CTX was used in a concentration of 0.5 μmol L^{-1}. The lower left panel (CAP) summarizes the results from a series of experiments with CAP which was used in a concentration of 1 μmol L^{-1}. The lower right panel (L-NAME) summarizes the results from a series of experiments with the nitric oxide synthase inhibitor L-NAME. L-NAME was used in a concentration of 100 μmol L^{-1}. In all panels with the exception of the upper right panel, Fc denotes gastric fundus circular muscle strips, Fl denotes gastric fundus longitudinal muscle strips, Cc denotes gastric corpus circular muscle strips, Cl denotes gastric corpus longitudinal muscle strips, Ac denotes gastric antrum circular muscle strips and Al denotes gastric antrum longitudinal muscle strips. In the upper right panel, F denotes gastric fundus, C denotes corpus and A denotes antrum. Bars represent mean ± SEM of three to 11 tissues from as many different animals. There were no significant differences between STW 5-treated controls and any of the inhibitor-treated tissues.

Intriguingly, while STW 5 effects on gastric motility were highly region-specific, circular and longitudinal muscle layers in a given region responded in a similar manner when exposed to STW 5. This observation is in agreement with previous findings of synchronous motor activity of both gastric muscle layers[24] which is physiologically mediated by polarized muscle motor pathways in the gastric myenteric plexus and most likely subserves the specialized function of the stomach as a storage organ.[25]

Notably, in our study the STW 5-induced inhibitory effects on gastric motility were resistant to blockade of nerve conduction by tetrodotoxin, blockade of synaptic transmission by the N-type Ca_V-channel blocker ω-conotoxin GVIA, defunctionalization of capsaicin-sensitive primary afferents by capsaicin or blockade of NO synthesis by the nitric oxide synthase inhibitor L-NAME, suggesting that the action of STW 5 was not neurally mediated but rather reflecting a direct effect of STW 5 on smooth muscle cells. Nevertheless, we cannot completely rule out the involvement of neural tetrodotoxin-insensitive mechanisms and/or ω-conotoxin-insensitive neural calcium channels. While the specific mediators underlying the putative direct effects of STW 5 on smooth muscle cells are as yet unknown, the notion of a direct myogenic action of STW 5 is well in keeping with previous reports of calcium-antagonistic properties of herbal alkaloids or coumarins.[26,27]

Our data indicate that STW 5 appears to be able to exert differential effects on gastric motility. On the one hand, STW 5 decreases muscle tone in the gastric

fundus and corpus while on the other it enhances antral contractility. This amazing property can be best explained by the assumption that the individual components of this compound drug have differential effects on gastric motility. This conjecture is supported by earlier reports demonstrating that the dried extracts of the herbs contained in STW 5, namely chamomile flower, peppermint leaves, caraway fruit, liquorice root, lemon balm leaves, angelica root, greater celandine herbs and milk thistle fruit exert mainly spasmolytic properties, while the ethanolic fresh plant extracts of *Iberis amara* do not have such spasmolytic properties but have been shown to augment basal tone in relaxed guinea-pig ileum.[17,19] We have collected preliminary evidence to suggest that the relaxatory STW 5 effects on fundus and corpus are mimicked by angelica extract while its excitatory effects in the antrum can be reproduced by greater celandine,[28] but a thorough investigation of all herbal constituents of STW 5 and their interactions is required to fully depict the individual effects of all herbal extracts contained in STW 5 on gastric motility. However, our observations of differential STW 5 effects could also be interpreted to manifest differences in smooth muscle physiology of proximal *vs* distal stomach. Specifically, calcium-handling properties may be different in smooth muscle from the fundic/corpus region *vs* the antrum which would be well in keeping with our assumption of a calcium-mediated direct myogenic action of STW 5.

It is perceivable that the observed effects of STW 5 on gastric motility may mediate the symptomatic efficacy of this compound which has been evidenced in a series of controlled clinical trials.[11,12,15,17] Hence, our data could be interpreted to provide a pathogenetic rationale for the treatment of FD patients with STW 5 (Iberogast™). While the origin of FD symptoms is still relatively poorly understood, disturbed mechanosensory function is considered to be a key mechanism and impaired gastric accommodation together with antral hypomotility and abnormal gastric emptying have been repeatedly demonstrated in FD patients.[29–32] Furthermore, it has been proposed that disturbance of gastric relaxation and disordered gastric emptying may be related to symptom development in dysmotility-like FD.[29,30] Based on our findings it could thus be suggested that STW 5 is able to specifically improve those alterations in gastric motility that are crucial for the pathogenesis of dyspeptic symptoms in FD patients – namely relaxation of the proximal stomach and stimulation of the antrum. In turn, because it has been recommended to classify FD into three types based on symptomatology (ulcer-like dyspepsia, dysmotility-like dyspepsia and unspecified dyspepsia) and to treat accordingly,[33,34] it can be argued that STW 5 may be specifically useful in patients suffering from dysmotility-like FD. However, it is highly controversial if therapeutic responses are influenced by FD symptom subgroups and several clinical trials suggest that the predictive value of symptoms for therapeutic efficacies is low in FD patients.[3,33,35] Therefore, it is well conceivable that although our data suggest specific improvement of motility-associated FD symptoms by STW 5, treatment effects may not be limited to specific symptoms and STW 5 efficacy may not necessarily be limited to FD patient subgroups.[36] Based on its clinically proven efficacy and its good tolerability[17] in comparison with other currently available prokinetic drugs, STW 5 (Iberogast®) may thus be an attractive treatment approach for symptomatic relief in FD patients.

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