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Region-specific effects of STW 5 (Iberogast®) and its components in gastric fundus, corpus and antrum

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Abstract

Functional dyspepsia (FD) is a disorder that involves impaired gastric accommodation, antral hypomotility, and upper abdominal pain. The herbal drug STW 5 (Iberogast®) is used to successfully treat FD patients. Here, we report in vitro data revealing the mode of action of STW 5 and its individual herbal extracts on gastric motility. STW 5 evoked a relaxation of the proximal stomach but increased antral motility. Both effects are myogenic. The extracts of Angelica root, chamomile flower and liquorice root mimicked the inhibitory effects in the proximal stomach whereas the extracts of greater celandine herb, Melissa leaf, caraway fruit and bitter candy tuft increased motility of the proximal stomach. All extracts increased motility in the antrum comparable to the effects of STW 5. We conclude that the differential effects of STW 5 on proximal and distal stomach motor activity are not caused by solely spasmolytic or anti-spasmolytic effects of the individual components. It is suggested that the individual extracts target transduction mechanisms that are specifically expressed in the proximal vs. distal stomach. We present a rationale for the differential effect of STW 5 which is a result of the combined actions of its individual components and reason that the inhibitory effects in the proximal and the excitatory effects in the distal stomach may contribute to symptom relief in FD patients treated with STW 5 (Iberogast®).

Keywords: Gastric fundus; Corpus; Antrum; Iberogast®; *Iberis amara*

Introduction

Functional dyspepsia (FD) – also known as ''non-ulcer dyspepsia'' – is amongst the most commonly seen functional gastrointestinal disorders (Koloski et al., 2002). It is characterized and defined by upper gastrointestinal symptoms-like heartburn, dyspepsia, fullness in the upper abdomen, early satiety, bloating, epigastric pain, or nausea and vomiting which occur in the absence of a detectable organic cause. Even though the origin of symptoms in FD remains relatively poorly defined, the diagnosis is mainly based on symptomatology and the clinical picture (Malfertheiner et al., 2001; Talley et al., 1998). It has been proposed to subdivide FD into three types, namely ulcer-like dyspepsia, dysmotility-like dyspepsia and unspecified dyspepsia which is merely based on symptomatology. With respect to pathophysiology, it has been suggested that dysmotility-like dyspepsia reflects impaired gastric relaxation together with antral hypomotility and abnormal gastric emptying (Stanghellini et al., 1996; Tack et al., 1998; Troncon et al., 1994, 1995), and it has been subsequently recommended to preferentially treat dysmotility-like dyspepsia with gastroprokinetics and ulcer-like

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dyspepsia with acid-suppressive substances (Fisher and Parkman, 1998; Talley et al., 1998). However, the optimum treatment of FD is uncertain and the beneficial effect of most drugs is relatively small (Moayyedi et al., 2003). Moreover, many patients need to take their medication on a long-term basis to achieve symptomatic relief. Particularly herbal preparations are appealing to many patients because they are perceived as "natural" and hence harmless (Stickel et al., 2003), as well as relatively inexpensive. The therapeutic efficacy of herbal drug preparations to ameliorate dyspeptic symptoms in FD patients has been repeatedly demonstrated in prospective, placebo-controlled clinical trials (Madisch et al., 2001; Gundermann et al., 2003; Holtmann et al., 2003a, b, 2004; Rösch et al., 2006) and in one study, it was even found that the herbal multi-compound preparation STW 5 (Iberogast®, Steigerwald Arzneimittelwerk GmbH, Darmstadt, Germany) had equivalent efficacy as the well-characterized prokinetic synthetic drug cisapride (Allescher et al., 2001; Rösch et al., 2002).

STW 5 is a fixed combination of hydroethanolic herbal extracts from bitter candy tuft (STW 6), peppermint leaf (STW 5-KII), chamomile flower (STW 5-KIII), liquorice root (STW 5-KIV), Angelica root (STW 5-KV), caraway fruit (STW 5-KVI), milk thistle fruit (STW 5-KVII), Melissa leaf (STW 5-KVIII), and greater celandine herb (STW 5-KIX) each of which is reported to have multiple pharmacological properties relevant for gastrointestinal pathophysiology (Saller et al., 2002).

In contrast to the gastroprokinetic cisapride, the effects of STW 5 on gastric motility have been largely unknown. Therefore, the present study was designed to investigate these effects as well as the contribution of the individual components of STW 5 to the observed phenomena.

In vitro studies of gastric motility

Throughout these studies, we have used isometric tension transducers to record the in vitro motility of muscle strip preparations from the entire guinea pig stomach which were cut either along the circular or the longitudinal muscle axis of fundus, corpus and antrum (Hohenester et al., 2004).

In all experiments, changes in muscle tension were calculated in comparison to pre-treatment baseline tension and expressed as mN. Treatment groups were compared using paired Student's *t*-tests and statistical significance was assumed if $p<0.05$.

Because no significant differences were observed between the responses from muscle strips cut in circular vs. longitudinal orientation, results from circular and longitudinal muscle strips were pooled for the final analyses which are presented here.

Effects of STW 5 on gastric motility

In this study, STW 5 was used as an ethanol-free lyophilisate (kindly provided by Steigerwald Arzneimittelwerk GmbH, Darmstadt, Germany) to avoid potentially confounding ethanol effects. Ethanol itself is well known to exert concentration-dependent effects on gastrointestinal motility (Wall et al., 1987).

The lyophilized STW 5 was dissolved in Krebs' buffer and added to mounted muscle strips in final concentrations ranging from 32 to 512 µg/ml. Dose-response studies were carried out in tissues from all gastric regions in a non-cumulative manner, with several wash out periods in between. In this set of experiments, STW 5 consistently evoked sustained relaxations of both fundus (mean relaxation in response to 512 µg/ml: $57.5\pm2.1\%$ of baseline tone; $p<0.05$) (Fig. 1A) and corpus (mean relaxation in response to 512 µg/ml: $56.5\pm5.1\%$ of baseline tone; $p<0.05$) (Fig. 1B) muscle strips in a dose-dependent manner. The decreases in muscle tone occured with a delayed onset, were not paralleled by changes in phasic activity, and were fully reversible upon wash-out without any residual stimulatory effects of STW 5 on basal muscle-tone (Hohenester et al., 2004). In addition to its robust inhibitory effects, STW 5 evoked immediate but small and transient increases in muscle tone in a fraction of the fundus and corpus muscle strips. This effect was not concentration-dependent and could not be further analyzed due to its unsteady nature (Hohenester et al., 2004).

In muscle strips from the antrum, STW 5 consistently induced immediate and long-lasting increases in contractile force even at the lowest concentration used (mean increase in response to 512 µg/ml: $73.1\pm4.6\%$ of baseline amplitude; $p<0.05$) (Fig. 1C). In these tissues, STW 5 augmented contraction amplitudes of the ongoing phasic activity without significantly affecting contraction frequencies (Fig. 2A); the STW 5-effects were dose-dependent (Fig. 1C) and fully reversible after wash-out.

As previously shown, the sustained STW 5-effects were resistant to pre-treatment with the fast sodium channel blocker tetrodotoxin, the synaptic transmission blocker ω-conotoxin GVIA, and defunctionalization of capsaicin sensitive primary afferents by long-term application of capsaicin (Hohenester et al., 2004). Moreover, the STW 5-induced significant increase in the contractile force of antral phasic contractions could not be blocked by the muscarinergic antagonist atropine (Hohenester et al., 2004). This provides evidence that the observed STW 5-effects are not nerve-mediated and very likely reflect a direct effect of STW 5 on smooth muscle cells. Blockade of NO-synthesis by the nitric oxide synthase inhibitor L-NAME could not block the STW 5-induced muscle relaxation, indicating that nitric

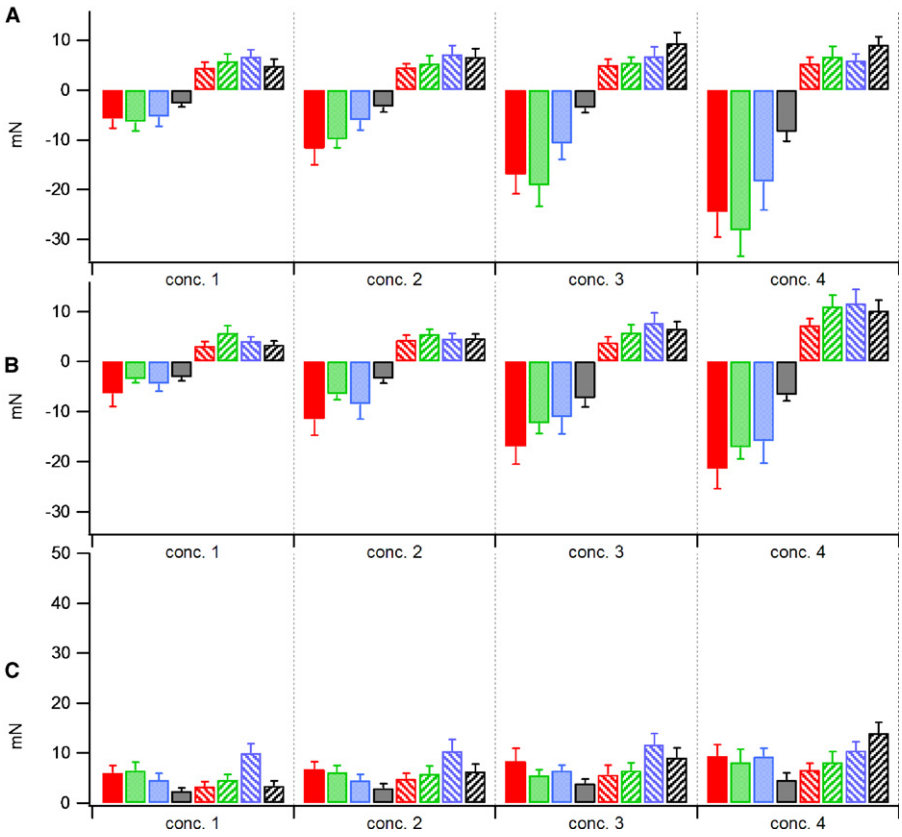

Fig. 1. Effects of different concentrations of STW 5 and its constituents on the motility of guinea pig stomach fundus (A), corpus (B) and antrum (C). "conc. 1" to "conc. 4" on the *X*-axis denote, in ascending order, the different concentrations used. These were for STW 5: 64, 128, 256, and 512 µg/ml, respectively; for bitter candy tuft extract (STW 6): 40, 81, 162, and 324 µg/ml; and for all other components: 24, 47, 94, and 188 µg/ml. The bars show the mean relaxatory (negative values) or contractile (positive values) effects for STW 5 and 7 of its constituents: ( ) STW5; ( ) Angelica root extract (STW 5-KV); ( ) Chamomile flower extract (STW 5-KIII); ( ) liquorice root extract (STW 5-KIV); ( ) bitter candy tuft extract (STW 6); ( ) caraway fruit extract (STW 5-KVI); ( ) lemon balm leaf extract (STW 5-KVIII); ( ) greater celandine herb extract (STW 5-KIX). Error bars denote standard error of the mean. STW 5 and STW5-KV, STW 5-KIII, and STW 5-KIV consistenly induced relaxation of smooth muscle preparations from fundus (A) and corpus (B), whereas STW 6, STW 5-KVI, STW 5-KVIII, and STW 5-KIX had contractile effects in fundus (A) and corpus (B). In smooth muscle strips from the antrum, STW 5 as well as STW 5-KV, STW 5-KIII, STW 5-KIV, STW 6, STW 5-KVI, STW 5-KVIII, and STW 5-KIX augmented the amplitudes of the phasic contractile activity. All effects were statistically significant ($p<0.05$) as compared to the respective control groups.

oxide pathways are also not involved in this response (Hohenester et al., 2004).

In summary, the application of an ethanol-free lyophilisate of STW 5 on muscle strips from all regions of the guinea pig stomach has provided strong evidence that STW 5 exerts multiple, region-specific effects on gastric motility. One possible explanation for this property could be that the individual components of the compound drug STW 5 have differential effects on gastric motility and that the overall actions of STW 5 reflects the activity profiles of its individual compounds and their interactions.

To test this hypothesis, we have performed a thorough investigation of all herbal constituents of STW 5 to fully depict the individual effects of all herbal extracts contained in STW 5 on gastric motility and to identify which extracts are specifically responsible for the inhibitory and excitatory STW 5-effects.

Effects of the single components of STW 5 on gastric motility

The experimental protocol used to study the effects of the individual compounds of STW 5 was analogous to the protocol used during the STW 5-experiments: The hydroethanolic herbal extracts constituting STW 5 were used as ethanol-free lyophilisates (kindly provided by Steigerwald Arzneimittelwerk GmbH, Darmstadt, Germany) which were dissolved in Krebs' buffer and individually added to mounted circular and longitudinal muscle strips. The final concentrations ranged

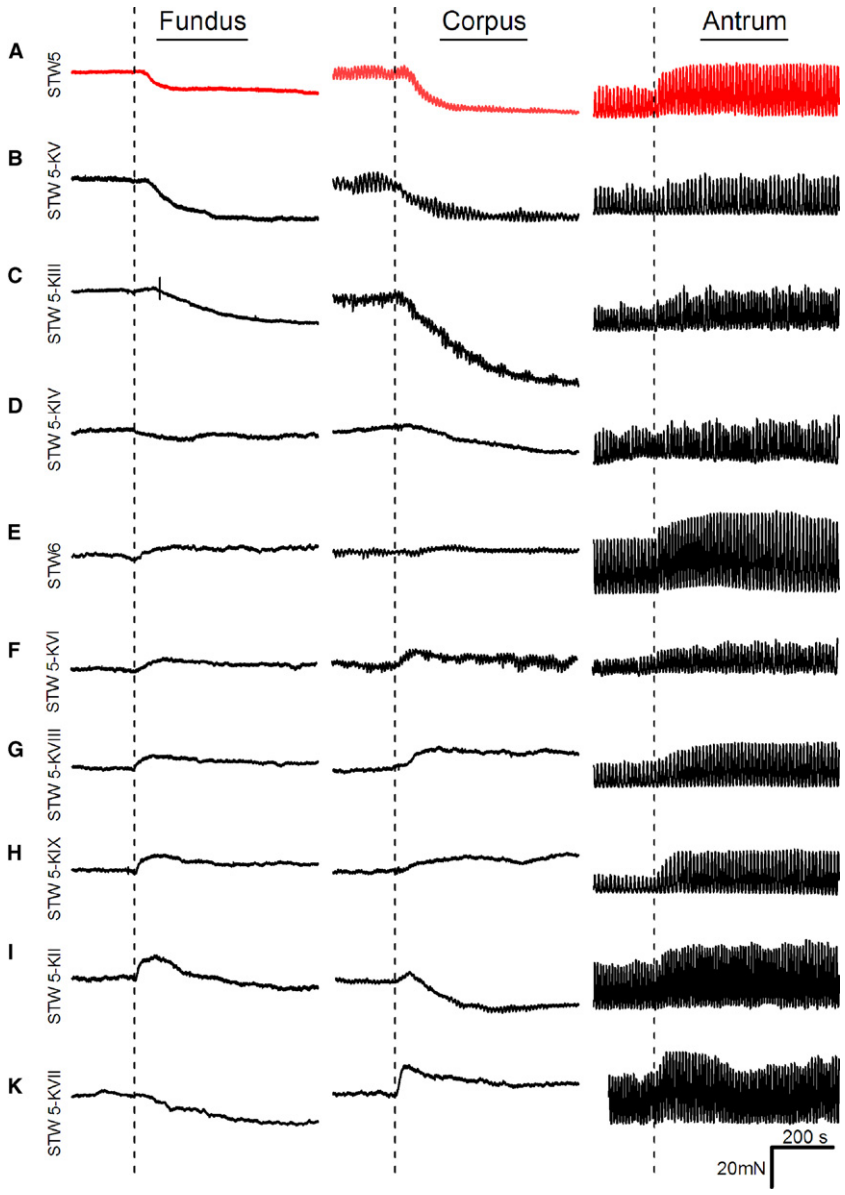

Fig. 2. Representative examples for the effects of STW 5 and its components on the contractility of smooth muscle preparations from guinea pig fundus (left-hand row of traces), corpus (middle row of traces) and antrum (right-hand row of traces). The traces are taken from different experiments; the scale bars in the lower right corner are valid for all traces. The dashed lines indicate when the respective drug was added to the organ bath. Shown are the responses to (A) STW 5, 256 µg/ml; (B) STW 5-KV (Angelica root extract), 94 µg/ml; (C) STW5-KIII (chamomile flower extract), 94 µg/ml; (D) STW 5-KIV (liquorice root extract), 94 µg/ml; (E) STW 6 (bitter candy tuft extract), 162 µg/ml; (F) STW 5-KVI (caraway fruit extract), 94 µg/ml; (G) STW 5-KVIII (Melissa leaf extract), 94 µg/ml; (H) STW 5-KIX (greater celandine herb extract), 94 µg/ml; (I) STW 5-KII (peppermint leaf extract), 94 µg/ml; and (K) STW 5-KVII (milk thistle fruit extract), 94 µg/ml.

from 40 to 324 µg/ml for *bitter candy tuft* (STW 6) and from 24 to 188 µg/ml for all other compounds (STW 5-KII to KIX). As for STW 5, dose-response studies were carried out in tissues from all gastric regions in a non-cumulative manner. For analysis, circular and longitudinal muscle strips from each region were pooled because there were no obvious differences in their responses to any compound studied. Changes in muscle tension were calculated in comparison to pre-treatment baseline tension and expressed as mN. Treatment groups were compared using paired Student's *t*-tests and statistical significance was assumed if $p < 0.05$.

Effects of the single components of STW 5 on proximal stomach motility

Three out of the 9 plant extracts constituting STW 5 mimicked the effects of STW 5 on gastric fundus and

corpus and consistently evoked a sustained and reversible relaxation of both circular and longitudinal muscle strips from gastric fundus and corpus. These were angelica root extract (STW 5-KV), chamomile flower extract (STW 5-KIII), and liquorice root extract (STW 5-KIV) (Figs. 1A, B and 2B–D). Similar to STW 5, STW 5-KV, KIII and KIV induced significant decreases in muscle tone which were concentration-dependent (Fig. 1A and B) and displayed a delayed onset of action (Fig. 2B–D). Further, these relaxations were fully reversible upon wash-out.

Angelica root extract (STW 5-KV) was the strongest relaxant of the proximal stomach and closely mimicked STW 5 effects; at the highest concentration it reduced fundus and corpus muscle tone by 59.1±3.5% and 59.5±4.0%, respectively (Fig. 1A and B). STW 5 K-V also mimicked the stimulatory STW 5 effects in the antrum by increasing contraction amplitudes at the highest concentration by 66.5±29.0% (Fig. 1C). Chamomile flower extract (STW 5-KIII) evoked a relaxation by decreasing the fundus and corpus tone by 29.6±7.0% and 37.2±5.3%, respectively, at the highest concentration (Fig. 1A and B). A relatively smaller, but still significant relaxation was observed with liquorice root extract (STW 5-KIV) that relaxed the fundus and corpus by 21.9±3.7% and 21.7±3.1%, respectively, at the highest concentration (Fig. 1A and B).

In contrast, four out of the 9 plant extracts constituting STW 5 failed to induce relaxations in gastric fundus or corpus muscle strips but rather evoked contractions. These were greater celandine herb extract (STW 5-KIX), melissa leaf extract (STW 5-KVIII), caraway fruit extract (STW 5-KVI), and bitter candy tuft extract (STW 6) (Figs. 1 and 2E–H). The contractile effects of those extracts were rather small, yet significant.

The remaining two herbal extracts contained in STW 5 – namely peppermint leaf extract (STW 5-KII) and milk thistle fruit extract (STW 5-KVII) – did not show consistent responses. In the proximal stomach, both extracts induced either contraction or relaxation (Figs. 2I, K, 3A, B and 4A, B). In some tissues, the observed effects (either contractions or relaxations) were reproducible and increased with higher drug concentrations, while in other tissues application of higher drug concentrations did not increase the previously observed responses but rather reversed the response from contraction to relaxation (Figs. 3A, B and 4A, B). Notably, reversals from initial relaxation to contraction with increasing drug concentration were rarely observed. Both, peppermint leaf extract and milk thistle fruit extract evoked additional immediate and transient increases in muscle tone in a fraction of the fundus and corpus muscle strips which were followed either by a sustained relaxation, contraction or by a return of the muscle tone to basal levels (Fig. 2I and K).

Effects of the single components of STW 5 on distal stomach motility

While the individual extracts exerted inhibitory or excitatory effects in the proximal stomach, all extracts, except two which had no consistent effects at all, evoked a contractile response in the antrum (Figs. 1C and 2B–H). The responses were immediate, long-lasting and fully reversible after wash-out, thus mimicking the exclusively excitatory effects of STW 5 on antral motility (Fig. 2A–K). The mean increase in antral contraction amplitudes for the highest concentration of each extract were: 188.9±27.1% for STW 5-KIX (greater celandine herb extract); 177.3±99.1% for STW 5-KVIII (Melissa leaf extract); 114.9±28.9% for STW 5-KIII (chamomile flower extract); 112.4±33.2% for STW 6 (bitter candy tuft extract); 71.9±16.2% for STW 5-KVI (caraway fruit extract); 66.5±29.0% for STW 5-KV (Angelica root extract); and 38.8±7.9% for STW 5-KIV (liquorice root extract) (Fig. 1C). Peppermint leaf extract (STW 5-KII) and milk thistle fruit extract (STW 5-KVII) did not have any consistent effect on antral contractility (Figs. 3C and 4C): In a fraction of the antral muscle strips, they enhanced contraction amplitudes (Figs. 2I, K, 3C and 4C), but due to the unsteady nature of these effects and the lack of concentration-dependency, this did not reach the level of statistical significance. None of the extracts had any inhibitory effects on antral motility.

How do the STW 5 effects relate to the action of its individual components?

We have provided evidence that the herbal compound drug STW 5 (Iberogast®) has profound, yet differential effects on gastric motility. In our experimental set-up, STW 5 significantly and dose-dependently decreased muscle tone in the gastric fundus and corpus while it enhanced antral contractility. Furthermore, we have found that three out of the 9 extracts constituting STW 5 closely mimicked the inhibitory effects of STW 5 on muscle tone in the proximal stomach, namely angelica root extract, chamomile flower extract and liquorice root extract. In contrast, four out of the remaining six extracts significantly enhanced the muscle tone in fundus and corpus; these were greater celandine herb extract, lemon balm leaf extract, caraway fruit extract and bitter candy tuft extract.

A discussion of the mechanisms putatively underlying these effects would be inevitably speculative. The scientific literature contains numerous reports on the effects of herbal preparations on smooth muscle activity. Some findings are apparently contradictory which is not surprising considering the different experimental

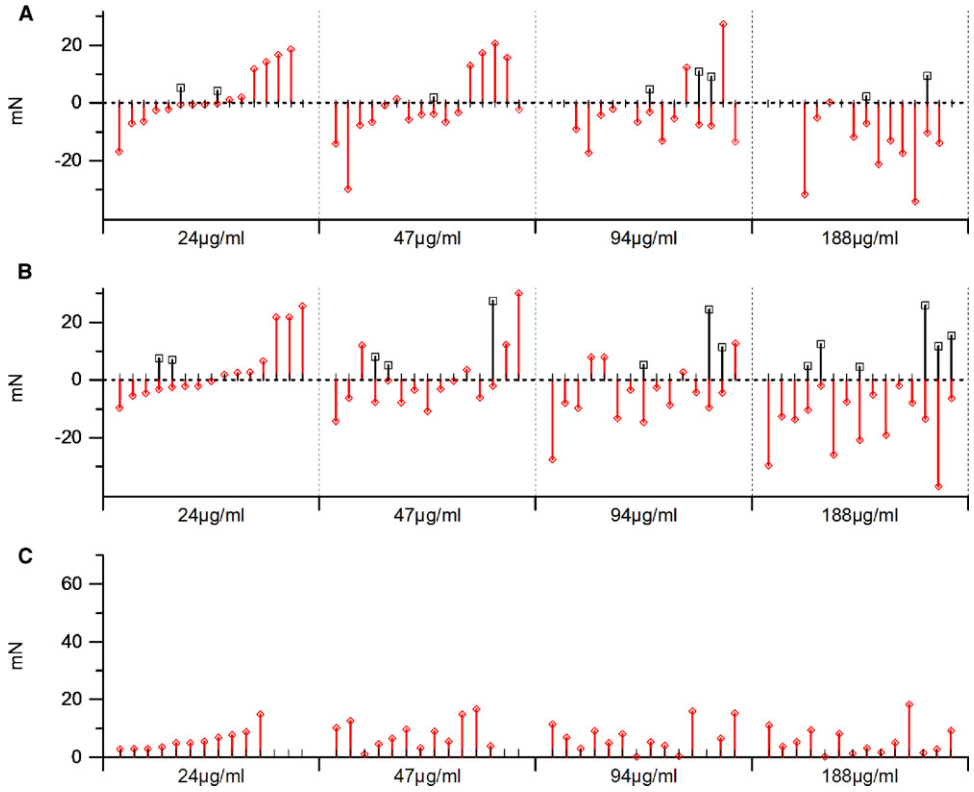

Fig. 3. Peppermint leaf extract (STW 5-KII) had irregular motility effects in gastric fundus and corpus muscle strips, and inconsistent contractility-enhancing effects in the antrum. For each concentration, a given point on the *X*-axis represents the response of a specific tissue when exposed to the indicated concentration of STW 5-KII. For each gastric region, corresponding points on the *X*-axis represent the responses of the same tissue to different concentrations of STW 5-KII. The different response types are coded: Points *below* the *X*-axis represent relaxatory responses; the strength of a given response can be read on the *Y*-axis. Points *above* the *X*-axis represent contractile responses; the strength of these responses is also indicated on the *Y*-axis. In addition, sustained (red diamonds) vs. transient (black squares) responses are marked differently. (A) In the fundus, lower concentrations of STW 5-KII evoked sustained contractions or relaxations. With higher concentrations, however, lower numbers of tissues displayed contractile responses. (B) Similar observations were made in the corpus region. In addition, the number of tissues with a transient contractile response also increased with drug concentrations. (C) In the antrum, STW 5-KII mostly induced weak contractile responses. However, due to its unsteady nature, this effect did not reach the level of statistical significane. Inhibitory effects of STW 5-KII on antral motility were not observed.

conditions. Data were obtained using different smooth muscle preparations from different species, and researchers have used different concentrations of ethanolic or ethanol-free extracts derived from various compositions or fractions of the herbal drugs (Reiter and Brandt, 1985; Hawthorn et al., 1988; Hills and Aaronson 1991; Harmala et al., 1992; Colombo and Bosisio 1996; Hiller et al., 1998; Boskabady and Shaikhi, 2000; Micklefield et al., 2000, 2003; Gansauge et al., 2002; Reichling and Saller, 2002; Saller et al., 2002; Boskabady et al., 2003; Carle, 2003; Hiki et al., 2003; Hoffmann-Bohm et al., 2003; Liersch et al., 2003; Reichling and Saller, 2003; Schöpke, 2003; Stahl-Biskup, 2003a, b; Vieweger, 2003; Vogt et al., 2005).

In our experiments, we have identified plant extracts with purely contractile effects and plant extracts with mixed relaxatory and contractile effects in proximal vs. distal stomach, but we did not find a single extract that exerted only relaxatory effects, both in proximal and distal stomach. The motility-enhancing effects of STW 5 and all of its individual compounds in the antrum were much weaker than the relaxatory effects of STW 5 and *Angelica* root extract, chamomile flower extract and liquorice root extract, respectively, in the proximal stomach. For the pure contractility-enhancers in the proximal stomach, the rank-order of potency was similar in antrum and fundus/corpus (greater celandine herb extract ⩾ lemon balm leaf extract ⩾ caraway fruit extract ⩾ bitter candy tuft fresh plant extract). Intriguingly, those drugs that induced the strongest relaxatory responses in the proximal stomach also had very pronounced contractility-enhancing effects in the antrum with a comparable rank-order of potency.

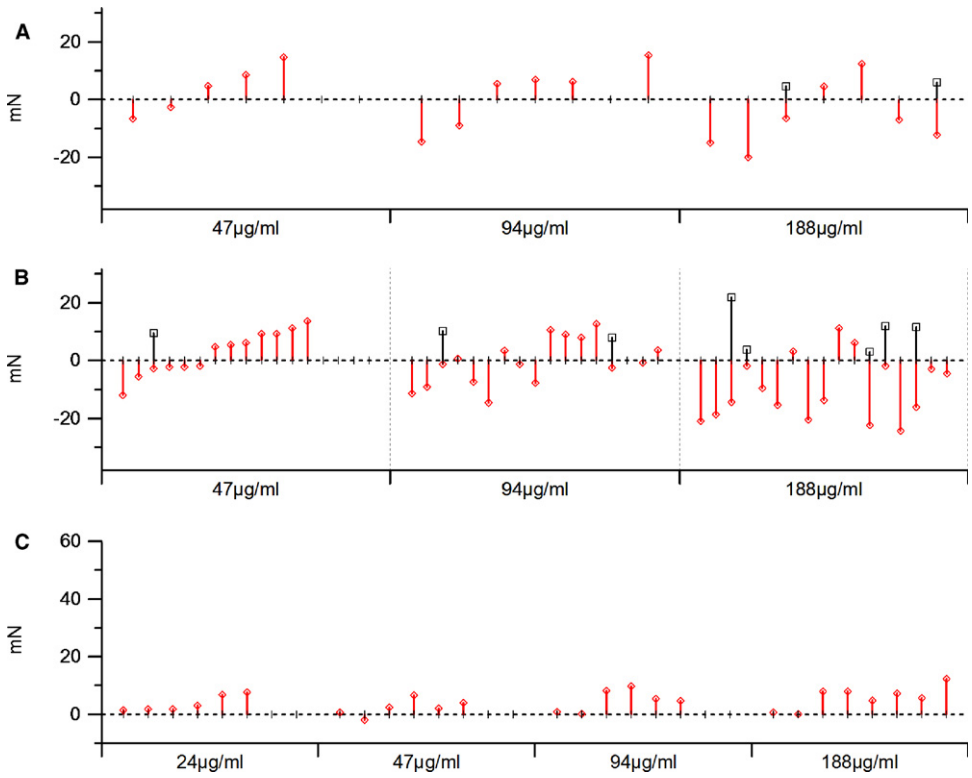

Fig. 4. Milk thistle fruit extract (STW 5-KVII) had irregular motility effects in gastric fundus and corpus muscle strips, and inconsistent contractility-enhancing effects in the antrum. For each concentration, a given point on the *X*-axis represents the response of a specific tissue when exposed to the indicated concentration of STW 5-KVII. For each gastric region, corresponding points on the *X*-axis represent the responses of the same tissue to different concentrations of STW 5-KVII. The different response types are coded: Points *below* the *X*-axis represent relaxatory responses; the strength of a given response can be read on the *Y*-axis. Points *above* the *X*-axis represent contractile responses; the strength of these responses is also indicated on the *Y*-axis. In addition, sustained (red diamonds) vs. transient (black squares) responses are marked differently. (A) In the fundus, sustained contractions and relaxations occured for all concentrations of STW 5-KVII used. Small transient contractions were observed only in two experiments with the highest STW 5-KVII concentration that was studied. (B) Similar observations were made in the corpus region. In addition, the number of tissues with a transient contractile response increased with drug concentrations. (C) In the antrum, STW 5-KVII had a trend towards enhancing motility; however, due to its unsteady nature, this effect did not reach the level of statistical significance. Inhibitory effects of STW 5-KII on antral motility were not observed.

These results indicate that our initial contention, namely that the differential effects of STW 5 on fundus/corpus vs. antrum motility reflected the differential effects of its individual components with some acting to decrease muscle tone in the proximal stomach, and others to enhance antral contractility, has to be revised. Instead, our results suggest that the same compound has one specific effect in fundus/corpus muscle strips and simultaneously the opposite effect in antral muscle strips. The observation that the effects of STW 5 – and very likely also those of its individual components – are not nerve-mediated (Hohenester et al., 2004), together with the finding that the same phytochemical can exert differential effects in the proximal vs. distal stomach, most likely suggests differences in smooth muscle physiology of proximal vs. distal stomach. Assuming a calcium-mediated direct myogenic action of STW 5 (Kong et al., 1986; Harmala et al., 1992), our data could reflect different calcium-handling properties in gastric fundus/corpus smooth muscle vs. antrum smooth muscle. In this scenario, the differential effects of the drug extracts could be interpreted to manifest selective actions of the extracts on various ion channels and/or signal transduction pathways.

We have previously shown that STW 5 frequently induces small transient contractions in the proximal stomach (Hohenester et al., 2004). This effect always preceded the dominant and sustained relaxatory response, strongly indicating that those components of STW 5 that relax the smooth muscle in the proximal stomach have the potential to overpower components that induce a contractile response if given alone.

The finding that none of the individual extracts inhibits smooth muscle contractility in the antrum further supports the notion that the molecular machinery in the distal stomach must differ from that in the

proximal stomach, the latter favoring relaxation over contraction.

Relevance of our results for the clinical situation

To our knowledge, this is the first systematic report directly demonstrating an effect of individual plant extracts – alone and in combination – on gastric motility. Our data demonstrate that STW 5 and its component extracts profoundly alter gastric motility in a highly region-specific, but not layer-specific manner and thus provide a pathogenetic rationale for the efficacy of STW 5 in the treatment of FD patients which has already been well-established in clinical studies (Madisch et al., 2001; Rösch et al., 2002; Saller et al., 2002; Gundermann et al., 2003; Rösch et al., 2006).

Although the etiopathophysiology of this functional gastrointestinal disorder is still unclear, there is growing evidence that dysregulation of gastrointestinal motility may contribute to the complaints of at least a subset of FD-patients: dyspepsia has been associated with disturbed gastric emptying – physiologically perceived to reflect antral hypomotility – and abnormalities in proximal gastric function, including impaired fundus accommodation with consecutive hypersensitivity to distension (Stanghellini et al., 1996, 1999; Cuomo et al., 2001; Sarnelli et al., 2003; Locke et al., 2005). Therefore, the region-specific STW 5-effects that we are reporting here, with a relaxation of the proximal stomach and a stimulation of the antrum, appears to be highly appropriate to correct gastric motility disorders associated with FD.

Finally, we have evidence that our data and conclusions are applicable to human gastric motility. Preliminary experiments on muscle preparations from human stomach revealed that STW 5 has a powerful relaxing effect in the proximal stomach (256 µg/ml: -6.2 ± 2.1 mN ($n = 4$), 512 µg/ml: -6.4 ± 1.5 mN ($n = 3$), corresponding to a reduction of $10.5 \pm 3.6\%$ and $9.0 \pm 2.5\%$ of baseline tone, respectively), very much comparable to what we have observed in the guinea-pig stomach (Fig. 5).

Fig. 5. As in the guinea pig proximal stomach, STW 5 induced a sustained relaxation of a smooth muscle strip from the human stomach (shown is a circular muscle preparation from corpus). The addition of STW 5 to the organ bath is marked with an arrow.

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References

Allescher, H.D., Bockenhoff, A., Knapp, G., Wienbeck, M., Hartung, J., 2001. Treatment of non-ulcer dyspepsia: a meta-analysis of placebo-controlled prospective studies. Scand. J. Gastroenterol. 36, 934–941.

Boskabady, M.H., Shaikhi, J., 2000. Inhibitory effect of *Carum copticum* on histamine (H1) receptors of isolated guinea-pig tracheal chains. J. Ethnopharmacol. 69, 217–227.

Boskabady, M.H., Ramazani, M., Tabei, T., 2003. Relaxant effects of different fractions of essential oil from *Carum copticum* on guinea pig tracheal chains. Phytother. Res. 17, 1145–1149.

Carle, R., 2003. Chamomilla. HagerROM, Springer, Heidelberg; HN.

Colombo, M.L., Bosisio, E., 1996. Pharmacological activities of *Chelidonium majus* L. (Papaveraceae). Pharmacol. Res. 33, 127–134.

Cuomo, R., Sarnelli, G., Grasso, R., Bruzzese, D., Pumpo, R., Salomone, M., Nicolai, E., Tack, J., Budillon, G., 2001. Functional dyspepsia symptoms, gastric emptying and satiety provocative test: analysis of relationships. Scand. J. Gastroenterol. 36, 1030–1036.

Fisher, R.S., Parkman, H.P., 1998. Management of nonulcer dyspepsia. N. Engl. J. Med. 339, 1376–1381.

Gansauge, F., Ramadani, M., Pressmar, J., Gansauge, S., Muehling, B., Stecker, K., Cammerer, G., Leder, G., Beger, H.G., 2002. NSC-631570 (Ukrain) in the palliative treatment of pancreatic cancer. Results of a phase II trial. Langenbecks Arch. Surg. 386, 570–574.

Gundermann, K.J., Godehardt, E., Ulbrich, M., 2003. Efficacy of a herbal preparation in patients with functional dyspepsia: a meta-analysis of double-blind, randomized, clinical trials. Adv. Ther. 20, 43–49.

Harmala, P., Vuorela, H., Tornquist, K., Hiltunen, R., 1992. Choice of solvent in the extraction of *Angelica archangelica* roots with reference to calcium blocking activity. Planta Med. 58, 176–183.

Hawthorn, M., Ferrante, J., Luchowski, E., Rutledge, A., Wei, X.Y., Triggle, D.J., 1988. The actions of peppermint oil and menthol on calcium channel dependent processes in intestinal, neuronal and cardiac preparations. Aliment. Pharmacol. Ther. 2, 101–118.

Hiki, N., Kurosaka, H., Tatsutomi, Y., Shimoyama, S., Tsuji, E., Kojima, J., Shimizu, N., Ono, H., Hirooka, T., Noguchi, C., Mafune, K., Kaminishi, M., 2003. Peppermint oil reduces gastric spasm during upper endoscopy: a randomized, double-blind, double-dummy controlled trial. Gastrointest. Endosc. 57, 475–482.

Hiller, K.O., Ghorbani, M., Schilcher, H., 1998. Antispasmodic and relaxant activity of chelidonine, protopine, coptisine, and *Chelidonium majus* extracts on isolated guinea-pig ileum. Planta Med. 64, 758–760.

Hills, J.M., Aaronson, P.I., 1991. The mechanism of action of peppermint oil on gastrointestinal smooth muscle. An analysis using patch clamp electrophysiology and isolated tissue pharmacology in rabbit and guinea pig. Gastroenterology 101, 55–65.

Hoffmann-Bohm, K., Stahl-Biskup, E., Gorecki, P., 2003. Chelidonium. HagerROM, Springer, Heidelberg; HN: 2021200.

Hohenester, B., Ruhl, A., Kelber, O., Schemann, M., 2004. The herbal preparation STW5 (Iberogast®) has potent and region-specific effects on gastric motility. Neurogastroenterol. Motil. 16, 765–773.

Holtmann, G., Adam, B., Haag, S., Collet, W., Grunewald, E., Windeck, T., 2003a. Efficacy of artichoke leaf extract in the treatment of patients with functional dyspepsia: a six-week placebo-controlled, double-blind, multicentre trial. Aliment. Pharmacol. Ther. 18, 1099–1105.

Holtmann, G., Haag, S., Adam, B., Funk, P., Wieland, V., Heydenreich, C.J., 2003b. Effects of a fixed combination of peppermint oil and caraway oil on symptoms and quality of life in patients suffering from functional dyspepsia. Phytomedicine 10 (Suppl. 4), 56–57.

Holtmann G, Adam B, Vinson, B., 2004. Evidenz-basierte Medizin und Phytotherapie bei funktioneller Dyspepsie und Reizdarmsyndrom: Eine systematische Analyse der verfügbaren Evidenz zum Präparat Iberogast®. Wiener Medizinische Wochenschrift, Nr. 154/21–22.

Koloski, N.A., Talley, N.J., Boyce, P.M., 2002. Epidemiology and health care seeking in the functional GI disorders: a population-based study. Am. J. Gastroenterol. 97, 2290–2299.

Kong, Y.C., Lee, C.M., Wong, M.K., Xu, S.B., 1986. Smooth muscle relaxant effect of dehydroindicolactone. Gen. Pharmacol. 17, 593–595.

Liersch, R., Grimminger, W., Leng-Peschlow, E., Mengs, U., 2003. HagerROM, Springer, Heidelberg; HN: 2052100.

Locke III, G.R., Zinsmeister, A.R., Fett, S.L., Melton III, L.J., Talley, N.J., 2005. Overlap of gastrointestinal symptom complexes in a US community. Neurogastroenterol. Motil. 17, 29–34.

Madisch, A., Melderis, H., Mayr, G., Sassin, I., Hotz, J., 2001. A plant extract and its modified preparation in functional dyspepsia. Results of a double-blind placebo controlled comparative study. Z. Gastroenterol. 39, 511–517.

Malfertheiner, P., Holtmann, G., Peitz, U., Birkner, B., Arnold, R., Hotz, J., Leodolter, A., Mossner, J., Robra, B.P., 2001. Guidelines of the German Society of Digestive and Metabolic Diseases for treatment of dyspepsia. Z. Gastroenterol. 39, 937–956.

Micklefield, G.H., Greving, I., May, B., 2000. Effects of peppermint oil and caraway oil on gastroduodenal motility. Phytother. Res. 14, 20–23.

Micklefield, G., Jung, O., Greving, I., May, B., 2003. Effects of intraduodenal application of peppermint oil (WS® 1340) and caraway oil (WS® 1520) on gastroduodenal motility in healthy volunteers. Phytother. Res. 17, 135–140.

Moayyedi, P., Soo, S., Deeks, J., Delaney, B., Innes, M., Forman, D., 2003. Pharmacological interventions for non-ulcer dyspepsia. Cochrane Database Syst. Rev. CD001960.

Reichling, J., Saller, R., 2002. *Iberis amara* L. (bitter candytuft) – profile of a medicinal plant. Forsch. Komplementarmed. Klass. Naturheilkd. 9 (Suppl. 1), 21–33.

Reichling, J., Saller, R., 2003. Iberis. HagerROM, Springer, Heidelberg; HN: 2001400.

Reiter, M., Brandt, W., 1985. Relaxant effects on tracheal and ileal smooth muscles of the guinea pig. Arzneimittelforschung 35, 408–414.

Rösch, W., Vinson, B., Sassin, I., 2002. A randomised clinical trial comparing the efficacy of a herbal preparation STW 5 with the prokinetic drug cisapride in patients with dysmotility type of functional dyspepsia. Z. Gastroenterol. 40, 401–408.

Rösch, W., Liebregts, T., Gundermann, K.-J., Vinson, B., Holtmann, G., 2006. Phytotherapy for functional dyspepsia: A review of the clinical evidence for the herbal preparation STW 5. Phytomedicine 13 (Suppl. v), 114–121.

Saller, R., Pfister-Hotz, G., Iten, F., Melzer, J., Reichling, J., 2002. Iberogast: a modern phytotherapeutic combined herbal drug for the treatment of functional disorders of the gastrointestinal tract (dyspepsia, irritable bowel syndrome) – from phytomedicine to "evidence based phytotherapy. A systematic review. Forsch. Komplementarmed. Klass. Naturheilkd. 9 (Suppl. 1), 1–20.

Sarnelli, G., Caenepeel, P., Geypens, B., Janssens, J., Tack, J., 2003. Symptoms associated with impaired gastric emptying of solids and liquids in functional dyspepsia. Am. J. Gastroenterol. 98, 783–788.

Schöpke, T., 2003. Glycyrrhiza. HagerROM, Springer, Heidelberg; HN, 2021000.

Stahl-Biskup, E., 2003a. Carum. HagerROM, Springer, Heidelberg; HN: 2004000.

Stahl-Biskup, E., 2003b. Melissa. HagerROM, Springer, Heidelberg; HN, 2037900.

Stanghellini, V., Tosetti, C., Paternic, M.A., Barbara, G., Morselli-Labate, A.M., Monetti, N., Marengo, M., Corinaldesi, R., 1996. Risk indicators of delayed gastric emptying of solids in patients with functional dyspepsia. Gastroenterology 110, 1036–1042.

Stanghellini, V., Tosetti, C., Paternico, A., De Giorgio, R., Barbara, G., Salvioli, B., Corinaldesi, R., 1999. Predominant symptoms identify different subgroups in functional dyspepsia. Am. J. Gastroenterol. 94, 2080–2085.

Stickel, F., Poschl, G., Seitz, H.K., Waldherr, R., Hahn, E.G., Schuppan, D., 2003. Acute hepatitis induced by Greater Celandine (*Chelidonium majus*). Scand. J. Gastroenterol. 38, 565–568.

Tack, J., Piessevaux, H., Coulie, B., Caenepeel, P., Janssens, J., 1998. Role of impaired gastric accommodation to a meal in functional dyspepsia. Gastroenterology 115, 1346–1352.

Talley, N.J., Silverstein, M.D., Agreus, L., Nyren, O., Sonnenberg, A., Holtmann, G., 1998. AGA technical review: evaluation of dyspepsia. American Gastroenterological Association. Gastroenterology 114, 582–595.

Troncon, L.E., Bennett, R.J., Ahluwalia, N.K., Thompson, D.G., 1994. Abnormal intragastric distribution of food during gastric emptying in functional dyspepsia patients. Gut 35, 327–332.

Troncon, L.E., Thompson, D.G., Ahluwalia, N.K., Barlow, J., Heggie, L., 1995. Relations between upper abdominal symptoms and gastric distension abnormalities in dysmo-

tility like functional dyspepsia and after vagotomy. Gut 37, 17–22.

Vieweger, U., 2003. Angelica. HagerROM, Springer, Heidelberg; HN: 2015800.

Vogt, A., Tamewitz, A., Skoko, J., Sikorski, R.P., Giuliano, K.A., Lazo, J.S., 2005. The benzo (C) phenanthridine alkaloid, sanguinarine, is a selective, cell-active inhibitor of mitogen-activated protein kinase phosphatase-1. J. Biol. Chem.

Wall, F.A., Suer, A.H., Hayter, A., Tugwell, A.C., 1987. The effect of ethanol on spontaneous contractions and on the contraction produced by periarterial nerve stimulation and by acetylcholine in the rat isolated ileum. Gen. Pharm.: Vasc. Syst. 18, 631–635.