REVIEW

The relevance of transient lower oesophageal sphincter relaxations in the pathophysiology and treatment of GORD

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ABSTRACT

Gastro-oesophageal reflux disease (GORD) is associated with the passage of gastric contents into the oesophagus resulting in potential oesophageal damage and impaired quality of life. GORD is a frequently encountered problem in today's population, with 25% of people in western populations reporting such symptoms at least once a month. Proton pump inhibitors (PPI) are the drug of choice, with surgery being employed in refractory cases. Although acid suppression is often effective, some patients remain symptomatic despite maximal PPI therapy. By delving into the mechanisms of the disease, it is clear that transient lower oesophageal sphincter relaxations are a key component of its pathophysiology. Research has demonstrated various therapeutic targets for reducing the frequency of such relaxations through GABA and glutamate modulation, for instance. This review highlights such modulations and hopes to explore these mechanisms and therapeutic targets in an area that will no doubt see a change in its pharmacological management in the near future.

TRANSIENT LOWER OESOPHAGEAL SPHINCTER RELAXATIONS—MECHANISMS

Transient lower oesophageal sphincter relaxations (TLOSRS) account for 65% of reflux episodes.^{1–2} They are vagally mediated by stretch receptor activation following stomach distension.³ Evidence for this has been provided, courtesy of the 5-hydroxytryptamine₁ agonist sumatriptan, which results in a higher frequency of TLOSRS and reduced gastric emptying.⁴ During such relaxations, diaphragmatic crural contraction inhibition hinders the

crural diaphragm pinch-cock effect around the sphincter.⁵

A variety of dietary factors increase the rate of TLOSRS, including chocolate, fats, alcohol and peppermint.⁶ A study by Piche *et al*⁷ analysed the effect of carbohydrates on colonic fermentation, and demonstrated an increase in the rate of postprandial TLOSRS most likely due to excess release of glucagon-like peptide 1. Obesity is also implicated in the pathogenesis of reflux disease and TLOSRS. Schneider *et al*⁸ concluded that obese individuals have two-thirds more TLOSRS per hour than non-obese patients with diffuse oesophageal spasm, with the majority of TLOSRS being complete and isolated in nature. Kahrilas *et al*⁹ demonstrated that the presence of a hiatus hernia is also associated with TLOSRS with frequency being directly proportional to the size of hernia. Posture might also play a role with the right recumbent position increasing the frequency of TLOSRS.¹⁰

The relevance of TLOSRS has long been underestimated. Kawahara *et al*¹¹ showed that in children if swallow induced lower oesophageal sphincter (LOS) relaxation-associated reflux was reclassified as, in fact, due to TLOSRS, the number of reflux episodes attributed to TLOSRS would rise from 58% to 81%.

The basal LOS pressure is also relevant. TLOSRS can occur even at low LOS pressures (less than 5 mm Hg) and certainly some reflux episodes in this setting are due to TLOSRS rather than a low basal pressure.¹²

Studies have also shown that the refluxate associated with TLOSRS is predominantly gastric acid rather than bile, which

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may be explained by anatomical dysfunction of the diaphragmatic hiatus or acid pocket environments below the LOS.¹² It has also been hypothesised that differences in the degree of gastric content mixing may be responsible for a more acidic refluxate.¹³

In children, studies have indicated that 23% of reflux episodes were strain associated (deep inspiration or cough related), with the majority of episodes occurring during LOS relaxations.¹⁴

Interestingly, Trudgill's group demonstrated that TLOSRS are no more frequent in patients with gastro-oesophageal reflux disease (GORD) than asymptomatic volunteers. Twenty patients were studied (10 GORD vs 10 asymptomatic), both age and sex matched with results demonstrating no significant difference in TLOSRS frequency between the two groups after meals. Of note, however, TLOSRS were more likely to be associated with acid reflux in patients as opposed to gas or non-acidic liquid reflux in volunteers.¹⁵

POTENTIAL THERAPEUTIC AGENTS

- ▶ gamma-aminobutyric acid (GABA)_B receptor agonists show the most promise as therapeutic agents. The receptor inhibits neuronal transmission through potassium channel activation and calcium channel closure.¹⁶ Blackshaw *et al* demonstrated in animal studies that the GABA_B agonist reduced TLOSRS in a dose-dependent manner without adversely affecting the basal tone of the LOS.^{17, 18} It was thought that this was induced by central reduction in swallowing frequency.¹⁹ A study of 16 patients with persistent heartburn, or regurgitation for at least 3 months, in spite of proton pump inhibitor (PPI) therapy, were given gradual escalating doses of 5 mg baclofen until a maintenance dose of 20 mg three times a day was established, the end result being an improvement in duodenogastro-oesophageal reflux (duodenal reflux) and associated reflux symptoms.²⁰ Side effects of baclofen include sedation, confusion and memory impairment, as well as the potential for seizures following withdrawal which may limit its use.¹⁹ A novel GABA_B receptor peripheral agonist, AZD3355, has been shown to inhibit TLOSRS in dogs resulting in a decrease of acid reflux episodes by half, and also a decrease in overall acid exposure time.^{21, 22} Similar results have been found with AZD9343.²³ In addition, a novel compound, XP19986, a pro-drug of R baclofen, reduced both heartburn and episodes of reflux in adults with GORD.²⁴
- ▶ Glutamate itself induces TLOSRS through its role in transmission from vagal afferents to the effector neurones in the brain stem.²⁵ Two glutamate receptors exist, metabotropic and ionotropic. Metabotropic receptors are essentially three-fold: Group I comprises receptors 1 and 5, involved primarily in excitatory transmission, and Group II and Group III, both of which are inhibitory.²⁵ Hirsch *et al*²⁶ demonstrated that the glutamate-releasing inhibitor, riluzole, used in the treatment of amyotrophic lateral sclerosis, reduced the frequency of TLOSRS during gastric distension. The metabotropic glutamate receptor-5 negative allosteric

modulator, ADX10059, decreased oesophageal acid exposure, reflux episodes and symptoms.²⁷

- ▶ Cholecystokinin (CCK) has also been shown to modulate TLOSRS. Novel agents include devazepide, a CCK_A antagonist, which lowers the rate of TLOSRS in humans²⁸ and lorglumide, another CCK_A antagonist, which inhibits postprandial TLOSRS.²⁹
- ▶ Intravenous atropine reduces TLOSRS presumably via central inhibition.³⁰ However, conflicting data exists with the use of anticholinergics with dicyclomine, demonstrating an increase in recumbent oesophageal acid exposure.³¹
- ▶ Boulant *et al*³² demonstrated inhibition of the rate of TLOSRS with the nitric oxide synthase inhibitor N^G-nitro-L-arginine-methyl ester (L-NAME) which was successfully reversed by L-arginine. Similarly, Hirsch *et al*³³ indicated that N^G-monomethyl-L-arginine (L-NMMA) inhibited TLOSRS induced by gastric distension by more than 75%. Nitric oxide inhibition, however, is linked to cardiovascular, urinary and respiratory side effects which limit its use in this setting.
- ▶ Opiates are known to induce sphincter spasm, and intravenous morphine has also been shown to reduce TLOSRS. A study by Penagini and Bianchi demonstrated inhibition of TLOSRS by 50%.³⁴
- ▶ The cannabinoid receptor agonist, WIN 55, 212-2, reduced TLOSRS following gastric distension by 80% in dogs.³⁵ In addition, the mixed CB₁/CB₂ receptor agonist delta⁹-tetrahydrocannabinol (Δ⁹-THC) decreases meal-induced TLOSRS.²⁵
- ▶ Other agents which have been shown to lower TLOSRS include the serotonin (5-HT₃) receptor antagonist ondansetron and granisetron in dogs, as well as somatostatin in humans.²⁸

It is important to note that advances in pharmaceutical pursuit are not without their drawbacks, and the continued development of such compounds are often hampered by problems of limited efficacy and toxicity. The above mentioned glutamate modulator ADX1009, and the GABA_B agonist, AZD3355, led to unacceptable transaminitis hindering further use.³⁶

Non-pharmacological treatment of TLOSRS, include surgical fundoplication and radiofrequency ablation. It is not yet clear how fundoplication is thought to reduce TLOSRS, and hypotheses have included a decrease in gastric receptor activation as well as vagal nerve damage as a consequence of the procedure.⁴ Allied to this is the benefit of radiofrequency energy delivery to aid in the increase of basal LOS pressures with a subsequent decrease in TLOSRS rate.³⁷ The precise mechanism behind this decrease is not yet known, but could be related to interruption of neural signalling of distension and altered mechanics of the gastric cardia.

CONCLUSION

Increasing evidence links TLOSRS with the pathogenesis of GORD. Although acid suppression is usually successful, GORD is multifactorial, and TLOSRS are

an overlooked cause. Of course, the use of simple antacids and, more importantly, PPI's have been set in stone for several years now. However, such drugs mask symptoms without focusing on the provoking factors responsible. As research continues in this rapidly evolving field, novel medicines will come to the forefront, along with refined surgical interventions to ensure not only symptom control but, most importantly, a potential cure.

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