Pharmacological control of transient lower oesophageal sphincter relaxations

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Thesis Summary

The work contained in this thesis investigates pharmacological control of transient lower oesophageal sphincter relaxations as a treatment of gastro-oesophageal reflux. Two major classes of pharmaceutical agents were explored; anticholinergic agents and the GABA_B agonist, baclofen.

Transient lower oesophageal sphincter relaxation is the principal mechanism of reflux in normal subjects and in the majority of patients with gastro-oesophageal reflux disease. The anticholinergic agent, atropine, has previously been shown to inhibit gastro-oesophageal reflux in normal subjects by inhibition of transient lower oesophageal sphincter relaxations. Because reflux occurs during absent basal lower oesophageal sphincter pressure in a significant minority of patients with gastro-oesophageal reflux disease, the effects of atropine may not be the same as in normal subjects. The effect of atropine in reflux patients was therefore examined. This study showed that atropine inhibits reflux in patients with reflux disease largely by inhibition of transient lower oesophageal sphincter relaxations.

The site at which atropine exerts its effect on transient lower oesophageal sphincter relaxations is unknown. Transient lower oesophageal sphincter relaxation is believed to be neurally mediated through vagal pathways, stimulated by gastric distension and integrated in the brainstem. Atropine could potentially act centrally, in the brainstem, or peripherally, by altering the mechanical properties of the proximal stomach. Therefore, the site of action of atropine was investigated by examining the effect of atropine on proximal gastric function and the effect of a peripherally acting anticholinergic agent on the triggering of transient lower oesophageal sphincter relaxations. These studies support the notion that atropine inhibits transient lower oesophageal sphincter relaxations by acting centrally in the brainstem.
As gamma-aminobutyric acid (GABA) is a major inhibitory neurotransmitter within the central nervous system and inhibitory GABA_B receptors are abundant in the brainstem, the effects of the GABA_B receptor agonist baclofen on transient lower oesophageal sphincter relaxations and gastro-oesophageal reflux were investigated in normal subjects. This study showed that baclofen significantly inhibited the rate of transient lower oesophageal sphincter relaxations and thereby reduced the rate of reflux episodes, suggesting that GABA_B receptor agonists may have a potential therapeutic role in the treatment of reflux disease.