M₁ and M₂ Muscarinic Receptor Subtypes in the Lower Esophageal Sphincter

S. Rattan

Background

The lower esophageal sphincter (LES) is a narrow zone of smooth muscle between the esophagus and stomach. The LES remains in a continuous state of closure except during a swallow and is demonstrated manometrically by a high-pressure zone. The resting tone in the LES is primarily myogenic in nature (Goyal and Rattan 1976) and the major intramural nerves are inhibitory. The rise of fall in the sphincter pressure in response to different neural or hormonal stimuli can be easily demonstrated. This model has served well in defining the locus and receptor differentiation of neurohormonal substances on the inhibitory neurons and sphincter muscle (Goyal and Rattan 1978; Rattan and Goyal 1983).

Our studies in the opossum LES in 1975 suggested the presence of two subtypes of muscarinic receptors. In 1978, they were named M₁ and M₂ muscarinic receptors (Goyal and Rattan 1978), M₁ muscarinic receptor being present on the inhibitory neuron and M₂ on the LES muscle.

The purpose of this paper is to summarize the role of two subtypes of muscarinic receptors in the control of the LES.

Experimental Procedure

The studies were performed in the opossum (Didelphis virginiana). The animals were anesthetized with pentobarbital sodium. The lower esophageal sphincter pressures were monitored using continuously perfused catheters assembly. The catheters assembly was anchored inside the LES (following laparatomy) in order to avoid any movement artifact (Goyal and Rattan 1976). All the pressures were recorded on a Beckman dynograph chart recorder. One of the brachial veins was cannulated for intravenous administration of different agents. In some experiments, the esophageal branch of the left gastric artery was cannulated for the administration of agents directly in the region of the LES (Goyal and Rattan 1973). In order to examine the influence of neural stimulation, two types of stimuli were used - vagal stimulation (Rattan and Goyal 1974) and local intramural stimulation (Rattan and Goyal 1976) of the LES.
Evidence for Muscarinic Receptor Subtypes

The Influence of Different Muscarinic Agonists on the LES Pressure and Their Site of Action

The presence of M₁ muscarinic receptor which lies on the postganglionic inhibitory neuron in the vagal inhibitory pathway could be further tested by the selective activation by an agonist. In that attempt, we examined the effect of a series of muscarinic agonists including McN-A-343 on the LES. McN-A-343 is an unusual muscarinic agonist which selectively stimulates muscarinic receptor on the sympathetic ganglia (Roszkowski 1961). McN-A-343 administered in the esophageal branch of the gastric artery produced dose-dependent LES relaxation after a transient contraction of the sphincter (Fig. 1). M₂ agonist, bethanechol, on the other hand, caused only contraction of the LES (Fig. 1) and it was dose dependent.

**Fig. 1.** Representative examples of effects of close i.a. administration of McN-A-343 and bethanechol on the LESP. Note that McN-A-343 causes relaxation after a brief initial contraction, whereas bethanechol causes only contraction of the sphincter. Examples of the effects of close i.a. administration of McN-A-343 and bethanechol after tetrodotoxin (TTX) treatment are given in the lower two panels of the figure. Note that after TTX treatment McN-A-343 lost its inhibitory effect. Both McN-A-343 and bethanechol caused sphincter contraction after TTX.