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2. **Title**

   Unraveling of Roles of Neurogenic Nicotinic Receptors in the Pathogenesis of Achalasia and Esophagogastric Junction Outflow Obstruction.

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4. **Summary**

Both achalasia and esophagogastric junction outflow obstruction (EGJOO) are characterized by impaired lower esophageal sphincter (LES) relaxation during swallowing, which causes main symptom of dysphagia. The objective of the present study was to determine the pathogenesis of esophageal disorders including achalasia and EGJOO in the regard with neurogenic nicotinic acetylcholine receptor (nAChR), which plays a central role in this swallow-induced LES relaxation. First of all, using porcine esophagus, we have determined the mechanism of LES relaxation induced by stimulation of nAChR with 1,1-dimethyl-4-phenyl-piperazinium (DMPP; a nicotinic acetylcholine receptor agonist). Membrane hyperpolarization of the interstitial cells of Cajal (ICC) via the activation of anoctamin-1 plays a central role in DMPP-induced relaxation. ATP may be a neurotransmitter for inhibitory enteric neurons, which stimulates the ICCs. The ICCs act as the interface of neurotransmission of nicotinic acetylcholine receptor, in order to induce the LES relaxation. Second, using the clinical samples from the patients, we have determined that EGJOO is characterized by upregulation of TNF-α, and achalasia was characterized by upregulation both of Th1 cytokines (TNF-α, IL-1β and IL-12) and Th17 cytokines (IL-17A, IL-23A and IL-6). Third, the proportion of smoker in the patients with achalasia was significantly higher than that in the patients with normal HRM, and the prevalence rate of anti-nAChR antibody in EGJOO was 5 %. In conclusion, a series of studies have strongly suggested that nAChR and smoking are associated with pathogenesis of achalasia and EGJOO..