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Animal models of diabetic gastroparesis to understand diabetic gastroenteropathy in humans

Background: Diabetic gastroparesis occurs in 30% to 50% of people with diabetes. Lack of interstitial cells of Cajal (ICC), vagal dysfunction and alterations of enteric nervous system are recognized as the most possible pathological mechanisms. After failure of behavioral and pharmacological measures, the gastric electrical stimulation (GES) represents an effective alternative. A previous study showed that GES promoted ICC proliferation in diabetic rats (*Chen Y et al. Gastroenterol Res Pract. 2018;2018:6309157*), although the mechanisms are not clear.
Aim: To explore the impact of GES on ICC and enteric neurons in diabetic rats and the possible mechanisms involved.
Methods: Sixty rats were randomized into six groups: the normal rats, diabetic rats (DM), diabetic rats with sham GES (DM+sGES), and diabetic rats with different stimulation pulse width of GES (DM+GES1, DM+GES2, DM+GES3). The proliferation of ICC and expressions of serotonin receptor 2B (5-HT2B), distributed in myenteric plexus in human colon and on mice ICC, neuronal oxide synthase (nNOS), expressed by inhibitory enteric neurons, choline acetyltransferase (CHAT), expressed by excitatory enteric neurons, protein gene product 9.5 and glia cell-derived neurotrophic factor (GDNF) proteins were evaluated by immunofluorescence staining or Western blot. The expressions of 5-HT in blood and tissue were determined by ELISA.
Results: ICC proliferation was hardly observed in the DM and DM+sGES groups, but significantly increased in the three DM+GES groups. The expression of 5-HT2B was decreased in DM and increased in the DM+GES groups. Similarly, 5-HT expression in the blood and stomach tissue were increased in the DM+GES groups. Both nNOS labeled neurons and CHAT-positive neurons were reduced in myenteric plexus of the DM group, while plenty of these neurons were observed in the DM+GES group. The expression of GDNF protein was down-regulated in diabetic rats, while GES increased the expression of GDNF.
Conclusion: Long pulse GES facilitated proliferation of ICC in diabetic rats probably via upregulated 5-HT/5-HT2B signal pathway. Simultaneously, GES also rescued the survival of nitrergic and cholinergic neurons potentially with the increased GDNF expression.

Comments. GES has demonstrated a significant reduction of cardinal symptoms in patients with refractory gastroparesis, particularly nausea and vomiting, whereas it has not been conclusively established to improve gastric emptying. The mechanisms involved in symptomatic improvement achieved by GES remain not explained, although activation of vagal afferent pathways and decreased gastric sensitivity to volume distention have been proposed. The present study suggests a new theoretical basis for GES mechanisms that involve 5-HT/5-HT2B signal pathway and alterations of enteric nervous system partly through the GDNF. From a pathophysiological perspective, applying concepts emanating from animal models could allow a better understanding of the pathogenetic mechanisms involved in human diabetic gastroenteropathy. Thus, this type of studies can allow understanding of GES effects on the enteric nervous system and at the same time can give impetus to the identification of novel therapeutical targets.

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Reference. Chen Y, Zhang S, Li Y, Yan H, Ba Y, Wang X, Shi N, Liu C. Gastric Electrical Stimulation Increases the Proliferation of Interstitial Cells of Cajal and Alters the Enteric Nervous System in Diabetic Rats. Neuromodulation. 2021 Dec 18:S1094-7159(21)06178-X. doi: 10.1016/j.neurom.2021.10.003.
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