

Role of sympathetic and parasympathetic nerves in the development of gastric cancer through antagonism

Jing Gao, Shu-Gang Liu

Traditional Chinese Medicine Department, The Fourth Hospital of Hebei Medical University, Shijiazhuang, Hebei 050011, China.

Previous studies have shown that the autonomic nervous system plays a role in the occurrence and development of gastric cancer (GC).^[1-3] Sympathetic and parasympathetic nerve fibers constitute a network in gastric wall submucosa and muscularis to control gastric peristalsis and secretion. These two groups of nerve fibers antagonize and coordinate with each other under the regulation of the central nervous system to complete their innervation function. Currently, most of the studies on the autonomic nervous system and GC focus on a single species nerve fiber or transmitter. The present study aimed to elucidate how the sympathetic and parasympathetic nervous systems antagonize and coordinate in the occurrence and development of GC. Simultaneously, some gastrointestinal hormones are also identified in the development of GC as helpers or tools of the sympathetic or parasympathetic nervous system.

The vagus nerve promotes the growth of GC through the high distribution of nerve fibers and the secretion of acetylcholine transmitters. Some studies showed that the incidence of tumors in the lesser curvature of the stomach was significantly higher than that of the greater curvature, while the lesser gastric curvature had a high vagal innervation. Zhao *et al*^[4] performed vagal neurectomy in mice to observe the growth of gastric tumors: the incidence of tumors after bilateral vagotomy and pyloroplasty (VTPP) was 17%, while with pyloroplasty (PP) alone, it was 86%. The incidence of anterior gastric tumors was 14%, and that of posterior gastric tumors was 76% after unilateral anterior vagotomy (UVT). Previous data showed that exogenous acetylcholine (ACh) stimulation promotes the proliferation of GC cells. Also, GC cells could synthesize and secrete ACh through choline acetyltransferase (ChAT) to form an autocrine loop, thereby promoting their own growth. Both endogenous and exogenous ACh promotes cell proliferation and

stimulates phosphorylation of extracellular signal-regulated kinase (ERK) and protein kinase B (AKT) in GC cells through M3 muscarinic receptor (M3R).^[5] At the same time, cholinesterase (CHE) inhibits the growth of GC cells through the decomposition of ACh.^[6]

Concurrent to vagus nerve excitation, the distribution of sympathetic nerve fibers and adrenergic receptors is decreased in GC. According to the immunohistochemical staining of 82 cases of GC surgical specimens, it was found that the small arteries of the normal gastric wall were completely covered by sympathetic nerve fibers, while the sympathetic nerve fibers in the cancer tissues were significantly reduced and there was little distribution of sympathetic nerve fibers in patients with lymph node invasion and metastasis.^[7] Moreover, Bae *et al*^[8] found that the density of sympathetic nerve fibers in patients with pT4 GC was significantly lower than that of pT1-3. The expression of the β 1-adrenergic receptor decreased with the increase in lymph node metastasis, and the expression of the β 2-adrenergic receptor was high in well-differentiated GC.^[8]

Furthermore, we observed that gastrin inhibits the occurrence of GC.^[9] It has been confirmed that gastrin secretion significantly increases after inhibiting or blocking vagal function.^[10] At the same time, the sympathetic nervous system stimulates gastrin secretion through β 2-adrenoceptor.^[11] Therefore, the sympathetic nervous system is excited at the same time, and the vagus is inhibited. Under this joint action, the production of gastrin is increased, thus inhibiting GC.

Globally, the incidence of GC in women is significantly lower than that in men. Wang *et al*^[12] demonstrated that the risk of GC was reduced by 60% in women who had undergone estrogen replacement therapy for >3 years.

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Quick Response Code:



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DOI:

10.1097/CM9.0000000000001348

Correspondence to: Prof. Shu-Gang Liu, Traditional Chinese Medicine Department, The Fourth Hospital of Hebei Medical University, No. 12, Jiankang Road, Chang'an District, Shijiazhuang, Hebei 050011, China
E-Mail: 11202811@qq.com

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Chinese Medical Journal 2021;134(8)

Received: 16-11-2020 Edited by: Peng Lyu

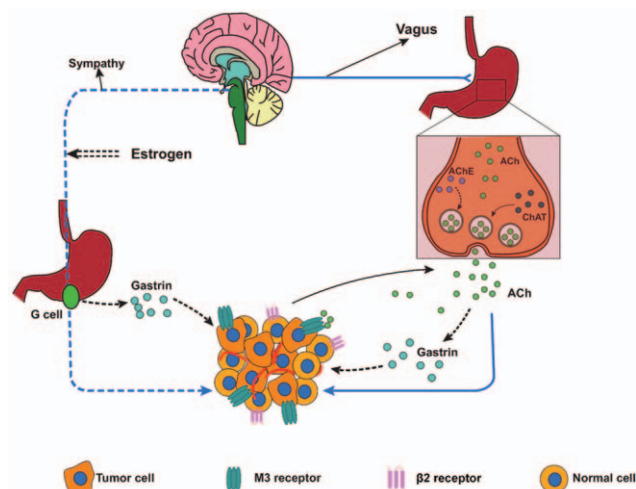


Figure 1: The sympathetic nervous system and parasympathetic (vagus) nervous system work together to promote the occurrence and development of GC. The weakening of sympathetic nervous system in the stomach is a promoting factor for the growth of GC. Estrogen can inhibit the development of GC by regulating the excitability of sympathetic nervous system. The high distribution of vagus nerve and its neurotransmitter ACh and cholinergic M3 receptor are the promoting factors of GC. At the same time, GC cells can also release ACh to promote their own growth through the action of related enzymes. As an inhibitory factor of GC, the secretion of gastrin can be promoted by inhibiting the excitability of vagus and increasing the excitability of sympathetic nervous system. ACh: Acetylcholine; ChAT: Choline acetyltransferase; GC: Gastric cancer.

When the estrogen concentration is low, it stimulates tumor growth by stimulating the estrogen receptor $\alpha 36$ ($ER\alpha 36$), and when the estrogen level is high in the body, it inhibits the expression of $ER\alpha 36$ and inhibits the growth of GC.^[13] Moreover, the lack of estrogen receptor β ($ER\beta$) in GC tissues is associated with a poor prognosis. Therefore, the increase in estrogen can inhibit the occurrence of GC. Estrogen is closely related to the sympathetic nervous system of the human body. It also improves the sympathetic nerve excitation status by regulating the neurotrophic protein receptors in neurons. In addition, the prolonged elevation of estrogen promotes the growth of sympathetic nerve fibers.^[14] According to the phenomenon, when the distribution of sympathetic nerve fibers and estrogen decreased, the risk of GC is increased. Based on the correlation between estrogen and the sympathetic nervous system, we speculate that estrogen affects the occurrence and development of GC through the sympathetic nervous system.

Thus, the above findings put forth that the combined action of the sympathetic and parasympathetic nervous systems, rather than a single factor, promotes the occurrence and development of GC [Figure 1]. Therefore, the overall state of the gastric autonomic nervous system should be considered in the treatment of GC, and traditional Chinese medicine has certain advantages regarding this aspect.

Funding

The study was supported by a Special Project of Academician Workstation Construction in the Fourth Hospital of Hebei Medical University (No. 199A7742H).

Conflicts of interest

None.

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How to cite this article: Gao J, Liu SG. Role of sympathetic and parasympathetic nerves in the development of gastric cancer through antagonism. *Chin Med J* 2021;134:908–909. doi: 10.1097/CM9.0000000000001348