The Pharmacological Actions of Nicotine on the Gastrointestinal Tract

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Abstract. Increasing use of tobacco and its related health problems are a great concern in the world. Recent epidemiological findings have demonstrated the positive association between cigarette smoking and several gastrointestinal (GI) diseases, including peptic ulcer and cancers. Interestingly, smoking also modifies the disease course of ulcerative colitis (UC). Nicotine, a major component of cigarette smoke, seems to mediate some of the actions of cigarette smoking on the pathogenesis of GI disorders. Nicotine worsens the detrimental effects of aggressive factors and attenuates the protective actions of defensive factors in the processes of development and repair of gastric ulceration. Nicotine also takes part in the initiation and promotion of carcinogenesis in the GI tract. In this regard, nicotine and its metabolites are found to be mutagenic and have the ability to modulate cell proliferation, apoptosis, and angiogenesis during tumorigenesis through specific receptors and signalling pathways. However, to elucidate this complex pathogenic mechanism, further study at the molecular level is warranted. In contrast, findings of clinical trials give promising results on the use of nicotine as an adjuvant therapy for UC. The beneficial effect of nicotine on UC seems to be mediated through multiple mechanisms. More clinical studies are needed to establish the therapeutic value of nicotine in this disease.

Keywords:nicotine, ulcer, cancer, ulcerative colitis

Epidemiology of cigarette smoking

The extensive use of tobacco and its associated problematic health issues have been a concern to mankind. The World Health Organization (WHO) estimates that approximately one-third of the global population aged 15 years or older are smokers and each smoker consumes an average of 15 cigarettes daily. Cigarette smoking, the most common form of tobacco use, has been found to account for hundreds of thousands of premature deaths and chronic diseases annually (1). It is well established that cigarette smoking can increase the risk of chronic obstructive pulmonary diseases, cardiovascular diseases, and several forms of cancer, in particular, cancers of the lung, oropharynx, larynx, and esophagus (2–4). Recent epidemiological evidence suggests that cigarette smoking is also deleterious to other parts of the gastrointestinal (GI) tract. In this respect, cigarette smoking increases both the incidence and relapse rate of peptic ulcer diseases and delays ulcer healing (5, 6). Smoking is also positively associated with cancers of the stomach, liver, and colon (7). Despite its detrimental effects on the GI system, cigarette smoking is currently the most consistent epidemiological finding associated with lowered incidence of ulcerative colitis (UC), a kind of inflammatory bowel disease (8). To this end, cigarette smoke seems to exert multiple pharmacological effects in the colon. These effects are interesting and would be worthwhile to clarify in what ways cigarette smoking exerts these beneficial influences. Cigarette smoke, nevertheless, comprises thousands of chemicals, making it difficult to delineate the contribution of an individual compound to the toxicological and pharmacological properties of cigarette smoke as just described.

Nicotine and cigarette smoking

Nicotine, a major component of cigarette, has been proposed to be responsible for many pharmacological effects of cigarette smoke. It has a bitter-taste and is a mildly alkaline and volatile liquid alkaloid. Each
cigarette contains 15–30 mg of nicotine. Nicotine is rapidly absorbed through mucous membranes, skin, alveoli, and the GI tract. The half-life of nicotine is 30–60 minutes. It is extensively metabolized in the liver to cotinine, and a considerable proportion is excreted unchanged in acidic urine. Venous nicotine levels in smokers range from 5 to 15 ng/mL and arterial nicotine levels peak as high as 80 ng/mL (9, 10). Remarkably, nicotine levels in smokers are shown to be extremely high in saliva and gastric juice, reaching more than 1300 and 800 ng/mL, respectively (11).

Nicotine has been used in the treatment of different neurological disorders, including Alzheimer’s disease (12) and Parkinson’s disease (13), and as a replacement therapy to aid smoking cessation (14). Activation of the classical and/or nonclassical nicotine receptors can stimulate respective signaling pathways (15–17). Stimulation of the nicotinic acetylcholine receptors (nAChRs) superfamily would lead to a generalized response, characterized by initial stimulation followed by desensitization. The nAChR gene family consists of the following subunits: ten \( \alpha \) (\( \alpha 1 \) to \( \alpha 10 \)), four \( \beta \) (\( \beta 1 \) to \( \beta 4 \)), one \( \gamma \), one \( \delta \), and one \( \epsilon \). Functional nAChRs in the neuromuscular junction are composed of five subunits arranged around a central ion channel, which non-specifically allows flow of cations across the membrane upon stimulation. Neuronal nAChRs only consist of \( \alpha \) and \( \beta \) subunits. Variations in association of subunits lead to different ion-gating and ligand-binding properties (18). Recent evidence suggests the expression of functional nAChRs can be found in non-excitable cells, which are unable to generate action potential, in the GI system but their roles remain largely elusive (19, 20). Unlike ionotropic nAChRs, the nonclassical nicotine receptor pathway is mediated through a noncholinergic metabotropic receptor, which is G protein-linked and positively coupled to phospholipase C (16).

Nicotine plays a key role in smoking-related diseases by exerting a dual influence. On the one hand, nicotine produces reinforcing effects, tolerance and physical dependence, and the pharmacological effects that smokers enjoy such as modulation of mood, appetite, and task performance (21), resulting in perpetuation of the smoking habit. The mechanism for the development of nicotine dependence is complex but it is pertinent to the desensitization and the longer-lasting persistent inactivation of nicotinic receptors in the central nervous system together with dopaminergic modulation of the reward center (22–24). On the other hand, nicotine is found to be actively involved in the pathogenesis of GI diseases including peptic ulcer formation and delayed wound healing (5, 6), promotion of carcinogenesis (25), and disease progression of UC (20). In the latter case, clinical trials have confirmed the use of nicotine as an alternative therapeutic option available to UC patients alongside with the standard mainstream treatment with sulphasalazine and corticosteroids (26).

In this review, the parts contributed by nicotine with particular relevance to peptic ulcer formation, carcinogenesis in the GI tract, and UC will be elucidated and the discussion will be focused on recent clinical and pre-clinical findings.

**Nicotine and ulcerogenesis**

Epidemiologic data show that cigarette smoking increases both the incidence and relapse rate of peptic ulcer diseases and also delays ulcer healing in humans (5, 6). To what extent the ulcerogenic action is attributable to nicotine in cigarette smoke remains poorly defined. Maintenance of the integrity of gastric and duodenal mucosal integrity, nevertheless, involves an interplay and balance between aggressive and defensive factors. There is evolving evidence indicating that nicotine may tilt the balance, favoring aggressive factors but attenuating defensive factors. Although other chemicals found in cigarette smoke as a whole may affect these factors, this discussion will be restricted to the actions of nicotine.

**Gastric acid secretion**

A number of factors take part in the process of ulcerogenesis but gastric acid secretion is still regarded as one of the major aggressive factors in ulcer formation. It is almost the primary target of contemporary drug therapy for peptic ulcer. However, the effect of nicotine on gastric acid secretion is controversial. It was found that chronic nicotine administration, at least 25 mg/kg for 10 days, increased the gastric secretory volume and acid output stimulated by pentagastrin or bethanechol in pylorus-ligated animals. The finding is consistent with the idea that chronic nicotine administration can lead to increased muscarinic receptor sensitivity, and consequently, basal acid secretion (27–29). It was also noted that pH during the lunch hour after nicotine was significantly lower than that after placebo, suggesting that nicotine might impair postprandial gastric neutralization (30). Likewise, acute nicotine treatment has the ability to dose-dependently abolish the depressing effect of ethanol on acid secretion and gastric secretion volume (31). Intravenous administration of nicotine in conscious cats also significantly stimulates basal gastric acid output. In vitro study demonstrated that nicotine could exert direct stimulatory effects on parietal cells and potentiate the histamine-mediated response in
the isolated cell model (32).

Contrasting findings, however, also pervade the literature. In one of the studies, the gastric acid secretion stimulated by intravenous pentagastrin was completely inhibited by nicotine (33). Another study also showed that acid output together with gastric secretory volume one hour after vagal stimulation induced by modified sham feeding was lower in human subjects on smoking than non-smoking days (11). Based on the contrasting and inchoate nature of evidence, the role of nicotine in gastric acid secretion remains elusive.

**Helicobacter pylori-induced ulcer**

*Helicobacter pylori* (*H. pylori*) and cigarette smoking are two major risk factors for gastroduodenal ulcers but the interaction between them on ulcerogenesis are complex. It was found that the *H. pylori* infection was positively associated with cigarette smoking (34, 35). Moreover, it was shown that the success rate of eradication of *H. pylori* was significantly lowered if the patient continues to smoke during medication (36). It was further suggested that cigarette smoking might exacerbate disease progression in *H. pylori*-positive subjects. Cigarette smoking might lead to progression of atrophic gastritis and intestinal metaplasia in patients infected with *H. pylori* (37). To this end, nicotine was found to have the ability to potentiate the vacuolating toxin activity of *H. pylori* in gastric cells (38).

**Pepsinogen and vasopressin secretions**

Both pepsinogen and vasopressin have completely different actions on the gastric mucosa. Pepsin bears powerful mucolytic properties and is recognized as a crucial aggressive agent in the pathogenesis of peptic ulcer disease (39). Pepsin secretion was shown to correlate with serum pepsinogen-1, the endocrine component of pepsinogen secreted by the chief cells (40). It was proposed that nicotine directly stimulated pepsinogen secretion probably via nicotinic receptors on the gastric chief cells, accompanied by a concomitant increase in free cytosolic calcium ions (41).

Vasopressin can cause vasoconstriction and provoke platelet aggregation, leading to an impaired tissue blood supply. It is believed that endogenous vasopressin plays an aggressive role in development of gastroduodenal ulceration. This is because the incidence of peptic ulcer is lower in vasopressin-deficient patients and different ulcerogenic substances can increase intramucosal vasoressin levels (42). It was found that nicotine chewing gum could induce non-osmotic vasopressin release in humans (43). It is suggested that by stimulating noradrenaline release in the supraoptic nucleus, nicotine facilitates vasopressin release from the neurohypophysis (44). The action is mediated at least in part by increased cytosolic Ca$^{2+}$ and activation of cAMP-dependent protein kinase A (45).

**Gastric mucosal blood flow**

The status of gastric microcirculation plays an important role in the protection of the mucosal barrier in the stomach. Disturbances in blood perfusion in the gastric mucosa result in the formation of erosions and ulcers (46). The ulcerogenicity of nicotine may be, therefore, mediated through the reduction of mucosal blood flow. In animal experiments, chronic administration of nicotine markedly reduces gastric mucosal blood flow (31, 47). It was also found that centrally administered nicotine had an inhibitory effect on mucosal blood flow (48). Likewise, high dose of nicotine (25 mg/ml) in drinking water could potentiate the decrease of gastric mucosal blood flow induced by ethanol (31).

**Mucosal restitution**

Gastric mucosal surface can be easily damaged by wear and tear. Gastric mucosa, however, possesses the ability to repair rapidly after injury and the process of restoration involves restitution and regeneration. During restitution, epithelial cells spread and migrate to reseal superficial wounds after injury, a process independent of cell proliferation (49) (Fig. 1). It was shown that nicotine suppressed the process of mucosal restitution through inhibition of ornithine decarboxylase, a key enzyme responsible for production of endogenous polyamines, and down-regulation of expression of voltage-gated potassium ion channel (50). Both of these biological processes have been implicated in tissue repair in the GI tract. (51)

**Mucus secretion**

Although cumulative evidence favors the proposition that nicotine is ulcerogenic, the alkaloid, nevertheless,
can be protective against gastric damage in some circumstances through enhanced production of mucus. Ethanol consumption is associated with depletion of mucosal mucus followed by chronic gastritis. Acute intragastric administration of nicotine was found to offer acute protection against ethanol-induced gastric injury (52). The protective effect was associated with a significantly larger luminal mucus volume, but was independent of opiate receptors, capsaicin-sensitive afferent sensory nerve fibers, and endogenous prostaglandin generation (53). However, chronic administration of nicotine potentiated ethanol-induced ulceration by depletion of mucosal mucus (52) and thereby weakened the mucosal defensive mechanisms of the mucosa. There are various endogenous mediators, especially epidermal growth factor (EGF) and prostaglandins, which have been demonstrated to enhancing the above-mentioned protective mechanisms of the gastric mucosa.

**EGF and prostaglandins**

Salivary gland is one of the major sources of EGF. Salivary EGF level is usually 5–10 times more than that found in blood or gastric juice (54). EGF is important in maintaining gastrointestinal mucosal integrity and ulcer healing (55). Moreover, EGF decreases gastric acid secretion and increases bicarbonate/mucus secretion (56). EGF can also enhance mucosal blood flow (57). To this end, it was demonstrated that nicotine could reduce the salivary EGF level (58, 59), which might be associated with the pathogenesis of smoking-related peptic ulcer disease. Prostaglandin inhibits gastric acid secretion and exerts protective actions including those on mucosal blood flow and mucus secretion in the gastric mucosa. It was discovered that prostaglandin E2 synthesis in the gastric mucosa was decreased in smokers (60). Likewise, both acute and chronic nicotine administrations were found to inhibit prostaglandin E2 production and increase the susceptibility to ulceration in the stomach (61–63).

**Glutathione (GSH)**

In addition to EGF and prostaglandins, GSH is another important protective mediator in providing a different protective action against mucosal injury in the GI tract. It is a free radical scavenger, which is able to prevent cellular injury induced by oxidative stress (64). The gastric mucosa contains a high concentration of reduced GSH (65). It is also proposed that the ulcerogenic action of cigarette smoking may be in part mediated through reactive oxygen species-induced apoptosis (66). Nicotine was found to deplete intracellular GSH. In this regard, it is interesting to note that nicotine can augment stress-induced reduction in gastric

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<th>Table 1. The potential aggressive and defensive factors modified by nicotine in the development of gastric ulcer</th>
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<td><strong>Aggressive factors likely aggravated by nicotine</strong></td>
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<td>Gastric acid secretion</td>
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<td><em>H. Pylori</em></td>
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<td>Pepsinogen</td>
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<td>Vasopressin</td>
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<td><strong>Defensive factors likely weakened by nicotine</strong></td>
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<tr>
<td>Gastric mucosal blood flow</td>
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<td>Mucosal restitution</td>
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<td>Mucus (chronic nicotine administration only)</td>
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<tr>
<td>Epidermal growth factor</td>
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<tr>
<td>Prostaglandin</td>
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<td>Glutathione</td>
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GSH level and hemorrhagic ulceration in rodents (67).

**Summary**

Although the influence of nicotine on gastric acid secretion remains inchoate and inconclusive, the alkaloid seems to aggravate other aggressive factors, like pepsinogen and vasopressin secretion, and potentiate *H. pylori*-induced ulcer. On the opposite end, the defensive factors, including gastric mucosal blood flow, mucosal restitution, EGF secretion, prostaglandin, and GSH levels, are attenuated by nicotine administration (Table 1). The evidence available so far is consistent with the notion that nicotine plays a negative role in the ulcerogenesis of stomachs.

**Nicotine and carcinogenesis**

It is well established that cigarette smoking increases the risk of cancer. Cigarette smoking causes cancer of various types, including cancers of the lung, oropharynx, larynx, and esophagus, and approximately one-third of all cancers of the pancreas, kidney, urinary bladder, and uterine cervix. More recent evidence points to the relationship between smoking and cancers of the stomach, liver, and colon (7). Conventionally, nicotine is regarded as a relatively inert chemical in carcinogenesis. A recent finding suggests that nicotine may at least be partially involved in the initiation, promotion, and even progression of tumor in the GI tract.

**Behavior influence**

Nicotine and carcinogens found in cigarettes are inalienable partners in carcinogenesis. Behaviorally, the addiction property of nicotine precipitates and perpetuates people to consume tobacco products. A nicotine-dependent individual voluntarily continues to
consume cigarettes and its carcinogens. Without the influence of nicotine or carcinogens, the cigarette is simply a commercial product possessing little or negligible health-damaging effect. Nevertheless, it is estimated that 30% of cancer-related deaths in developed countries could be attributable to this deadly amalgamation (68).

**Mutagenicity**

Previous studies indicated that nicotine was generally accepted as a weak carcinogen. In this regard, the mutagenicity of nicotine had been widely studied. Nicotine is a potential genotoxic compound because nicotine could time- and dose-dependently induce sister-chromatid exchanges and chromosome aberration in CHO cells at concentrations achievable in the saliva of tobacco chewers (69, 70).

Recently, more sensitive mutagenicity assaying methods are employed to study the mutagenic properties of nicotine. Leydig cells are the cells of the testis, which are currently used to determine the carcinogenicity of compounds tested in rodent bioassays. Nicotine, previously demonstrated to have no association between its exposure and induction of Leydig cell hyperplasia or adenomas in humans, was able to induce Leydig cell tumor in rats (71). Experiment utilizing the ultrasensitive method of accelerator mass spectrometry also showed that nicotine could dose-dependently form adducts with liver DNA, lung DNA, histone H1/H3, Hb, and albumin in mice (72, 73). The formation of DNA adduct plays a crucial role in chemical carcinogenesis.

**Mutagenicity of metabolites of nicotine**

Nicotine is extensively metabolized to cotinine in the body. Recent evidence suggests that cotinine is also mutagenic. It was shown that cotinine was directly mutagenic in the Mutatox test (74). Another study also showed that cotinine was mutagenic in the bacterial luminescence genotoxicity test in the absence of the S9 metabolic activation system and nicotine could potentiate the mutagenic effect of cotinine with or without S9 (75). Nicotine may therefore exert its genotoxic effect through metabolic conversion to cotinine.

In addition, cigarette contains many nicotine-derived tobacco specific nitrosamines (Table 2), like 4-(methyl-nitrosamino)-1-(3-pyridyl)-1-butanol (NNK) and \(N’\)-nitrosomornicotine (NNN), which are strong carcinogens. It is not yet known, however, whether nicotine could be converted to these more carcinogenic counterparts endogenously through a yet unattended metabolic pathway. One of the studies showed that nicotine could be metabolized by 2’-hydroxylation to form aminoketone, which could be converted endogenously to NNK (76). It was also found that urine of an animal treated with nicotine contained NNN, \(N’\)-nitrosoanabasine (NAB) and \(N’\)-nitrosoanatabine (NAT), all of which are carcinogenic nicotine-derived nitrosamines (77). However, a finding from another study showed that the use of a nicotine patch would not alter the levels of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) and NNAL-glucosiduronic acid in the blood and urine, in which NNAL is the immediate product metabolized from NNK, indicating that NNK is not formed endogenously from nicotine (78). The evidence available so far remains inconclusive and more studies on the metabolic conversion of nicotine to its carcinogenic counterparts are warranted.

It is noted that tumor growth is highly dependent on the balance between cell formation and cell death at the tumor site, and the tumorigenesis highly relied on the new blood vessels supplying the required nutrients in supporting tumor growth in the tissue. How nicotine affects these biological processes in promoting the development of tumors is being extensively studied.

**Cell proliferation**

Recent evidence indicates that nicotine could directly act as a cancer promoter. Nicotine could stimulate human colon cancer cell line SW1116 proliferation and enhance tumor growth in vivo in the nude mice xenograft model. The cancer-promoting effect of nicotine is found to be dependent on EGF receptor (EGFR) and c-Src phosphorylation and upregulation of 5-lipoxygenase (5-LOX) expression. EGFR and c-Src are, respectively, membrane and intracellular tyrosine kinases mediating many important mitogenic signals, while 5-LOX is pertinent to the metabolism of arachidonic acid. Inhibitors of EGFR, c-Src, and 5-LOX all significantly abolished the nicotine-induced tumor growth (25).

The effect of nicotine on cell proliferation has also been studied in non-epithelial cells. It has been demonstrated that hybridoma and myeloma cells express both homomeric and heteromeric nicotinic receptors containing \(\alpha4\) and \(\alpha7\) subunits. Nicotine was able to

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**Table 2.** Nitrosamines in cigarette smoke

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<th>Tobacco-specific N-nitrosamines</th>
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<td>(N’)-Nitrosornornicotine (NNN)</td>
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<td>(N’)-Nitrosoanabasine (NAB)</td>
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<tr>
<td>(N’)-Nitrosoanatabine (NAT)</td>
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<tr>
<td>4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)</td>
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<td>4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL)</td>
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<tr>
<td>4-(Methylnitrosamino)-4-(3-pyridyl)-1-butanol (iso-NNAL)</td>
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<tr>
<td>4-(Methylnitrosamino)-4-3-pyridyl)butyric acid (iso-NNAC)</td>
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stimulate hybridoma cell proliferation whilst α-bungarotoxin, a specific α7 blocker, inhibited cell proliferation. In addition, the expression of nicotinic receptor was found to correlate with cell proliferation, and long-term exposure to nicotine could up-regulate both the expression of α4 and α7 subunits (79). Interestingly, our recent results also show that nicotine can significantly up-regulate mRNA levels of the α7 subunit of nicotinic receptor in a colon cancer line.

**Apoptosis**

Apoptosis is crucial in carcinogenesis by which cells accumulate when the rate of cell death is lower than that of cell division. Suppressed apoptosis also renders the cell more readily to accumulate genetic lesions and tolerate DNA mistakes. It is also proposed that apoptosis actively takes part in the process of immune surveillance, growth factor/hormone independence, angiogenesis, metastasis, chemoresistance, and radioresistance (80). Evolving evidence indicates that nicotine can suppress apoptosis. It was found that nicotine suppressed apoptosis induced by tumor necrosis factor (TNF), UV light, chemotherapeutic drugs, and calcium ionophore in a variety of species and tissues, including tumor cell types related to tobacco use (15). Mitogen-activated protein kinase, specifically extracellular signal-regulated kinase, and subsequent overexpression of anti-apoptotic protein bcl-2 are proposed to be the major signaling pathway for nicotine-induced suppression of apoptosis (81).

**Angiogenesis**

Angiogenesis is the growth of new blood vessels from the pre-existing vasculature by budding and sprouting of endothelial cells. It is recognized that the growth of solid tumors is angiogenesis-dependent (82, 83). All tumors are unable to grow larger than a few millimeters in diameter unless they are able to recruit their own vascular bed. Experimental findings showed that nicotine accelerated the growth of tumor supported by increased neovascularization. The crucial role of nicotine in angiogenesis is confirmed by molecular and cellular evidence. It was found that nicotine increased endothelial-cell growth and tube formation in vitro and accelerated fibrovascular growth in vivo (84). Nicotine also up-regulated vascular endothelial growth factor (VEGF), MMP-2, and MMP-9, all of which are important mediators in angiogenesis, in colon cancer xenograft in nude mice when the cancer cells were pretreated with nicotine before inoculation (25). A previous finding from our laboratory suggested that cigarette smoke could increase UC-associated colonic adenoma formation in mice, which was associated with increased angiogenesis. The increased blood vessel count was also accompanied by upregulation of VEGF expression (85). Nicotine may, therefore, in part play a key role in this process.

**Summary**

Current experimental evidence supports the notion that nicotine is actively involved in the initiation and promotion of cancer. Nicotine and its metabolite cotinine possess intrinsic mutagenic activity that may result in DNA damage. Nicotine also promotes cancer growth through the modulation of cell proliferation, apoptosis, and angiogenesis (Fig. 2.) Nevertheless, the effect of nicotine on other cellular processes relevant to carcinogenesis, that is, metastasis and cancer immunology, warrants further investigation. Furthermore, although there is still no epidemiologic evidence to date supporting the notion that the use of nicotine increases cancer risk, pre-clinical findings converge to suggest that nicotine may pose a safety issue to current nicotine users. Therefore, a close monitoring and survey on these subjects on carcinogenic potential is justified. However, it would be unwise at this stage to conclude the use of nicotine could promote carcinogenesis in humans. In order to fully address this issue, more complete clinical and epidemiologic studies are required.

**Nicotine and UC**

Several epidemiologic studies have shown a reduced risk of developing UC in cigarette smokers when com-
pared with nonsmokers (8, 86, 87). Intermittent smokers often find their symptoms actually improved with smoking (88); and a dose-response relationship exists, with a decreased risk of UC with increasing amounts of cigarettes smoked (89–91). Cessation of smoking by individuals having smoked a greater number of cigarettes also confers a greater risk of developing UC (92). Nicotine, a major component of tobacco, has therefore been examined as a possible pharmacological agent accounting for the associations and led to clinical trials of nicotine patches in the treatment of UC.

Clinical trials for UC

The clinical beneficial effect of transdermal nicotine on UC is confirmed by a randomized, placebo-controlled trial. It was found that the remission rate was doubled after 6 weeks of treatment (26). Furthermore, it was reported that nicotine liquid enemas was beneficial for the treatment of distal colitis (93). Ex-smokers with UC also show symptomatic improvement with nicotine gum (94). Moreover, the addition of transdermal nicotine to treatment with mesalamine enemas is beneficial to patients with distal ulcerative colitis refractory to rectal mesalamine alone (95). One study, however, argued that nicotine therapy was not effective for maintaining remission, and another study reported that the relapse rate was identical to placebo (87). It is suggested that nicotine is not effective as a monotherapy. In a 6-week trial comparing transdermal nicotine (15 to 25 mg/day) with prednisone (15 mg/day), only 30% of patients had a clinical and endoscopic improvement with nicotine versus 60% with prednisone (96). In addition, findings from several clinical trials also reveal that nicotine is poorly tolerated by patients and long-term compliance is questionable due to the significant adverse profile of nicotine (97). Side effects commonly encountered with transdermal nicotine include contact dermatitis, nausea, and lightheadedness (98). However, adverse effects on other biological systems remain to be elucidated.

Mechanisms of the beneficial effect of nicotine on UC

Various mechanisms have been considered to explain the beneficial effect of nicotine on UC, including effects on the epithelial mucus, gut motility, eicosanoid metabolism, and production of pro-inflammatory cytokines (Fig. 3). Nicotine was found to boost the mucin synthesis and thus provide a protective mucus layer in the colon (99). Nicotine also reduces circular muscle activity, predominantly through the release of nitric oxide (100). Nicotine may also modify eicosanoid-mediated inflammation in patients with UC. It was found that nicotine reduced prostaglandin F1α, prostaglandin F2α, and 15-hydroxy-eicosatetraenoic acid levels in the rectal mucosa of rabbits (101). In addition, both in vivo and in vitro studies showed that nicotine inhibited proinflammatory cytokines including IL-1β, IL-2, IL-8, IL-10, and TNFα production (102–104). The amelioration of colonic inflammation was accompanied by upregulation of somatostatin and intestinal trefoil factor mRNA expression (105). Recent evidence also demonstrates the expression of nAChRs in colon epithelium (20). It is therefore worthwhile to investigate whether the beneficial action of nicotine is mediated

![Fig. 3. Mechanisms mediating the beneficial effects of nicotine on ulcerative colitis.](image-url)
through these cholinergic receptors in the colon.

Summary

Despite the promise of being used as an adjunctive therapy for UC, nicotine at this stage cannot yet be recommended as a mainstay therapy for the disease. The beneficial effect of nicotine seems to be mediated by the actions on the epithelial mucus, gut motility, eicosanoid metabolism, and production of pro-inflammatory cytokines. However, a holistic study investigating the pathogenic mechanism of the disease together with the clinical efficacy and toxicity profile of nicotine is necessary.

Conclusion

The association between cigarette smoking and various GI diseases including peptic ulcer and cancer is established. Interestingly, cigarette smoking is also associated with lower incidence of UC and more benign disease progression. Nicotine, a major component of cigarette smoke, may play a pivotal role in the pathogenesis of these cigarette smoking-associated diseases.

Nicotine plays a crucial role in the development of gastroduodenal ulceration, in part, by aggravating the detrimental actions of aggressive factors and attenuating the protective mechanisms of defensive factors. Further investigation is required to address these issues fully at the molecular level. Nicotine is also actively involved in the cigarette smoking-related carcinogenesis in the GI tract. The intrinsic mutagenic properties of nicotine and its metabolites may probably be pertinent to the initiation of carcinogenesis. Meanwhile, nicotine has the ability to promote cancer development through the modulation of cell proliferation, apoptosis, and angiogenesis. The above findings may pose a safety issue to the current use of nicotine as a replacement therapy to aid smoking cessation as well as adjuvant treatment of UC. Moreover, the therapeutic value of nicotine on UC remains to be established and must be supported by larger scale clinical trials with defined efficacy and safety issues to be fully addressed. Due to the complexity of the pathogenesis of different GI disorders and the multiple actions of nicotine in the biological system, there is a long way to fully understand the involvement and therapeutic application of nicotine in different kinds of diseases in the GI tract. It is justifiable that further research from molecular to animal studies and further on to clinical trials in humans concerning the whole pharmacological profile of nicotine is warranted.

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