

# The Role of Alpha-2 Adrenergic Receptors in Anti-ulcer Activity

## *Antiülser Aktivitede Alfa-2 Adrenerjik Reseptörlerinin Rolü*

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### Abstract

Although peptic ulcer disease has long been recognized, the proposed mechanisms of its etiopathogenesis change every year. This review shows that gastric ulcers have a significant relationship with alpha-2 adrenergic receptors. The aggravating factors of gastric ulcer formation have been reported to act by blocking alpha-2 adrenergic receptors, whereas drugs possessing anti-ulcer activity have been shown to ensure gastric protection by stimulating the alpha-2 adrenergic receptors. The data derived from the literature indicate the likelihood that any drug or substance selectively stimulating the alpha-2 adrenergic receptors may possess anti-ulcer activity.

**Key Words:** Adrenergic receptor, Estrogen, Luteinizing hormone, Oxidant, Ulcer

### Özet

Ülser hastalığının uzun yıllardan beri bilinmesine rağmen, etiopatogenezi hakkındaki fikirler her geçen yılda değişiklikler göstermektedir. Bu derlemede mide ülserinin alfa-2 adrenerjik reseptörlerle çok önemli ilişkisinin olduğu gösterilmiştir. Mide ülserine yol açan agresif faktörlerin alfa-2 adrenerjik reseptörlerini bloke ettikleri, antiülser etkili ilaçların ise alfa-2 adrenerjik reseptörlerini uyarak mideyi korudukları rapor edilmiştir. literatürlerden edinilen bilgiler alfa-2 adrenerjik reseptörlerini selektif uyaran her türlü ilaç ve maddelerin antiülser aktivitesinin olabileceğini göstermektedir.

**Anahtar Kelimeler:** Adrenerjik reseptör, Östrojen, Luteinizan hormonu, Oksidan, Ülser

Although peptic ulcer disease has long been recognized as a distinct pathology, the proposed mechanisms of its etiopathogenesis change every year. However, the etiological factor in approximately 60-80% of patients has yet to be elucidated [1]. A disruption in the balance between aggravating and protective factors has been shown in gastric ulcer formation. Gastric acid, pepsin, bile acids and endogenous oxidant agents are viewed as aggravating factors likely to inflict damage to the stomach, whereas mucous, endogenous bicarbonate, cytoprotective prostaglandins and antioxidant agents are regarded as protective factors. A negative trade-off between aggravating and protective factors in favor of the aggravating factors has been suggested to cause the majority of alpha-2 adrenergic receptor blockages, whereas the opposite is suggested to lead to alpha-2 adrenergic receptor stimulation [2]. Gyires K et al. [3] also demonstrated that the stimulation of the alpha-2 adrenergic receptors is responsible for gastroprotective effects. The anti-ulcer activity exerted by clonidine, an alpha-2 adrenergic receptor agonist, can be suggested as evidence that the stimulation of alpha-2 adrenergic receptors provides gastric protection [4]. Likewise, it has been reported in a

different study that estrogen and Luteinizing hormone (LH) exert significant protection against indomethacin-induced gastric ulcers. Moreover, LH was determined in that study to possess more potent anti-ulcer activity than estrogen, thereby mediating the anti-ulcer effects of both hormones (estrogen and LH) through alpha-2 adrenergic receptor blockage [5]. Estrogen has been known to act either through binding to its own receptors (genomic effect) or without binding (non-genomic effect) [6, 7]. Estrogen has been suggested to exert an antioxidant effect independent of its own receptors [8, 9]. The molecular steroid ring system and the phenolic group contained within the structure of estrogen have been demonstrated to be responsible for estrogen's antioxidant effects. Estrogen has been shown to display an antioxidant effect by directly scavenging free oxygen radicals, activating antioxidant enzymes and repressing the production of superoxide and hydroxyl radicals [10]. Kumtepe et al., [11] however, demonstrated an antioxidant effect of estrogen and LH through the stimulation of alpha-2 adrenergic receptors. That same study also revealed an increase in oxidant levels and a decrease in antioxidant levels in the gastric tissues of animals administered yohimbine, an alpha-2 adrenergic receptor blocker.

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There appears to be a sizable number of studies reporting a decrease in antioxidant parameters and an increase in oxidant parameters in damaged gastric tissue. Malondialdehyde (MDA), and Myeloperoxidase (MPO) levels have been shown to be increased, whereas the levels of enzymatic and non-enzymatic antioxidant parameters, such as glutathione (GSH), glutathione S-transferase (GST), superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx), have been observed to be decreased [12]. The previously mentioned data suggest the role of toxic oxygen radicals in gastric ulcer formation and emphasize the importance of reducing toxic oxygen products in the anti-ulcer activity of drugs. Furthermore, these data also demonstrate a significant correlation between antioxidant activity and the anti-ulcer effect and note the cardinal role of the stimulation of alpha-2 adrenergic receptors in both antioxidant and anti-ulcer activities.

Adrenaline was shown to experimentally boost the activity of COX-1 through the stimulation of alpha-2 adrenergic receptors and to decrease the activity of COX-2 through the stimulation of beta-2 adrenergic receptors in the gastric tissue models of both rats with intact adrenal glands and adrenalectomized rats. This study showed that the anti-ulcer activity of adrenaline was mediated through the induction of COX-1 activity, whereas its anti-inflammatory activity was mediated through the inhibition of COX-2 activity [13]. Indomethacin has been known to inflict damage to the stomach by reducing PGE-2 levels through COX-1 inhibition [14]. The administration of exogenous PGE-2, however, prevented indomethacin-induced damage to the gastric mucosa [15]. PGE-2 has been suggested to provide gastroprotective effects through several mechanisms, such as reducing gastric acid secretion, increasing the thickness of the mucous layer and enhancing blood flow to the mucosa [16]. These data clearly show a direct correlation between gastric protection and the roles of COX-1 and the alpha-2 adrenergic receptor.

A glucocorticoid agent, prednisolone, was shown to exhibit anti-ulcer effects in adrenalectomized animals and ulcerogenic effects in animals with intact adrenal glands. That study showed that prednisolone possessed anti-ulcer properties not only in adrenalectomized animals but also in animals with intact adrenal glands in which blood adrenaline levels were decreased through the administration of metirosine. These results indicate that prednisolone exhibits a gastroprotective effect through alpha-2 adrenergic receptors in the absence or, to a lower extent, in the presence of adrenaline [17]. Alpha-2 adrenergic recep-

tors have been reported to contribute to the inhibition of ulcers induced by indomethacin, aspirin and ethanol; stress; and pylorus suturing [18, 19]. Alpha-2 adrenergic receptors are composed of the subunits Alpha-2a, Alpha-2b and Alpha-2c. The Alpha-2a subunit has been shown to be responsible for gastric emptying and the inhibition of increased motor activity, whereas the Alpha-2b and Alpha-2c subunits have been shown to be responsible for gastric protection [3, 20]. Alpha-2 adrenergic receptors act through multiple mechanisms to exhibit a gastroprotective effect [3]. Once stimulated, the presynaptic Alpha-2 adrenergic receptors located in the vagus nerve mediate the inhibition of gastric secretion and motility [20]. In conclusion, the Alpha-2 adrenergic receptors have been determined to be the receptors responsible for gastric protection, antioxidant activity and the production of the cytoprotective COX-1 enzyme. Furthermore, any type of drug or substance selectively stimulating the Alpha-2 adrenergic receptors may be assumed to possess anti-ulcer activity.

**Conflict of interest statement:** The authors declare that they have no conflict of interest to the publication of this article.

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