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RESEARCH ARTICLE

Direct Role of α_2-Adrenoreceptors in Antiulcer Effect Mechanism of Tianeptine in Rats [1]

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Summary

Tianeptine is an anti-depressant drug that also has an anti-ulcer activity. In this study, it was investigated whether or not α_2-adrenoreceptors have a role in the anti-ulcer effect mechanism of tianeptine. Furthermore, we investigated both intact and adrenalectomized rats to determine whether or not the anti-ulcer activity of tianeptine is related to adrenal gland hormones involved in this mechanism. In all rats, 25 mg/kg indomethacin produced gastric ulceration. Tianeptine was administered to the indomethacin-induced ulcers in the rats at different doses. Yohimbine, selective α_2-receptor blocker, was given (10 mg/kg) to some rats (adrenalectomized 6 groups and intact 4 groups), for blockage of the α_2-receptor. Tianeptine showed antiulcer effects of 59.6-81.6% in all animals. The results of this study show that tianeptine caused a significant anti-ulcer activity in both adrenalectomized and intact rats. Tianeptine does not have an anti-ulcer effect in rats which have been given yohimbine. Thus, the adrenal gland hormones do not have a direct effect on the anti-ulcer activity of tianeptine. This drug may be directly related to the α_2-adrenoreceptors. Moreover, the anti-ulcer effect shows an increase in parallel with increasing dose. This property of tianeptine could make it suitable for use in the treatment of both depression and peptic ulcer patients.

Keywords: *Tianeptine, Adrenalectomy, Indomethacin, Ulcer, α_2-receptor, Rat*

Sıçanlarda Tianeptinin Antiülser Etki Mekanizmasında α_2-Adrenoreseptörlerin Direkt Etkisi

Özet

Tianeptin antiülser aktiviteye de sahip antidepresan bir ilaçtır. Bu çalışmada tianeptinin antiülser mekanizmasında α_2 reseptörlerin rollerinin olup olmadığı araştırılmıştır. Ayrıca, tianeptinin antiülser mekanizmasında adrenal bez hormonları ile ilişkili olup olmadığını hem sağlıklı hem de adrenalektomi yapılan ratlarda incelenmiştir. 25 mg/kg indometazin tüm ratlarda gastrik ülserasyon meydana getirdi. İndometazinle indüklenerek ülser oluşturulan ratlara farklı dozlarda tianeptin uygulanmıştır. Seçici bir α_2-reseptör blokörü olan yohimbin (10 mg/kg) reseptör blokajı için hayvanların bir kısmına (adrenalektomili 6 grup ve sağlam 4 grup) verilmiştir. Tianeptin tüm hayvanlarda %59.6-81.6 anti-ülser etki meydana getirdiği tespit edilmiştir. Bu sonuçlar göstermektedir ki tianeptin hem sağlıklı hem de adrenalektomili hayvanlarda önemli bir anti ülser etki meydana getirdiği gözlenmiştir. Yohimbin verilen hayvanlarda ise antiülser etki oluşturmadığı tespit edilmiştir. Bu yüzden, tianeptinin anti ülser etki mekanizmasında adrenal bez hormonları direk bir role sahip olmadığı gözlenmiştir. Bu ilaç α_2-reseptörlerle direk alakalı olabilir. Ayrıca anti ülser etki doza parallel olarak doz arttıkça artmaktadır. Tianeptinin bu özelliği onu hem depresyonlu hem de gastrik ülserli hastaların tedavisinde kullanıma uygun hale getirebilir.

Anahtar sözcükler: *Tiyaneptin, Adrenalektomi, Indometazin, Ülser, α_2-reseptör, Rat*

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INTRODUCTION

Peptic ulcer is a multi-etiologic, chronic disease that features relapses. Although the disease has been known for many years, opinions about its etiology have recently changed. Nevertheless, the ethological factors are not known in roughly 60-80% of cases [1]. The role of balance disorder between aggressive and preventive factors in the occurrence of peptic ulcer is known. Drugs (non-steroidal anti-inflammatory drugs-NSAIDs), alcohol use, stress and *Helicobacter pylori* are the most important aggressive factors leading to peptic ulcers [2-5]. Previous studies have confirmed the occurrence of gastroduodenal damage in longterm NSAID users [6]. NSAIDs, especially indomethacin, are used to produce an experimental ulcer model in animals [7]. Evidence suggests that indomethacin causes gastric damage by inhibiting COX-1, PGE2, bicarbonate, and mucus production by increasing acid secretion. Moreover, it is known that classic anti-ulcer drugs comprise an anti-ulcer effect, contrary to indomethacin (by increasing COX-1, PGE2, bicarbonate, and mucus production by decreasing acid secretion) [8]. However, while it has been shown that aspirin inhibits PGE2, intraperitoneal administration of aspirin prevented indomethacin-induced ulcers [9]. It has also been reported that lansoprazole has an anti-ulcer effect without affecting gastric PGE2 synthesis [10], and that although morphine decreased gastric acid secretion, it did not prevent indomethacin-induced ulcers [11]. Researchers have also revealed that atropine reduced gastric acid secretion via blockage of muscarinic receptors in parietal cells, but there was no anti-ulcer activity of atropine after bilateral vagotomy surgery [12, 13]. Some alcholoids could also have an anti-ulcer effect without affecting mucus secretion, for example, famotidine [14, 15]. These studies indicate that the relationship in stimulation of PG, bicarbonate, mucus production and inhibition of acid secretion between anti-ulcer effect is unreliable. Previous studies on receptor activity have demonstrated that α_2-adrenoreceptors play a role in the basic mechanism of gastric ulcer prevention [8]. It has been shown that stimulation of α_2-adrenoreceptors leads to a gastro-protective effect, and the blockage of these receptors leads to gastric injury. Moreover, the stimulation of α_2-adrenoreceptors by prednisolone (with adrenalectomy) causes a gastro-protective effect [16].

In our study, we used tianeptine, which is an atypical anti-depressive drug, to stimulate α_2-adrenoreceptors. Previous studies have reported that tia-neptine prevented indomethacin-induced ulcers in rats [17]. However, there are currently no studies investigating a possible link between the anti-ulcer effect mechanism of tianeptine and receptors.

Therefore, the aim of this study was to investigate whether α_2-adrenoreceptors have a role in the anti-ulcer effect mechanism of tianeptine.

MATERIAL and METHODS

Animals

In this study, a total of 220 male Albino Wistar Rats (200-200 g) were used. The animals were received from the Medicinal and Experimental Application Research Center of Ataturk University. They were housed and fed in the laboratory at 22°C under standard conditions (CCAC, 1993). Animal experiments were performed in accordance with the national guidelines for the use and care of laboratory animals and approved by the local animal care committee of Ataturk University (No:47/2009).

Chemicals

Yohimbine and misoprostol were obtained from Sigma (Turkey), thiopental sodium was provided by IE Ulugay (Turkey), indomethacin was purchased from Deva (Turkey) and tianeptine was supplied from Pfizer (Turkey).

Effects of Tianeptine on the Indomethacin-Induced Ulcers in Intact Rats

In this experiment, the anti-ulcer effect of tianeptine was investigated in the indomethacin-induced ulcers in rats [18]. Initially, the rats were divided into 22 groups (n=10). Tianeptine was administered by oral gavage at a single dose to the rat groups (groups 1, 2, and 3) which had been fasted for 24 h at doses of 5, 10 and 20 mg/kg, respectively. Misoprostol was given orally to another group of rats (group 4) at a dose of 200 mg/kg. The control group (group 5) was treated with an equal volume of distilled water, orally. Five minutes after the drug treatments, a 25 mg/kg dose of indomethacin was administered to all animal groups by oral gavage. The rats were euthanatized by overdose of a general anesthetic (thiopental sodium, 50 mg/kg) 6 h after administration of the indomethacin. The stomachs of the animals were then removed and the ulcerated areas were examined macroscopically. The ulcerated areas on the surface of the stomachs were measured in square millimeters. The numerical results obtained from the tianeptine and misoprostol groups were evaluated by comparing them with the results of the control group.

Effects of Tianeptine on the Indomethacin-Induced Ulcers in Adrenalectomized Rats

In this second series of experiments, the anti-ulcer activity of tianeptine was investigated in the indomethacin-induced ulcers in rats which had been adrenalectomized. The adrenal glands of the rats had been removed under anesthesia by intra-peritoneal injection of thiopental sodium at a dose of 25 mg/kg. We waited for one week after the rats had been adrenalectomized, and during that time they were watered with 1% NaCl and fed pellet feed. After that week, the groups of rats which had been

fasted for 24 h were administered tianeptine (5, 10, and 20 mg/kg) and misoprostol (200 mg/kg) according to the procedure described above and 5 minutes after the drug treatments, a 25 mg/kg dose of indomethacin was administered to all animal groups by oral gavage. Six hours after the indomethacin administration, rats were killed by overdose of thiopental sodium. After this, the stomachs were removed and the ulcerated areas on the stomach surfaces were measured and the numerical results were compared with those of the control group.

Effects of Tianeptine on the Indomethacin-Induced Ulcers in Adrenalectomized and Intact Rats Given Yohimbine

In this experiment, yohimbine was administered at a dose of 10mg/kg intra-peritoneally to the first four adrenalectomized rat groups that had been fasted for 24 h (groups 1, 2, 3, and 4). Thirty minutes after the yohimbine injection, tianeptine was administered by oral gavage to the first three groups (groups 1, 2, and 3) at doses of 5, 10 and 20 mg/kg, respectively. Misoprostol was given to group 4 by the same route at a dose of 200 mg/kg. The control group (group 5) received an equal volume of distilled water as a solvent. Five minutes after the tianeptine and misoprostol administration, a 25 mg/kg dose of indomethacin was given to all rat groups by oral gavage. Six hours after the indomethacin treatment, the animals were killed by overdose of anesthetic (thiopental sodium). After this, the stomachs were removed and the ulcerated areas on the stomach surfaces were evaluated macroscopically. Then all stomachs were evaluated by measuring ulcerated areas on square millimeter paper. After measuring the ulcerated areas on the mucosa of the stomachs, the results were compared with those of the control group.

In parallel to this experiment, the same drug administrations were also given to intact rats. The results obtained from the intact rats were compared with those of the adrenalectomized rats.

The results obtained from the experiments are shown as means±SD. All data were numerical and appropriate for normal distribution. So we could perform parametric ANOVA test. Thereby differences between groups were calculated using one-way ANOVA with Fisher's post-hoc LSD (least significant differences). All statistical analyses were carried out using SPSS 18.0 software (SPSS Inc, Chicago, Ill) and the significance level was $P< 0.05$.

RESULTS

Tianeptine Test on the Indomethacin-Induced Ulcers in Intact Rats

As shown in *Table 1*, the mean ulcer areas were 13.8±1.2, 9.6±0.8, and 6.3±0.8 mm^2 at the doses of 5, 10, and 20 mg/kg in tianeptine treated intact rats, respectively, while they were 6.6±0.8 and 34.1±1.7 mm^2 in misoprostol treated rats and the control group, respectively.

Tianeptine Test on the Indomethacin-Induced Ulcers in Adrenalectomized Rats

The mean ulcerated areas were 16.3±0.8, 13.6±1.1, and 8.1±0.7 mm^2, at the doses of 5, 10, and 20 mg/kg in tianeptine treated adrenalectomized rats, respectively, while in the misoprostol treated rats and the control group they were 7.0±0.9 and 42.0±1.9 mm^2, respectively *(Table 2)*.

Yohimbine Test on the Indomethacin-Induced Ulcers in Adrenalectomized and Intact Rats

As depicted in *Table 3*, the mean ulcerated areas were 41.3±2.4, 39.8±2.4, and 42.8±2.1 mm^2 at the doses of 5, 10, and 20 mg/kg in tianeptine treated adrenalectomized rats, respectively. The area in the misoprostol treated group was 1.8±0.6 mm^2, while it was measured as 43.6±3.2 mm^2 in the control group. No ulcers were detected in the group which received only yohimbine, while a mean ulcerated area of 37.0±1.9 mm^2 was seen in the group administered yohimbine plus indomethacin.

In intact animals which had received yohimbine, the ulcerated areas of used tianeptine at the doses 5, 10, and 20 mg/kg were 35.3±2.6, 40.5±2.5 and 33.8±2 mm^2 while these areas were 2.0±0.3 and 38.0±3.4 mm^2 in the misoprostol and control groups, respectively *(Table 4)*.

Table 1. *Effects of tianeptine and misoprostol on the indomethacin-induced ulcers in intact rats (*=P<0.05 when compared to control group)*
Tablo 1. *Sağlıklı sıçanlarda indometazinle indüklenen ülser modelinde tianeptin ve mizoprostolün etkisi (*= kontrole göre P<0.05 oranında anlamlı şekilde farklı)*

Drugs	Animal Number (n)	Dosage	Ulcer Area mm^2	Antiulcer Effect (%)	P
Tianeptine + Indomethacin	10	5 mg/kg + 25 mg/kg	13.8±1.2*	59.6	<0.0001
Tianeptine + Indomethacin	10	10 mg/kg + 25 mg/kg	9.6±0.8*	71.9	<0.0001
Tianeptine + Indomethacin	10	20 mg/kg + 25 mg/kg	6.3±0.8*	81.6	<0.0001
Misoprostol + Indomethacin	10	200 mg/kg + 25 mg/kg	6.6±0.8*	80.7	<0.0001
Indomethacin (Control)	10	25 mg/kg	34.1±1.7	-	-

Table 2. *Effects of tianeptine and misoprostol on the indomethacin-induced ulcers in adrenalectomized rats (*=P<0.05 when compared to control group)*

Tablo 2. *Adrenelektomi yapılan sıçanlarda indometazinle indüklenen ülser modelinde tianeptin ve mizoprostolün etkisi etkisi (*= kontrole göre P<0.05 oranında anlamlı şekilde farklı)*

Drugs	Animal Number (n)	Dosage	Ulcer Area mm²	Antiulcer Effect (%)	P
Tianeptine + Indomethacin	10	5 mg/kg + 25 mg/kg	16.3±0.8*	61.2	<0.0001
Tianeptine + Indomethacin	10	10 mg/kg + 25 mg/kg	13.6±1.1*	67.7	<0.0001
Tianeptine + Indomethacin	10	20 mg/kg + 25 mg/kg	8.1±0.7*	80.8	<0.0001
Misoprostol + Indomethacin	10	200 mg/kg + 25 mg/kg	7.0±0.9*	83.4	<0.0001
Indomethacin (Control)	10	25 mg/kg	42.0±1.9	-	-

Table 3. *Effects of tianeptine and misoprostol on the indomethacin-induced ulcers in yohimbine given adrenalectomized rats (*=P<0.05 when compared to control group)*

Tablo 3. *Adrenelektomi yapılan ve yohimbine verilen sıçanlarda indometazinle indüklenen ülser modelinde tianeptin ve mizoprostolün etkisi etkisi (*= kontrole göre P<0.05 oranında anlamlı şekilde farklı)*

Drugs	Animal Number (n)	Dosage	Ulcer Area mm²	Antiulcer Effect (%)	P
Yohimbine + Tianeptine + Indomethacin	10	10 mg/kg + 5 mg/kg + 25 mg/kg	41.3±2.4	5.3	> 0.05
Yohimbine + Tianeptine + Indomethacin	10	10 mg/kg + 10 mg/kg + 25 mg/kg	39.8±2.4	8.8	> 0.05
Yohimbine + Tianeptine + Indomethacin	10	10 mg/kg + 20 mg/kg + 25 mg/kg	42.8±2.1	1.9	> 0.05
Yohimbine + Misoprostol + Indomethacin	10	10 mg/kg + 200 mg/kg + 25 mg/kg	1.8±0.6*	95.9	<0.0001
Yohimbine + Indomethacin	10	10 mg/kg + 25 mg/kg	37.0±1.9	15.2	> 0.05
Yohimbine	10	10 mg/kg	0±0	-	-
Indomethacin (Control)	10	25 mg/kg	43.6±3.2	-	-

Table 4. *Effects of tianeptine and misoprostol on the indomethacin-induced ulcers in yohimbine given intact rats (The P value shows comparison between control group and other groups, % calculation is made according to the control group. *=P<0.05 when compared to contro group)*

Tablo 4. *Yohimbin verilen intakt sıçanlarda indometazinle indüklenen ülser modelinde tianeptin ve mizoprostolün etkisi (P değeri kontrol grubu ile diğer gruplar arasındaki karşılaştırmayı göstermektedir, % hesabı kontrol grubuna göre yapılmıştır. *= kontrole göre P<0.05 oranında anlamlı şekilde farklı)*

Drugs	Animal Number (n)	Dosage	Ulcer Area mm²	Antiulcer Effect (%)	P
Yohimbine + Tianeptine + Indomethacin	10	10 mg/kg + 5 mg/kg + 25 mg/kg	35.3±2.6	7.2	> 0.05
Yohimbine + Tianeptine + Indomethacin	10	10 mg/kg + 10 mg/kg + 25 mg/kg	40.5±2.5	6.5	> 0.05
Yohimbine + Tianeptine + Indomethacin	10	10 mg/kg + 20 mg/kg + 25 mg/kg	33.8±2.0	11.1	> 0.05
Yohimbine + Misoprostol + Indomethacin	10	10 mg/kg + 200 mg/kg + 25 mg/kg	2.0±0.3	94.8*	<0.0001
Indomethacin (Control)	10	25 mg/kg	38.0±3.4	-	-

DISCUSSION

In the present study, we investigated whether α_2-adrenoreceptors have a role in the anti-ulcer effect mechanism of tianeptine. It has been reported in the literature that the α_2-adrenoreceptors have a gastro-protective effect [19]. It has also been demonstrated that clonidine, an α_2-receptors agonist, prevents the development of indomethacin-induced ulcers because α_2-adrenoreceptors have a role in gastro-protection [20]. Furthermore, Dijoseph et al.[21] and Del Soldato [22] revealed that presynaptic α_2-adrenoreceptors have a role in the inhibition of indomethacin-, aspirin-, ethanol-, stress-, and pyloric-ligation-induced ulcers. The α_2-gastro-protective effect

of adrenoreceptors is thought to be mediated through multiple mechanisms [23]. The stimulation of α_2-adrenoreceptors inhibits gastric acid secretion and motility, and these effects occur with the activation of presynaptic α_2-adrenoreceptors in the vagus nerve and during the inhibition of acetylcholine release [19]. One of the multiple gastro-protective mechanisms of α_2-adrenoreceptors may be stimulation of cyclooxygenase-1 (COX-1), because previous experimental studies have shown that the stimulation of α_2-adrenoreceptors produced an increase in the activity of COX-1 [24]. Moreover, it is known that the COX-1 enzyme is responsible for gastro-protection, and that metyrosine caused a gastro-protective preventing that COX-1 enzyme which inhibited by indomethacin [25]. It has also been revealed that the stimulation of α_2-adrenoreceptors causes a decrease in oxidant parameters while increasing anti-oxidant parameters [26]. These data demonstrate that the α_2-adrenoreceptors produced the gastro-protective effect via different mechanisms. Furthermore, it has been suggested that tianeptine exposed a gastro-protective effect by inhibiting oxidant parameters while increasing anti-oxidant parameters which had been decreased by indomethacin in the stomach tissue of rats [17].

In this study, we investigated both intact and adrenalectomized rats to determine whether or not the anti-ulcer activity of tianeptine is related to adrenal gland hormones that are involved in the anti-ulcer effect mechanism of tianeptine. Some studies have demonstrated that the anti-ulcer activity is reduced by adrenalectomy. Moreover, it has been reported that the anti-ulcer activity in intact rats was reversed via adrenalectomy [27,28]. A further study suggested that nimesulide produced a gastro-protective effect via the stimulation of α_2-adrenoreceptors by means of adrenal gland hormones [16]. In the present study, tianeptine also caused an anti-ulcer effect in adrenalectomized animals. Thus, it appears that the adrenal gland hormones do not have a direct affect on the anti-ulcer activity of tianeptine. It has also been determined that the α_2-adrenoreceptors have a direct role in the anti-ulcer effect mechanism of tianeptine using the yohimbine test. The results obtained show that tianeptine does not have an anti-ulcer effect in rats given yohimbine and tianeptine and that a direct gastro-protective effect occurs via the α_2-adrenoreceptors. In addition, it is known that yohimbine is a selective blocker of α_2-receptors [29]. However, it cannot be assumed that the gastro-protective potential of tianeptine and others anti-depressants results from their anti-depressant effects, as fluvoxamine, tianeptine, and mirazapine have a significant anti-ulcer effect, while trazodone and venlafaxine do not [17,30,31]. It must also be noted that, in our study, tianeptine was given as a single dose and the influence of a single dose does not occur in the short-term. Tianeptine is an atypical anti-depressant drug, which is different from other selective serotonin reuptake inhibitors (SSRIs) and tricyclic anti-depressants. While classic tricyclic anti-depressants and SSRIs inhibit serotonin reuptake, in contrast, tianeptine enhances this reuptake [32].

Consequently, we have shown in the present study that tianeptine caused a significant anti-ulcer activity in both intact and adrenalectomized rats. We determined that the anti-ulcer activity of tianeptine was directly related to the α_2-adrenoreceptors. Moreover, tianeptine's anti-ulcer effect increased in parallel with increasing dose. This property of tianeptine could make it suitable for use in the treatment of both depression and peptic ulcer patients.

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