Research Article

Gastric Mucosa Re-epithelisation, Oxidative Stress and Apoptosis During Healing of Acetic Acid-Induced Ulceration in Thyroxine Treatment and Thyroidectomy on Rats

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Keywords: Ulcer Healing; Thyroxine; Lipid peroxidation; Apoptosis

ABSTRACT

We had earlier reported that thyroxine treatment accelerates gastric ulcer healing while thyroidectomy delayed the processes of healing. Thus, this research was carried out to gain more insight about the mechanisms by which thyroxine affect ulcer healing. Male albino rats (160 – 200g) were used. They were divided into four groups viz: control, thyroidectomised, thyroidectomised with thyroxine treatment (100µg/kg/day) and Sham operated animals treated with thyroxine. After 35 days of drug treatment and surgery, ulcer was induced in stomach of animals using acetic acid method. Animals were sacrificed on days 3, 7 and 10 post ulcer induction for ulcer healing assessment. Healing was observed by measuring ulcer depth and width, lipid peroxidation and DNA fragmentation during healing. Result showed that by day 10, thyroxine treatment significantly decreased the ulcer width and depth by 69.3 ± 1.5% and 65.7 ± 1.4% (p< 0.01) respectively while thyroidectomy significantly reduced by (34.1 ± 0.5%) and (35.6 ± 7.5%) (p< 0.05) compared with control (40.5 ± 2.2%) and (53.9 ± 1.6%). Thyroxine treated animals had highest reduction in lipid peroxidation (57.0 ± 0.5% [p< 0.001]) and the least reduction in thyroidectomised animals (15.7 ± 1.6% [p< 0.05]) as compared with control (19.6 ± 1.6%). DNA fragmentation was low in all groups by day 3, but by day 10 the higher DNA fragmentation in thyroxine treated animal supports the rapid reduction in ulcer dimensions recorded. In conclusion, thyroxine treatment accelerated gastric ulcer healing by accelerating mucosa re-epithelization, reduction of lipid peroxidation and apoptotic mechanism.

INTRODUCTION

Reactive oxygen species has been implicated in the pathogenesis of many diseases in the body including gastric ulcer through oxidative damage (Halliwell and Gutteridge, 1986). Reactive oxygen species have been reported to be involved in stress (Das et al., 1997), nonsteroidal anti-inflammatory drugs (Langman et al., 1991), H. pylori (Konturek et al., 1999) and acetic acid induced ulcer (Olaleye et al., 2007). Thus lipid peroxidation, an important parameter for OH-induced oxidative damage of membrane, is increased in gastric lesions (Pihan et al., 1987; Yoshikawa et al., 1993; Yoshikawa et al., 1986; Olaleye et al, 2007). Therefore any agent that inhibit generation of reactive oxygen species, inhibit lipid peroxidation or generate antioxidants to mop up the reactive oxygen species is capable of reduce ulcer formation or accelerate the process of healing (Rodriguez et al, 2006; Ray et al, 2002)

Wound healing involves a series of rapid increases in specific cell populations that prepare the wound for
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repair, deposit new matrices and finally, mature the wound. Upon completing their tasks, these specific cell types must be eliminated from the wound prior to the progression to the next phase of healing. The most logical method of cellular down-regulation is through apoptosis. Apoptosis allows for the eliminations of entire populations without tissue damage or an inflammatory response (Greenhaugh, 1998). During healing, rapid increase in cell proliferation is allowed by an initial decrease of apoptosis. Later, when the inflammatory process begins to shut down with wound closure and scar evolution, there is a dramatic decrease of cellularity, which has been clearly shown to be mediated by an increase of apoptotic cell death (Desmouliere et al, 1995).

Studies on the effect of thyroxine on oxidative stress revealed that hyperthyroidism and hypothyroidism leads to increase generation of superoxide radical and hydrogen peroxide (Fernandez and Videla, 1993; Yilmaz et al., 2003; Resch et al., 2002), with resultant increase in lipid peroxidation in the liver and testis of rats (Chandra et al., 2010; Chattopadhyay et al., 2003). On the other hand, Chandra et al., (2010), Sal’nikova and Dubinina, (1985) reported that thyroxine treatment increased SOD, catalase, glutathione peroxidase and glutathione activities in response to oxidative stress, revealing that antioxidant status is enhanced in hyperthyroid state. Fernandez et al., (1988) however reported that hyperthyroid state reduces the activities of SOD, catalase and GSH in the hepatocytes and kupffer cells. Hypothyroidism is reported to decrease the activity of antioxidant defense system (Pasupathi and Latha, 2008; Chattopadhyay et al., 2003).

We had earlier reported that thyroid hormone is important in maintaining the integrity of the gastrointestinal tract and that thyroxine accelerated gastric ulcer healing by accelerating inflammatory and proliferative phases of healing and increased white blood count during healing while thyroidectomy delayed these processes (Olaleye et al., 2013). Thus, this research aims to further investigate the mechanisms by which thyroid hormone affect gastric ulcer healing by considering the effects of the hormone on the histomorphometry, oxidative stress and apoptosis.

MATERIALS AND METHODS

Drug and Animal Grouping
Levothyroxine was purchased from Octavis, Barnstaple, UK, thiopentone sodium was purchased from Rotex Medica, Germany and procaine penicillin was obtained from China Medical Medicines, Guorui Pharmaceuticals Co. Ltd.

Male albino Wistar rats (160 -200g) were obtained from animal house, College of Medicine, University of Ibadan, Nigeria. They were randomly divided into four groups with adequate matching of weight. The animals were grouped as follows: Group1, were control, sham operated euthyroid rats; group 2 were untreated thyrodecomised rats; group 3 were thyroidectomised animals treated with thyroxine (T4) at a dose of 100µg/kg per day p.o for 35 days and group 4 were animals Sham operated animals treated with thyroxine (100µg/kg per day p.o) for 35 days. They were kept in wire meshed cages and fed with standard diet of commercial rat chow and tap water ad libitum.

Surgical procedures:

Sham operation:
The animals were anaesthetised using 50mg/kg thiopentone sodium. A midline incision was made in the neck region, the thyroid gland was exposed, but the thyroid gland was left intact. The incision was sutured back, dabbed with procain penicillin and the animals were returned to standard diet and tap water.

Thyroidectomy:
The animals were anaesthetized using thiopentone sodium (50mg/kg). A midline incision was made in the neck region, the skin was bilaterally retracted, the fascia and the muscle covering the thyroid gland were carefully removed, the thyroid gland was then extirpated. Care was taken so that the parathyroid glands are not removed. The incision was sutured back, cleaned with procain penicillin and the animals were returned to standard diet and tap water.

Ulcer induction:
After 35 days drug treatment and post surgery, ulcer was induced in the stomach of animals. The rats were fasted for 18 h before ulcer induction. Gastric ulcers were produced by the method of Wang et al. (1989) with slight modifications. Animals were anaesthetised using 50mg/kg thiopentone sodium. Laparatomy was performed and stomach was exposed. Acetic acid (0.5 ml, 80% vol/vol) was applied to the serosal surface of glandular portion of the stomach for 1 minute using a 2ml syringe barrel that had been cut and smoothed. The acid was removed by aspiration and the area was washed with sterile saline. The abdomen was sutured

close. Thereafter, the animals were returned to standard diet of laboratory chow and tap water.

**Measurement of Animal Weight**
Each animal was weighed weekly for the total period of study using digital weighing scale (Citizen Model MP 2000).

**Histomorphometry**
On days 3, 7 and 10 respectively, five animals were randomly picked from each group, each was sacrificed by cervical dislocation and their stomachs were removed, opened along greater curvature, rinsed with normal saline. Stomachs were fixed with 10% formalin, small pieces of tissue, including ulcers, were embedded in paraffin and sectioned at 5µm in an automated microtome, tissues were stained with haematoxylin and eosin (Ogihara and Okabe, 1993). Using the histological slides prepared, a graticle having 1 to 100µm calibration was attached to a microscope, and the ulcer depth and width were then measured.

**Biochemical study (Lipid peroxidation)**
Assessment of lipid peroxidation was carried out following the procedure described by Varshney and Kale (1990). It is based on the reaction of malondialdehyde (MDA) produced during lipid peroxidation with thiobarbituric acid (TBA) forming a pink colour MDA-TBA adduct that absorbs strongly at 532nm. Each animal was sacrificed, laparatomy was performed and the stomach was brought out. The stomach was cut open along the greater curvature, rinsed with normal saline, the mucosa of the ulcerated area was scraped and homogenised in phosphate buffer (tissue to buffer ratio - 1:3), 0.2ml of test sample was added to 0.8ml of Tris-KCl (Ajeigbe et al., 2008; Derin et al., 2004). The solution was quenched with 0.25ml of TCA. 0.25ml of TBA was then added and the solution was then incubated for 45 minutes at 80°C. A pink coloured reaction mixture was formed. The reaction mixture was then centrifuged at 1400 rpm for 15 minutes. The absorbance of the supernatant was read at 532 nm.

**Assessment of Index of Apoptosis - DNA Fragmentation**
The gastric mucosa was scraped and homogenized by maceration in PBSE (phosphate buffer solution and EDTA in the ratio of 1 EDTA: 24 PBS. Stomach tissue (~0.05 g in solution) was digested in a solution containing proteinase K (5 ul) added to 1mL of digestion buffer (final 0.5 mg/ml), it was then incubated at 65°C for 2 hours. It was mixed by vortexing, then centrifuged at 13,000 rpm for 15 min (Iwalokun et al., 2001). Supernatant was transferred into a new tube. Protein and cell debris was precipitated by adding 1/10 volume of sodium acetate, 3M pH 5.2 (final 0.3M), it was inverted to mix and then incubated at -20°C for 20 minutes. After this it was centrifuged at 13,000 rpm for 20 minutes. Supernatant was then transferred into another tube. Nucleic acid was precipitated out by adding 98% ethanol (twice vol of supernatant). It was inverted to mix and incubated at -20°C for 15 min and then centrifugated at 13,000 rpm for 15 min. Pellets were washed twice with 70% ethanol by spinning at 13,000rpm for 5mins, allowed to air dry and then re-suspended in Tris EDTA buffer (Iwalokun et al., 2001).

Agarose gel (0.8%) was prepared by dissolving 0.8g of agarose powder in 100 mL of x1 TBE (prepared by 1:10 dilution of x10 TBE stock with distilled water). The gel was boiled and allowed to cool to 50°C before adding 50 uL of 1 mg/mL ethidium bromide. After this, the ethidium bromide-stained gel was poured into the gel casting tray with comb inserted for well creation. DNA sample was loaded (8 uL of DNA sample + 2 uL Loading buffer) into each well of the gel submerged in x1 TBE (pH 8.3) buffer in the electrophoretic tank. The circuit was closed and run at 10V/cm for 45 min (Itoh et al., 1995).

DNA bands were visualized under UV light using a UV transilluminator. Photograph of DNA bands was taken using a digital camera. The size of DNA was extrapolated based on mobilities and sizes of the DNA markers co-electrophoresed with the sample.

**Statistical Analysis**
Results were expressed as Mean ± SEM, the difference between the means was determined using independent sample students t-test. The level of statistical significance was p<0.05.
RESULTS

Total Body Weight
Result showed that after 35 days of surgery and drug treatment, all groups of animals had gained weight. Control animals had 22.7 ± 1.7% increase in total body weight. Thyroidectomy significantly increased the percentage weight gain (29.1 ± 1.8%) (p< 0.05) while thyroxine treatment significantly decreased the percentage weight gain (18.4 ± 1.2%) (p< 0.05) as compared with control (Figure 1).

Histomorphometry
Histomorphometry showed that ulcer width in control animals was (106.2 ± 5.3 µm) on day 3 post ulcer induction. Ulcer width was significantly higher in thyroidectomised and throxine treated rats (126.0 ± 4.0 µm) (p< 0.05) and (176.0 ± 1.9 µm) (p< 0.01) respectively as compared with control on day 3 (Table 1). However, there was significant reduction in ulcer width on days 7 and 10 respectively in all groups of animals (p< 0.05). Figure 2, showed that on day 7, thyroxine treatment significantly decreased the ulcer width by 58.5 ± 3.7% (p< 0.01) as compared with control animals (21.3 ± 4.6%), the reduction in ulcer width in thyroidectomised animals was significantly low (13.6 ± 1.7%) (p< 0.05). By day 10, likewise as on day 7 thyroxine treatment significantly decreased the ulcer width by 69.3 ± 1.5% (p< 0.01) as compared with control (40.5 ± 2.2%). The reduction was significantly less in thyroidectomised animals (34.1 ± 0.5%) (p< 0.05) as compared with control animals.

Fig. 1
Percentage Weight Change in Animals Groups after 35 days of Drug and Surgical Treatment. N= 15, values are mean ± SEM; a= significant compared with animals in Control group on same day at p < 0.05

Fig. 2
Percentage decrease in ulcer width in Thyroxine Treated and Thyroidectomised Animals after Ulcer Induction as Compared With Day 3. N= 5, values are mean ± SEM
a= significant compared with animals in Control group on same day at p < 0.05. aa= significant compared with animals in Control group on same day at p < 0.01
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Fig. 3 Percentage decrease in ulcer depth in Thyroxine Treated and Thyroidectomised Animals after Ulcer Induction as Compared With Day 3. N= 5, value are mean ± SEM

a= significant compared with animals in Control group on same day at p < 0.05  aa= significant compared with animals in Control group on same day at p < 0.01

Table 1:
Ulcer width in Thyroxine Treated and Thyroidectomised Animals after Ulcer Induction

<table>
<thead>
<tr>
<th>Groups</th>
<th>Day 3 (µm)</th>
<th>Day 7 (µm)</th>
<th>Day 10 (µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>106.2 ± 5.3</td>
<td>83.0 ± 4.3x</td>
<td>62.8± 1.2xx</td>
</tr>
<tr>
<td>Thyroidectomised</td>
<td>126.0 ± 4.0</td>
<td>109.0 ± 4.6</td>
<td>83.0± 2.5xx</td>
</tr>
<tr>
<td>Thyroidectomised + T4</td>
<td>135.0 ± 6.3aa</td>
<td>84.0 ± 1.9xxx</td>
<td>69.0± 1.9xxx</td>
</tr>
<tr>
<td>Thyroxine treated</td>
<td>176.0 ± 1.9aa</td>
<td>73.0 ± 6.2xxx</td>
<td>54.0± 2.4xxx</td>
</tr>
</tbody>
</table>

N= 5, value are mean ± SEM. a= significant compared control on day 3 at p < 0.05, aa= significant compared control on day 3 at p < 0.01, x= significant compared with animals in same group on day 3 at p < 0.05, xx= significant compared with animals in same group on day 3 at p < 0.01, xxx= significant compared with animals in same group on day 3 at p < 0.001

Table 2:
Ulcer depth in Thyroxine Treated and Thyroidectomised Animals after Ulcer Induction

<table>
<thead>
<tr>
<th>Groups</th>
<th>Day 3 (µm)</th>
<th>Day 7 (µm)</th>
<th>Day 10 (µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>34.0 ± 1.9</td>
<td>21.0 ± 1.0xx</td>
<td>15.6± 0.6xx</td>
</tr>
<tr>
<td>Thyroidectomised</td>
<td>40.0 ± 4.4</td>
<td>27.0 ± 2.5x</td>
<td>24.4 ± 0.2xx</td>
</tr>
<tr>
<td>Thyroidectomised + T4</td>
<td>54.0 ± 4.4aa</td>
<td>28.0 ± 2.0xxx</td>
<td>18.8 ± 0.5xxx</td>
</tr>
<tr>
<td>Thyroxine treated</td>
<td>42.0 ± 1.2a</td>
<td>22.3 ± 1.1xxx</td>
<td>14.4 ± 0.6xxx</td>
</tr>
</tbody>
</table>

N= 5, value are mean ± SEM. a= significant compared control on day 3 at p < 0.05, aa= significant compared control on day 3 at p < 0.01, x= significant compared with animals in same group on day 3 at p < 0.05, xx= significant compared with animals in same group on day 3 at p < 0.01, xxx= significant compared with animals in same group on day 3 at p < 0.001

Biochemical study (Lipid Peroxidation)

On day 3 after ulcer induction, lipid peroxidation was significantly higher in thyroxine treated (271.6 ± 9.9 nmolMDA/mg protein) than in thyroidectomised animals (181.3 ± 6.8 nmolMDA/mg protein) (p< 0.001) and control (171.4 ± 6.5 nmolMDA/mg protein) (p< 0.001).
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By day 10, control and thyroxine treated rats had a significant reduction in lipid peroxidation (P< 0.01, 0.01) respectively, but there was no significant difference in thyroidectomised animals (Table 3). However, Figure 4, showed that on day 7, thyroxine treatment and thyroxine replacement therapy significantly reduced peroxidised lipid by 35.6 ± 2.4 (p< 0.01) and 15.4 ± 0.7% (p< 0.01) respectively as compared with control (12.4 ± 0.5%).

Table 3: Lipid peroxidation after Ulcer Induction

<table>
<thead>
<tr>
<th>Groups</th>
<th>Day 3 nmolMDA/mg protein</th>
<th>Day 7 nmolMDA/mg protein</th>
<th>Day 10 nmolMDA/mg protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>171.4 ± 6.5</td>
<td>151.6 ± 4.0x</td>
<td>140.1 ± 1.3xx</td>
</tr>
<tr>
<td>Thyroidectomised</td>
<td>181.3 ± 6.8</td>
<td>171.7 ± 7.5</td>
<td>166.6 ± 5.4</td>
</tr>
<tr>
<td>Thyroidectomised + T4</td>
<td>170.3 ± 6.3</td>
<td>158.2 ± 7.3</td>
<td>136.0 ± 1.7xx</td>
</tr>
<tr>
<td>Thyroxine treated</td>
<td>271.6 ± 9.9a</td>
<td>160.7 ± 8.3xxx</td>
<td>120.0 ± 13.9xxx</td>
</tr>
</tbody>
</table>

N= 5, value are mean ± SEM, a= significant compared control on day 3 at p < 0.001, x= significant compared with animals in same group on day 3 at p < 0.05, xx= significant compared with animals in same group on day 3 at p < 0.01, xxx= significant compared with animals in same group on day 3 at p < 0.001.

On day 10, thyroxine treatment and replacement therapy further decreased lipid peroxidation by 57.0 ± 0.5% (p< 0.001) and 23.7 ± 0.6% (p< 0.05) as compared with control animals (19.6 ± 1.6%). The reduction in lipid peroxidation was significantly less in thyroidectomised animals 15.7 ± 1.6% (p< 0.05) as compared with control.

Assessment of Index of Apoptosis (DNA Fragmentation)

Plate 1 shows that by day 3 after ulcer induction, there was DNA fragmentation in all groups of animals. As observed, DNA fragmentation was least in control animals and higher in thyroidectomised and thyroxine treated animals. Apoptosis was lower in all groups of animals on day 3 than on day 7 (Plate 2). By day 10, DNA fragmentation reduced in all groups as compared with that on day 7. However DNA fragmentation was lower in thyroidectomised that in thyroxine treated rats by day 10 (Plate 3).
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**DISCUSSION**

The result of this study further supports the earlier finding that thyroxine treatment accelerates gastric ulcer healing, while thyroidectomy delays ulcer healing (Olaleye et al, 2013). In this study, thyroxine treatment significantly decreased ulcer depth and width as compared with control animals, while thyroidectomy significantly reduced the rate of healing of ulcer. This is in line with the report that thyroxine treatment accelerates fibroblast proliferation, collagen deposition and epithelial cell proliferation, while thyroidectomy decreases these processes (Olaleye et al, 2013). This claim is also consistent with previous reports about the effects of thyroxine on healing in other tissues (organs) of the body (Kranz et al, 1976; Talmi et al, 1989; Safer et al, 2004, Lennox and Johnston, 1973). The effect of thyroxine in reduction of ulcer depth is important because depth is an important parameter that actually characterizes ulcer - penetrating the muscularis mucosa (Tarnaswski, 2000). The ability of thyroxine to accelerate healing of ulcer might be due to the ability of the hormone to stimulate biochemical process involved in cell growth and increase the mitotic activity of cells in the digestive system of rat (Adeniyi and Oloowokorun, 1989). Hypothyroidism on the other hand slowed down the rate of healing.

The effects of thyroxine treatment and thyroidectomy on body weight in this research are in line with earlier reports. Hyperthyroidism leads to decrease in weight because thyroid hormone increases basal metabolic rate (BMR), which invariably leads to increase increased caloric requirements to maintain weight. If the person does not increase the calories consumed to match the excess calories burned, then weight loss ensues (Thyroid and weight, 2014). Hypothyroidism on the other hand decreases energy expenditure, leading to a slight net gain in energy.
stores. Body weight increases on average due to an increase if body fat and retention of water and salt (Wiersinga, 2014)

The result of this research also revealed that there was lipid peroxidation in all groups of animals on day 3. This agrees with reports that free oxygen radicals are involved in the aetiology of acetic acid induced gastric ulceration (Olaleye et al., 2007, Demir et al., 2003). By day 10 after ulcer induction, there was greater reduction in peroxidised lipid in thyroxine treated rats as compared with control, while there was no significant change in lipid peroxidation in thyroidectomised animals. Experimental and clinical studies suggested that the reactive oxygen species have an important role in the aetio-pathogenesis of the inflammation and ulceration of the digestive tract (Perry et al., 1986, Olaleye et al., 2007). This is evidenced by the increased oxidative stress by pro-ulcerative factors in the gut such as H pylori (Janulaityte-Gunther et al., 2003), use of non-steroidal anti-inflammatory drugs (Rostom et al., 2000), smoking (Ma et al., 2000), psychological stress, corticosteroid use (Levenstein, 1999), and loss of sleep (Guo et al., 2005).

The significantly higher lipid peroxidation in thyroxine treated animals on day 3 as compared with control animals might be due to the ability of thyroxine to increase cellular respiration and thus increase the production of reactive oxygen species (Videla, 2000; Chandra et al., 2010). The increased oxidative stress then increase; size of ulcer and lipid peroxidation. However, the accelerated healing found in thyroxine treated animals might be due to the antioxidant effect of thyroxine (Wynn, 1968). Hence, there was greater reduction of lipid peroxidation in thyroxine treated animals by day 7 and 10. Authors had earlier reported that thyroxine increased the activities of SOD, catalase and glutathione peroxidase (Sal’nikova and Dubinina, 1985; Seven et al., 1996). Chandra et al., (2010) reported that thyroxine administration developed oxidative stress, but the organism defends itself against the effects of oxidative stress by increasing SOD and catalase activities as a protective mechanism. The insignificant reduction in lipid peroxidation in thyroidectomised rats might be due to the decrease antioxidant defense system, which had been reported in thyroidectomised animals (Pasupathi and Latha, 2008; Chattopadhyay et al., 2003), hence there was slower rate of healing in this group.

The result of this work also agrees with reports that apoptosis plays a significant role in gastric ulceration (Konturek et al., 1999; Fuji et al., 2000). By day 3, apoptosis occurred in the gastric mucosa of all groups of animals. Animals in control group showed less DNA fragmentation as compared with thyroidectomised and thyroxine treated animals. By day 7, apoptosis increased in all groups of animals, while on day 10, DNA fragmentation reduced in all groups of animals. However DNA fragmentation was higher in hyperthyroid animals than in hypothyroid animals on day 10. The initial decrease in apoptosis was important for proliferation to occur. In wound healing when healing processes had advanced, granulation tissue containing mainly small vessels, inflammatory cells, fibroblasts and myofibroblasts are removed by apoptosis, at the same time cell proliferation and reepithelisation is taking place (Desmouliere et al., 1997). Thus the increase in apoptosis on day 10 in hyperthyroid animals might be important for faster healing process (Desmouliere et al., 1997). Brown, et al., (1997) reported that apoptosis might signal the end of the inflammatory phase of healing. Cellular activity is lower in hypothyroid animals and healing is slow in the group, this might be as a result of the reduced apoptosis in the group by day 10. Sanchez-Fidalgo et al., (2004) reported that agents that reduced apoptosis slowed down gastric ulcer. Desmouliere et al., (1997) suggested that in cutaneous wounds as well results of other laboratories (particularly in lungs and kidney), apoptosis is the mechanism responsible for the evolution of granulation tissue into a scar.

In conclusion, thyroxine treatment accelerates gastric ulcer healing by accelerating re-epithelization, reducing lipid peroxidation and by apoptotic mechanism while thyroidectomy decreases the rate of healing by reducing re-epithelization and increased oxidative stress.

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