

News and reviews

Effects of burns on gut motor and mucosa functions

Hsien-Hao Huang^{a,b}, Yu-chi Lee^{c,1}, Chih-Yen Chen^{b,d,e,*}^a Department of Emergency Medicine, Taipei Veterans General Hospital, Taipei, Taiwan^b Faculty of Medicine, National Yang-Ming University School of Medicine, Taipei, Taiwan^c Graduate Institute of Medical Science, National Defense Medical Center, Taipei, Taiwan^d Division of Gastroenterology and Hepatology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan^e Taiwan Association for the Study of Small Intestinal Diseases, Guishan, Taiwan

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ABSTRACT

This review analyzed the published studies on the effects of thermal injury on gastrointestinal motility and mucosal damage. Our strategy was to integrate all available evidence to provide a complete review on the prokinetic properties of variable reagents and the potential clinical treatment of mucosal damage and gastrointestinal dysmotility after thermal injury. We classified the studies into two major groups: studies on gastrointestinal dysmotility and studies on mucosal damage. We also subclassified the studies into 3 parts: stomach, small intestine, and colon. This review shows evidence that ghrelin can recover burn-induced delay in gastric emptying and small intestinal transit, and can protect the gastric mucosa from burn-induced injury. Oxytocin and β -glucan reduced the serum inflammatory mediators, and histological change and mucosal damage indicators, but did not show evidence of having the ability to recover gastrointestinal motility. Using a combination of different reagents to protect the gastrointestinal mucosa against damage and to recover gastrointestinal motility is an alternative treatment for thermal injury.

1. Introduction

Severe thermal injury is usually an emergency event. Extensive dermal and tissue damage requires urgent medical intervention and fluid resuscitation. Immediately following thermal injury, local tissue damage consists of hypovolemia and ischemia. Early resuscitation with fluid replacement is the most crucial treatment, although it is typically accompanied by reperfusion injury. Initial fluid resuscitation via the peripheral vein is the most rapid and effective way to resuscitate patients with shock (Chen et al., 1982). However, on-site intravenous therapy is usually unavailable and difficult to establish, especially in cases of injury to the extremities and face, which are the most commonly affected areas in patients with burn injury. Enteral feeding through an orogastric route is an alternative and convenient way for emergent fluid resuscitation and nutrient support at the early stage of thermal injury. Unfortunately, reperfusion injury induced by thermal injury causes remote gastrointestinal disorders, the most common of which include adynamic ileus, decreased gastric emptying, increased gastric secretion and ulcer incidence, and gastrointestinal hemorrhage (Czaja et al., 1974). Gastroduodenoscopy findings have suggested

ischemic change of the mucosa within 72 h after a thermal injury (Czaja et al., 1974). This involves breakage of the intestinal mucosal barrier and disruption of mucosal integrity. Then, gut bacteria translocate into the systemic organs (Baron et al., 1994) and cause damage to multiple organs that are distant from the original local cutaneous burn injury (Deitch and Berg, 1987; Baron et al., 1994). In light of the importance of early resuscitation and its disadvantages, we offer a detailed review of studies on gastric, small intestinal and colonic damage, and the effect of different reagents on gastrointestinal motility and mucosal function, after a thermal injury.

1.1. Survey methodology

This review evaluated published research and review articles on thermal injuries and intestinal motility and permeability. Animal and cell culture studies on the effect of burns on motor function and the intestinal mucosa were included as in vivo studies, because such studies in humans are currently sparse. Related articles were searched without time restriction by using various medical databases, including PubMed, Google, and Google Scholar. The search was performed by combining

* Corresponding author at: Division of Gastroenterology and Hepatology, Department of Medicine, Taipei Veterans General Hospital, No. 201, Section 2, Shih-Pai Road, Taipei 112, Taiwan

E-mail address: chency@vghtpe.gov.tw (C.-Y. Chen).

¹ Current address: Department of Microbiology and Immunity, University of Rochester, Rochester, NY, U.S.A.

Table 1
Effects of hormones or enzyme inhibitors on intestinal permeability after thermal injury.

	Dose	Serum	Stomach	Small intestine	Colon	Species
Hormones						
Bombesin (Alican et al., 2000)	10 µg/kg/day, sc			MPO _i , P _↔ (2 h, 3d) ^a		Rat
Epidermal growth factor (Berlenga et al., 2002; Jahovic et al., 2004)	10 µg/kg, sc or licking			MPO _↔ , G _↔ , MDA _↔ (5d)		Rat
Estrogen (Ozveri et al., 2001)	10 µg/kg, ip	TNF-α↓	MDS _↔ , MPO _↔ (1d)	MDS _i (1d)		Rat
Ghrelin (Sehirli et al., 2008)	10 mg/kg, sc		MPO _i , D _i , G _i , MDA _i (6 h, 2d)			Rat
Hemin (heme oxygenase-1 inducer) (Gan and Chen, 2007)	10 ng/kg/day, sc (Sehirli et al., 2008)	TNF-α↓, IL-1β↓, LDH↓		MPO _i (1d)		Rat
Insulin-like growth factor-1 (Jeschke et al., 2007)	50 µmol/kg, ip					Rat
Leptin (Cakir et al., 2005)	10 mg/kg, iv q12h	TNF-α↓, IL-1β↓, IL-6 _↔		MDS _i (2d, 5d, 7d)	MDS _i , MPO _i (6 h, 1d)	Rat
Melatonin (Sener et al., 2002)	10 µg/kg, ip					Rat
Octreotide (somatostatin analogue) (Sener et al., 2003)	10 µg/kg, sc			MPO _i , G _i , MDA _i , P _i (3 h, 1d)		Rat
Oxytocin (İşeri et al., 2008; İşeri et al., 2010)	10 µg/kg, sc			MPO _i , G _i , MDA _i (3 h, 1d)		Rat
Oxytocin (İşeri et al., 2008; İşeri et al., 2010)	5 µg/kg, sc bid for 5 days	TNF-α ↓ (İşeri et al., 2008; İşeri et al., 2010); IL-6 ↓ (İşeri et al., 2008)	MDS _i , MPO _i , D _i , MDA _i (2d)	MDS _i , MPO _i , D _i , MDA _i (2d, 5d) (İşeri et al., 2010)		Rat
Enzyme inhibitors						
Androgen receptor blocker (cyproterone acetate) (Ozveri et al., 2001)	25 mg/kg, sc	TNF-α ↓ (1d)	MDS _↔ , MPO _↔ (1d)			Rat
Leukotriene-1 receptor blocker (montelukast) (Kabasakal et al., 2005)	10 mg/kg, ip	TNF-α ↓ LDH ↓ (1d)	MPO _i , G _i , MDA _i (1d)	MPO _i , G _i , M _i (1d)	MPO _i , G _i , MDA _i (1d)	Rat
COX-1 inhibitor (ketorolac) (Oktar et al., 2002)	3 mg/kg, orogastrically			MDS _↔ , MPO _i , G _↔ (6 h)		Rat
COX-2 inhibitor (nimesulide) (Oktar et al., 2002)	10 mg/kg, sc			MDS _↔ , MPO _i , G _i , MDA _↔ (6 h)		Rat
COX inhibitor (piroxicam) (Oktar et al., 2002)	5 mg/kg, orogastrically			MDS _↔ , MPO _i , G _i (6 h)		Rat
Endothelin-1 antagonist (PD156252) (Unluer et al., 2000)	10 mg/kg, iv			MPO _↔ , P _↔ (2 h, 3d)		Rat
Specific p38 MAPK inhibitor (SB203580) (Gan et al., 2007)	10 mg/kg, ip			MPO _i (1d)		Rat
6- <i>n</i> -propyl-2-thiouracil (Sener et al., 2006)	10 mg/kg, ip	TNF-α ↓	MPO _i , G _i , MDA _i (1d)			Rat
Others						
β-Glucans (Toklu et al., 2006)	50 mg/kg, orogastrically	TNF-α ↓				Rat
Cyclosporin A (Gürbüz et al., 1997)	3.75 mg/kg, local ointment	TNF-α ↓				Rat
	25 mg/kg/day, im for 3 days		MPO _↔ , P _↔ (2 h, 1d)			Rat

ip: intraperitoneally, iv: intravenously, sc: subcutaneously, q12h: every 12 h, im: intramuscularly.

MDS: microscopic damage score, histological examination.

MPO: myeloperoxidase activity, tissue polymorphonuclear leukocyte accumulation.

Damage of membrane and increased permeability (D: DNA fragmentation, G: glutathione, MDA: malondialdehyde, P: protein oxidation).

^a Time of rat decapitation after burn injury (h: hour, d: day).

Table 2

Effects of different fluids, hormones, and enzyme inhibitors on gastric emptying, intestinal transit, and colon transit after thermal injury.

	Dose	Gastric emptying	Small intestinal transit	Colon transit	Species
Various enteral fluid feeding					
Water (Hu et al., 1993)	200 mL/person, po	No effect (4d)			Human
Saline solution (Alican et al., 1995)	3 mL 300 mOsm/kg, po	Delayed (18 h)			Rat
WHO ORS (Sallam et al., 2011)	10 mg/kg, po	No effect (7d)			
Hyperosmolar saline solution (Alican et al., 1995)	3 mL 900 mOsm/kg, po	No effect (1 h, 6 h)	Delayed (1 h, 6 h)		Rat
Hydrochloric acid (Alican et al., 1995)	3 mL 50 Mm, po	Delayed (18 h, 7d)			Rat
Peptone solution (Alican et al., 1995)	3 mL 4.5%, po	No effect (18 h, 7d)			Rat
Vivonex (a caloric meal) (Sallam et al., 2011)	10 mg/kg, po	Delayed (1 h, 6 h)	No effect (1 h)		Rat
			Delayed (6 h)		
Methylcellulose (semi-solid) (Sallam et al., 2011)	1.5 mL, po	Delayed (1 h, 6 h)			Rat
Hormones					
Bombesin (Alican et al., 2000)	10 µg/kg/day, sc		Improved (2 h, 3d)		Rat
Ghrelin (Sallam et al., 2007; Sallam et al., 2011)	2 nmol/rat, ip	Improved (6 h) (Sallam et al., 2007; Sallam et al., 2011)	Improved (6 h) (Sallam et al., 2007)	No effect (6 h) (Sallam et al., 2007)	Rat
Heme oxygenase-1 inducer (hemin) (Gan and Chen, 2007)	50 µmol/kg, ip		Improved (1d)		Rat
Insulin (Sallam et al., 2011)	5 IU/kg, sc	Improved (6 h)			Rat
Oxytocin (Işeri et al., 2008)	5 µg/kg, sc	No effect (2d)			Rat
Enzyme inhibitors					
COX-1 inhibitor (ketorolac) (Oktar et al., 2002)	3 mg/kg, orogastrically		No effect (6 h)		Rat
COX-2 inhibitor (nimesulide) (Gan and Chen, 2005; Gan et al., 2007; Sallam et al., 2011)	10 mg/kg, ip (Gan and Chen, 2005; Gan et al., 2007; Sallam et al., 2011)	Improved (6 h) (Sallam et al., 2011)	Improved (12h) (Gan et al., 2007)	Improved (12 h) (Gan and Chen, 2005)	Rat
	10 mg/kg, sc (Oktar et al., 2002)		Improved (6 h) (Oktar et al., 2002)		Rat
COX-2 inhibitor (SC-58125) (Oliveira et al., 2009)	10 mg/kg, ip	Improved (6 h)	No effect (6 h)		Rat
COX inhibitor (piroxicam) (Oktar et al., 2002)	5 mg/kg, orogastrically		Improved (6 h)		Rat
Endothelin-1 antagonist (PD156252) (Unlüer et al., 2000)	10 mg/kg, iv		No effect (2 h)		Rat
Specific p38 MAPK inhibitor (SB203580) (Gan et al., 2007)	10 mg/kg, ip		Improve (3d)		Rat
			Improved (12 h)		
Selective iNOS inhibitor (SMT) (Gan and Chen, 2005; Gan et al., 2007)	5 mg/kg, ip		Improved (12 h) (Gan et al., 2007)	Improved (12 h) (Gan and Chen, 2005)	Rat
Selective neuronal NOS inhibitor (7-nitroindazole) (Gan and Chen, 2005)	20 mg/kg, ip			No effect (12 h)	Rat

po: orally, ip: intraperitoneally, iv: intravenously, sc: subcutaneously.

WHO ORS: World Health Organization oral rehydration solution, a citrate-buffered electrolyte solution.

Vivonex: a caloric meal.

Hyperosmolar saline solution: 900 mOsm/kg NaCl.

SMT: S-methylisothiourea.

ST-36: located at 5 mm below the head of the fibula under the knee joint and 2 m lateral to the anterior tubercle of the tibia.

the terms “burn” and “thermal injury” with “gastrointestinal motility” or “intestinal permeability.” Articles were selected for citation if they were deemed to have relevance in exploring the relationships between thermal injury and intestinal motility and permeability. We classified the studies into two major groups: studies on gastrointestinal motility and studies on intestinal permeability. We also subclassified the studies into the stomach, small intestine, and colon groups, and provided information about scientific advances in the field. We combined all the available information from previous studies, to provide a complete review on the effects of thermal injury on gastrointestinal motility and permeability, and the potential applications of our findings to the treatment of thermal injury (summarized in Tables 1 and 2, and illustrated as Fig. 1, respectively).

1.2. Effect of enteral fluid resuscitation on thermal injury

Thermal injuries considerably alter the function of many organ systems, including the cardiovascular, pulmonary, renal, and gastrointestinal systems (Wilson, 1996). Delayed gastric emptying time, decreased small intestinal transit time, and prolonged colon transit time are among the obvious effects of a burn injury, whereas fluid

resuscitation with saline infusion can substantially recover burn-induced gastrointestinal dysfunction (Chen et al., 1982). Fluid resuscitation within 2 h of a thermal injury may be one of the most important steps in preventing multiple organ failure and mortality (Barrow et al., 2000). However, sterile intravenous fluid therapy is usually difficult to implement during mass casualty scenarios or in wilderness settings. Enteral fluid resuscitation has been proven to have equivalent effect to that of intravenous fluid resuscitation in terms of hematocrit values, hemodynamics, and measured plasma volume in a swine study (Michell et al., 2006). In that study, about 93% of fluid infused into the duodenum was absorbed within 4 h after the thermal injury (Michell et al., 2006). Therefore, enteral resuscitation through drinking is an alternative and convenient way to restore the fluid status effectively and emergently after a thermal injury.

2. Effects of burns on serum mediators

Serum tumor necrosis factor (TNF)-α (Ozveri et al., 2001; Kabasakal et al., 2005; Sener et al., 2006; Toklu et al., 2006; Jeschke et al., 2007; Işeri et al., 2008; Şehirli et al., 2008; Işeri et al., 2010), interleukin (IL)-1β (Jeschke et al., 2007; Şehirli et al., 2008), and IL-6 (Jeschke et al.,

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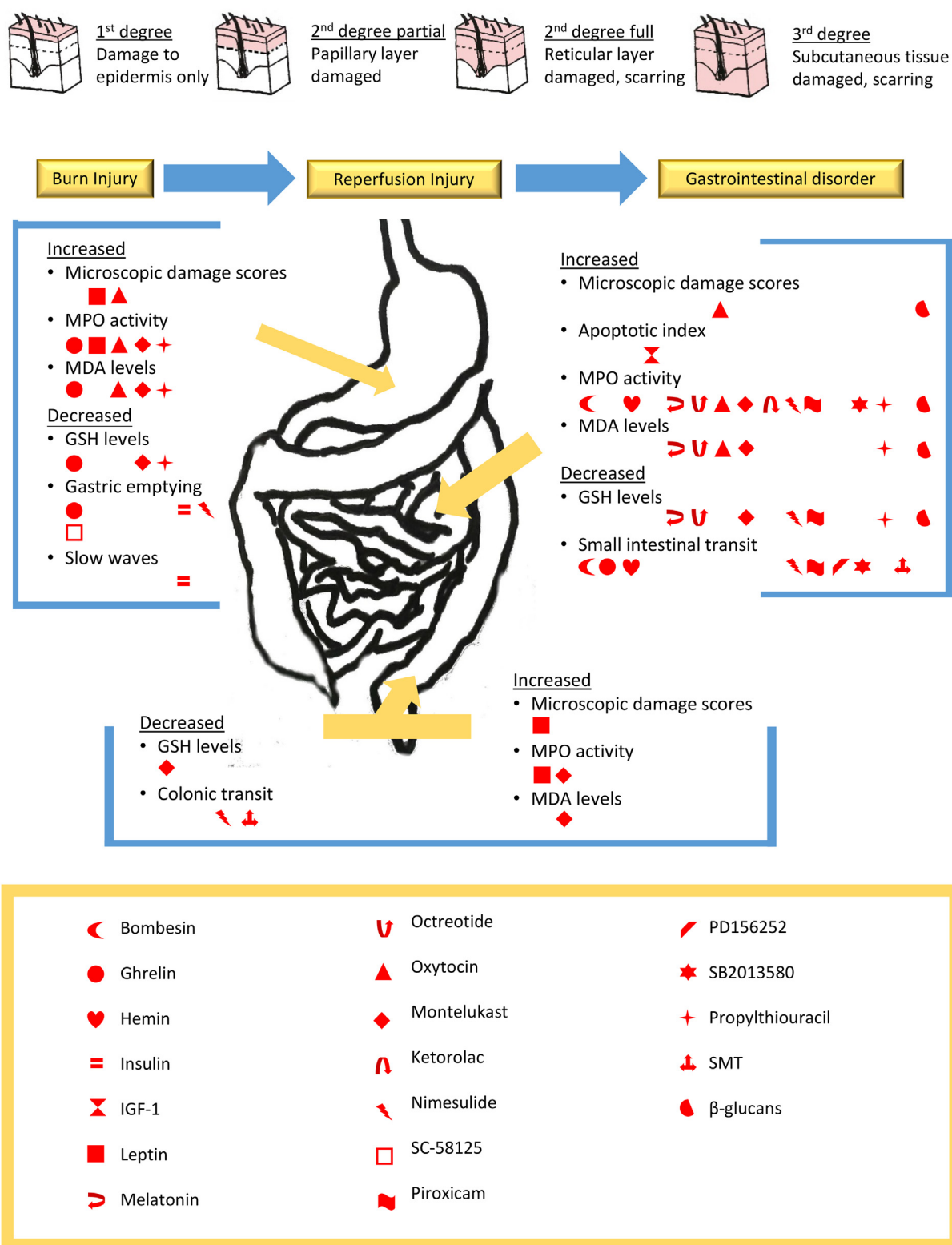


Fig. 1. Burn classification, effects of burn injury on the gastrointestinal tract and the treatments to remedy burn-induced gastrointestinal disorder. The arrows denote affected area and each shape denotes a specific substance. MPO: Myeloperoxidase; MDA: Malondialdehyde; IGF-1: Insulin-like growth factor-I; GSH: Glutathione; SMT: S-methylisothiourea.

2007; Işeri et al., 2008) were shown to be increased after burn injury.

2.1. Hormonal effects on serum cytokines

2.1.1. Estrogen

Normal immune response after trauma or hemorrhage was noted in female and castrated male rats; however, the immune response was observed to be suppressed in male rats (Wichmann et al., 1996, 1997). Testosterone has been reported to enhance vasoconstriction after trauma (Ajayi et al., 1995). Estrogen treatment, castration (testosterone elimination) and cyproterone acetate (androgen receptor blocker) considerably reduced the serum TNF- α levels at 1 day after the burn injury (Ozveri et al., 2001). Estrogen or antiandrogen may have clinical applications in abolishing burn-induced systemic inflammation (Ajayi et al., 1995).

2.1.2. Ghrelin

Ghrelin, a 28-amino-acid peptide hormone, is the endogenous ligand for the growth hormone secretagogue receptor secreted by the oxyntic mucosa of the gastric fundus (Chen et al., 2009, 2010; Chen et al., 2016; Huang et al., 2016). Ghrelin abolished the elevations of serum TNF- α and IL-1 β levels at both 6 h and 2 days after burn injury (Sehirli et al., 2008). Ghrelin inhibited the release of the inflammatory mediators, TNF- α and IL-1 β (Sehirli et al., 2008).

2.1.3. Insulin-like growth factor-1 (IGF-1)

IGF-1 is a small protein that has been shown to improve gut mucosal function after a thermal injury. IGF-1 improved the gut mucosal weight and reduced the rate of bacterial translocation to the mesenteric lymph nodes (Huang et al., 1993). The serum IGF-1 level was decreased after burn injury (Jeschke et al., 2007). IGF-1 considerably reduced the serum TNF- α and IL-1 β levels at 1 day after burn injury, but not the IL-6 level (Jeschke et al., 2007).

2.1.4. Oxytocin

Oxytocin considerably reduced the serum TNF- α level at 2 days (Işeri et al., 2008) and 5 days (Işeri et al., 2010) after burns, and reduced the serum IL-6 level at 2 days after burns (Işeri et al., 2008). Oxytocin can abolish burn-induced proinflammatory reaction.

2.2. Effects of enzyme inhibitors on serum cytokines

2.2.1. Leukotriene-1 receptor antagonist (montelukast)

Leukotrienes are important modulators of various neutrophil functions including adherence and chemotaxis. Neutrophil adherence to extracellular matrices is diminished in the acute stages of burn injury. Decreased release of leukotrienes from burn neutrophils was reported to be due to enhanced degradation and decreased synthesis of leukotrienes (Damte et al., 1993). Montelukast considerably reduced the increased TNF- α and lactic dehydrogenase (LDH) levels at 1 day after burn (Kabasakal et al., 2005). Montelukast has an anti-inflammatory effect on burn-induced injury (Kabasakal et al., 2005).

2.2.2. Propylthiouracil

Thyroid hormones are important hormones affecting the basal metabolic rate. Increased thyroid hormone levels facilitate aerobic metabolism and stimulate free radical generation (Venditti et al., 1997). Decreased thyroid hormone levels protect tissues against lipid peroxidation by decreasing oxidant production (Swaroop and Ramasarma, 1985; Paller, 1986). Propylthiouracil was found to considerably reduce the serum levels of T3 and T4; however, it increased the aspartate transaminase and alanine transaminase levels. Propylthiouracil also considerably reduced the TNF- α and LDH levels at 1 day after burn injury (Sener et al., 2006).

2.3. Others

2.3.1. β -Glucans

β -Glucans are structural cell wall polymers of yeast, fungi, and cereal plants that can modify the immune response (Brown and Gordon, 2003). β -Glucans stimulate the generation of nitric oxide, cytokines, and prostaglandins in isolated and tissue macrophages (Ljungman et al., 1998). They also enhance the production of inducible nitric oxide (iNOS) protein in the presence of interferon- γ (Hashimoto et al., 1997), as well as the responses of TNF- α , IL-1 α , and IL-6 (Ohno et al., 1996). Oral and local administrations of β -Glucans were shown to considerably reduce the elevated serum TNF- α levels at both 6 h and 2 days after burn injury (Toklu et al., 2006).

2.4. Brief summary

Estrogen, ghrelin, IGF-1, oxytocin, androgen receptor blocker, leukotriene-1 receptor blocker, propylthiouracil, β -Glucans, and cyclosporin A can inhibit the burn-induced release of inflammatory mediators.

3. Effects of burns on the gastro-intestinal mucosa

Gut barrier failure and increased bacterial translocation may lead to sepsis after hemorrhagic shock (Magnotti et al., 1998). Increased sympathetic nervous system is well recognized to decrease the intestinal blood flow (McGregor, 1965). Both increased apoptosis and proliferation of gut epithelial cells after burn injury have been observed (Wolf et al., 1999). Impaired intestinal function was noted after burn injury, and may be related to the increase in the turnover of gut epithelial cells (Wolf et al., 1999). Intestinal mucosal loss has been shown to be associated with small-bowel dysfunction and increased gut permeability (Magnotti et al., 1998; Sun et al., 1998). In addition, increased sympathetic nervous system activity also considerably decreased the intestinal blood flow and increased the intestinal permeability (Jaworska et al., 2017). Increased gut permeability enhances the rate of bacterial translocation, as well as the risk of infection or sepsis and multiple-organ failure (Magnotti et al., 1998; Sun et al., 1998). Upregulation of apoptosis and apoptosis-related genes has been shown to be triggered by severe thermal injury (Jeschke et al., 2007).

Histological analysis revealed the degeneration of the epidermis and dermis, including loss and detachment of the epidermis, accumulation of polymorphonuclear leukocytes (PMNs), and congestion of blood vessels. Microscopic damage was semiquantitatively graded by scoring five microscopic areas in each specimen as 0 (none), 1 (mild), 2 (moderate), and 3 (severe), for each of the following criteria: epithelial desquamation, glandular injury, villar degeneration, hemorrhage, leukocytic infiltration, and vasocongestion (Işeri et al., 2010).

Myeloperoxidase (MPO) is a predominant enzyme found in PMNs. The activity of MPO is used to estimate tissue PMN accumulation in inflamed tissues (Bradley et al., 1982). DNA fragmentation level is an indicator of cell death by apoptosis. Malondialdehyde (MDA) levels are assayed for products of lipid peroxidation by monitoring the formation of thiobarbituric acid reactive substances (Buege and Aust, 1978; Lin et al., 2017). Protein carbonyls are checked through a precipitation reaction with 2,4-dinitrophenylhydrazine (Levine et al., 1990). Protein oxidation level is a representative marker of oxidative damage to cellular proteins. Glutathione (GSH), a reduced thiol agent, can interact with free radicals to yield more stable elements and to repair membrane lipid peroxides (Ross, 1988).

Considerably increased microscopic damage scores (Ozveri et al., 2001; Cakir et al., 2005), MDA levels (Kabasakal et al., 2005; Sener et al., 2006; Işeri et al., 2008; Sehirli et al., 2008), and MPO activity (Ozveri et al., 2001; Cakir et al., 2005; Kabasakal et al., 2005; Işeri et al., 2008; Sehirli et al., 2008), and decreased GSH level (Kabasakal et al., 2005; Sener et al., 2006; Sehirli et al., 2008) were noted in the

gastric mucosa after burn injury.

3.1. Effects of burns on the gastric mucosa

3.1.1. Hormonal effects on the gastric mucosa after thermal injury

3.1.1.1. Estrogen. Estrogen treatment with castration (to eliminate testosterone) and cyproterone acetate (androgen receptor blocker) failed to reduce microscopic damage scores and MPO activity in gastric tissue but successfully reduced microscopic damage scores and MPO activity in lung and liver tissue at 1 day after burn (Ozveri et al., 2001). Although estrogen considerably reduced the serum TNF- α levels, it did not protect the gastric mucosa from burn-induced injury (Ozveri et al., 2001). On the other hand, estrogen and cyproterone acetate reduced the burn-induced injury in the lungs and liver.

3.1.1.2. Ghrelin. Ghrelin considerably reduced the elevations of MDA level and MPO activity, but increased the GSH levels at both 6 h and 2 days after burns (Sehirli et al., 2008). Ghrelin protected distant organs from burn-induced oxidative injury by inhibiting tissue neutrophil infiltration and lipid peroxidation (Sehirli et al., 2008). Ghrelin has a neutrophil-dependent anti-inflammatory effect and protects remote organs, such as the lungs and stomach, against oxidative damage (Sehirli et al., 2008).

3.1.1.3. Leptin. Leptin is an adipose tissue derived hormone that balances energy intake and energy expenditure (Buyse et al., 2001). Leptin plays a role in innate and acquired immunity. The lack of leptin increases the susceptibility to infection and inflammatory stimulation associated with dysregulation of cytokine production (Faggioni et al., 2001). Plasma leptin levels have shown positive correlations with IL-1 β or IL-6 after burn injury (Kino et al., 2003). Leptin considerably reduced the microscopic damage scores and MPO activity at 1 day after burn injury (Cakir et al., 2005). Leptin may provide a therapeutic benefit in abolishing the effects of burn-induced injury in remote organs such as the lungs, liver, stomach, colon, or kidneys (Cakir et al., 2005).

3.1.1.4. Oxytocin. Oxytocin considerably reduced the microscopic damage score, MDA level, and MPO activity of gastric tissues at 2 days after burn (İşeri et al., 2008). Oxytocin may have a clinical benefit in terms of abolishing burn-induced gastric inflammation.

3.1.2. Effects of enzyme inhibitors on the gastric mucosa after thermal injury

3.1.2.1. Leukotriene-1 receptor antagonist (montelukast). Montelukast considerably reversed the elevations of MDA level and MPO activity back to the control levels, and inhibited the depletion of GSH stores (Kabasakal et al., 2005). Montelukast protected against gastric damage caused by burn-induced oxidative injury (Kabasakal et al., 2005).

3.1.2.2. Thyroid hormones. Propylthiouracil treatment considerably reduced the tissue MDA level and MPO activity, and increased the GSH levels at 1 day after burn injury (Sener et al., 2006). Propylthiouracil-induced hypothyroidism reduced burn-induced oxidative damage in the stomach, liver, and ileum (Sener et al., 2006).

3.1.3. Brief summary

Ghrelin, leptin, oxytocin, leukotriene-1 receptor antagonist, and propylthiouracil are potential therapeutic agents that may protect the gastric mucosa from burn-induced injury.

3.2. Effects of burns on the small intestinal mucosa

Increased apoptotic index, decreased proliferation of intestinal mucosal cells, and decreased villus height were noted after burn injury (Jeschke et al., 2007). Burn injury caused severe epithelial desquamation, glandular injury, villar degeneration, hemorrhage, leukocytic

infiltration, and vasocongestion, and considerably increased the microscopic damage scores (Toklu et al., 2006; İşeri et al., 2010). Burn injury caused oxidative damage of the intestine and increased the MDA levels (Wallace et al., 1993; Sener et al., 2002; Kabasakal et al., 2005; Toklu et al., 2006; İşeri et al., 2010). Burn injury induced a considerable increase in neutrophil infiltration to the intestine, as well as increased the MPO activity (Wallace et al., 1993; Alican et al., 2000; Unlüer et al., 2000; Oktar et al., 2002; Sener et al., 2002; Jahovic et al., 2004; Kabasakal et al., 2005; Toklu et al., 2006; Gan and Chen, 2007; Gan et al., 2007; İşeri et al., 2010). GSH levels were considerably decreased following burn injury (Wallace et al., 1993; Oktar et al., 2002; Sener et al., 2002; Kabasakal et al., 2005). DNA fragmentation was considerably increased after burn (Toklu et al., 2006; İşeri et al., 2010).

3.2.1. Hormonal effects on the small intestinal mucosa after thermal injury

3.2.1.1. Bombesin. Bombesin, a tetradecapeptide, is analogous to mammalian gastric releasing peptide (Spindel et al., 1993). Bombesin prevented mucosal atrophy and improved survival in methotrexate-induced enterocolitis (Chu et al., 1994). Bombesin considerably reduced the elevated intestinal MPO activity at 2 h after burns, but increased intestinal protein oxidation at 3 days after burns (Alican et al., 2000). Bombesin abolished the burn-induced intestinal inflammation via a neutrophil-dependent mechanism, but did not reduce the intestinal oxidative damage at 3 days after burns. More studies are needed to evaluate and confirm the intestinal protection of bombesin at > 3 days after burn.

3.2.1.2. Epidermal growth factor (EGF). Commonly found in saliva, EGF is a polypeptide known to accelerate the rate of wound healing in the skin and gastric mucosa (Niall et al., 1982; Olsen et al., 1984). EGF provided substantial mucosal protection, reducing the intestinal mucosal damage by 15% at 1 day after burn injury, thus attenuating intestinal complications (Berlenga et al., 2002). In a rat study, licking of the injured area reduced the microscopic damage scores and MPO activity in burned skin at 5 days after burn injury, as did treatment with EGF (Jahovic et al., 2004). However, neither licking nor EGF treatment attenuated the MPO elevation nor reversed the GSH levels in the intestine at 5 days after burn injury (Jahovic et al., 2004). EGF only reversed the GSH levels in the liver (Jahovic et al., 2004). Therefore, the study concluded that EGF enhances the healing of burned skin but does not improve intestinal damage, as evaluated 5 days after burn injury.

3.2.1.3. Heme oxygenase (HO)-1 inducer (hemin). Hemin considerably reduced the burn-induced increase in the expression of iNOS, cyclooxygenase (COX)-2, and IL-1 β , as well as the MPO activity of intestinal tissues (Gan and Chen, 2007). Hemin has the ability to downregulate iNOS, COX-2, and IL-1 β expression after burn injury.

3.2.1.4. IGF-1. IGF-1 considerably improved villus height and cell number per villus, reduced intestinal cell apoptosis, and increased cell proliferation at 2, 5, and 7 days after burn injury (Jeschke et al., 2007). IGF-1 improved gut mucosal integrity through downregulation of the Fas pathway after a severe thermal injury (Jeschke et al., 2007).

3.2.1.5. Melatonin. Melatonin, the chief secretory product of the pineal gland, has been proven to protect tissues against oxidative injury (Melchiorri et al., 1995; Sewerynek et al., 1995). This hormone protected the liver from degenerative change after exposure to lipopolysaccharides, presumably owing to its antioxidant activity (Sewerynek et al., 1995). Melatonin also considerably reduced the elevated MDA levels and MPO activity, and reversed the decreased GSH levels in the intestine, lungs, and liver at both 3 h and 1 day after burn injury (Sener et al., 2002). Melatonin may be considered an effective free radical scavenger and an antioxidant. It can serve as a potential therapeutic agent for remote organ damage induced by burns.

3.2.1.6. Somatostatin analogue (octreotide). Somatostatin, an endogenous cyclic tetradecapeptide, inhibits gastric acid and pepsin secretion as well as gastric and small intestinal motility. Somatostatin protected the gastric mucosa from ischemia/reperfusion injury induced by hemorrhagic shock (Wallace et al., 1993). Octreotide considerably reversed the elevated MDA levels and MPO activity, and increased the decreased GSH levels at both 3 h and 1 day after burns (Sener et al., 2003). Octreotide may be a therapeutic agent by reducing neutrophil-dependent injury and lipid peroxidation after burns.

3.2.1.7. Oxytocin. Oxytocin considerably abolished the burn-induced elevations of microscopic damage scores, MDA levels, and MPO activity of the ileum at 2 and 5 days after burns (İşeri et al., 2010). Oxytocin is a potential agent for treating burn-induced injury to distant organs.

3.2.2. Effects of enzyme inhibitors on the small intestinal mucosa after thermal injury

3.2.2.1. Leukotriene-1 receptor antagonist (montelukast). Montelukast considerably reversed the elevations of MDA levels and MPO activity back to the control levels, and inhibited the depletion of GSH stores (Kabasakal et al., 2005). Montelukast protected against burn-induced gastrointestinal damage through the anti-inflammatory effect of a neutrophil-dependent mechanism (Kabasakal et al., 2005).

3.2.2.2. COX inhibitors (ketorolac, nimesulide, and piroxicam). None of the three inhibitors reduced the intestinal microscopic damage score, but both the COX-1 inhibitor (ketorolac) and the COX inhibitor (piroxicam) lowered the hepatic microscopic damage score at 6 h after burn injury (Oktar et al., 2002). Both the COX-2 inhibitor (nimesulide) and the COX inhibitor (piroxicam) increased the hepatic and intestinal GSH level; however, the COX-1 inhibitor (ketorolac) did not increase the intestinal GSH level at 6 h after burn injury. All of the three inhibitors reduced the intestinal MPO activity at 6 h after burn injury (Oktar et al., 2002). Additional studies are needed to prove that the protection provided by COX inhibitors could extend to > 1 day after burn injury in remote organs.

3.2.2.3. Endothelin-1 (ET-1) antagonist (PD156252). ET-1 is a 21-amino-acid peptide whose circulating blood levels are increased in patients with burn injury (Huribal et al., 1995a; Huribal et al., 1995b). PD156252 reversed the increased intestinal MPO activity at 2 h after burns but considerably increased the MPO activity and protein oxidation at 3 days after burns (Unlüer et al., 2000). PD156252 does not protect the intestine from burn-induced injury at 3 days after burns.

3.2.2.4. Specific p38 mitogen-activated protein kinase (MAPK) inhibitor (SB203580). SB203580 considerably abolished the increased iNOS, COX-2, IL-1 β protein, and MPO activity in the intestinal mucosa induced by burn injury (Gan et al., 2007). Inhibition of the p38 MAPK pathway may abolish the effects of burn injury by inhibiting iNOS, COX-1, and IL-1 β expression.

3.2.2.5. Propylthiouracil. Propylthiouracil treatment considerably reduced the tissue MDA levels and MPO activity, and increased the GSH level at 1 day after burn injury (Sener et al., 2006). Propylthiouracil-induced hypothyroidism reduced burn-induced oxidative damage in the stomach, liver, and ileum (Sener et al., 2006).

3.2.3. Others

3.2.3.1. β -Glucans. Oral or local treatment with β -glucans considerably abolished the elevation of MDA level and MPO activity, and restored the GSH levels to the control values at both 6 h and 2 days after burn injury (Toklu et al., 2006). The clinical application of β -glucans via the oral or topical route is considered an effective treatment for burn injuries at both the local and remote levels (Toklu et al., 2006).

3.2.3.2. Cyclosporin A. Cyclosporin A, a potent immunosuppressive agent, has obvious suppressive effects on T lymphocytes (Bunjes et al., 1981). Cyclosporin A failed to abolish the elevated MPO activity and carbonyl content at both 2 h and 1 day after burns (Gürbüz et al., 1997). Cyclosporin A does not protect remote organs (stomach, lungs, and liver) from burn-induced injury.

3.2.4. Brief summary

Hemin, IGF-1, melatonin, octreotide, oxytocin, montelukast (leukotriene-1 receptor blocker), SB203580 (specific p38 MAPK inhibitor), propylthiouracil, and β -Glucans can protect the small intestine from burn-induced injury.

3.3. Effects of burns on the colonic mucosa

Both a considerable decrease in GSH level and an increase in MPO activity and MDA level were noted in the colonic mucosa after burn injury (Kabasakal et al., 2005).

3.3.1. Hormonal effects on the colonic mucosa after thermal injury

3.3.1.1. Leptin. Leptin considerably reduced the microscopic damage score and MPO activity at 1 day after burn injury (Cakir et al., 2005). Leptin may provide a therapeutic benefit in abolishing the effects of burn-induced injury and associated injury in the lungs, liver, stomach, colon, and kidneys (Cakir et al., 2005).

3.3.2. Effects of enzyme inhibitors on the colonic mucosa after thermal injury

3.3.2.1. Leukotriene-1 receptor antagonist (montelukast). Montelukast considerably reversed the elevations of MDA level and MPO activity back to control levels and inhibited the depletion of GSH stores (Kabasakal et al., 2005). Montelukast can protect the colon from burn-induced oxidative injury (Kabasakal et al., 2005).

4. Effects of burns on the gastro-intestinal motility

4.1. Gastric motility after thermal injury

The gastric emptying time was obviously delayed at 4 h after thermal injury and recovered by fluid resuscitation in a rat study (Chen et al., 1982). Gastric distention and dysfunction are common complications of thermal injury. The gastric emptying rate was decreased by about 37–42% at 6 h after burn (Sallam et al., 2007; Oliveira et al., 2009; Sallam et al., 2011). Burn injury considerably reduced the dominant frequency and percentage of normal slow waves, but increased the percentage of bradygastria (Sallam et al., 2011). In a human study, oral acetaminophen was used to evaluate the gastric emptying due to the absorption rate constant of acetaminophen being compatible with the true absorption rate constant (Clements et al., 1978). Patients with burn injury were subjected to an 8-h fast for an average of 4 days post-injury, after which acetaminophen was taken with 200 mL water. The serum levels of acetaminophen showed no anomalies in terms of gastric emptying kinetics (Hu et al., 1993).

4.1.1. Effect of various enteral fluids on gastric emptying

4.1.1.1. Normal saline, hyperosmolar saline, HCl, and peptone. Under normal conditions, the gastric emptying rate of normal saline (300 mOsm/kg) is higher than that of hyperosmolar saline (900 mOsm/kg), 50 mM HCl and 4.5% meat peptone (Alican et al., 1995). At 18 h after full-thickness thermal injury, normal saline and hyperosmolar saline delayed the gastric emptying rate as compared with the uninjured condition. On the other hand, 50 mM HCl and 4.5% meat peptone, as usual, did not delay the gastric emptying rate. After 7 days, normal saline, HCl, and peptone tests showed recovery of normal gastric emptying rates; however, the hyperosmolar saline test did not. This means that although full-thickness thermal injury delayed

the gastric emptying rate of normal saline at 18 h after thermal injury, the rate was still compatible with that of HCl and peptone without thermal injury, and better than that of hyperosmolar saline in both acute and chronic cases.

4.1.1.2. Oral rehydration solution (ORS), vivonex, and methylcellulose. ORS (Michell et al., 2006) is a high salt solution (Na: 90 mmol/L) modified from the World Health Organization ORS. Thermal injury did not delay the gastric emptying rate of ORS after 1 h and 6 h, but delayed the gastric emptying rate of vivonex (a caloric meal) and methylcellulose (semisolid) (Sallam et al., 2011). The gastric emptying rate of ORS was accelerated at 1 h and 6 h after burn, compared with that of vivonex or methylcellulose (Sallam et al., 2011). Hematocrit values were assessed for the effect of resuscitation, and by 6 h after burn injury, ORS was shown to be 50% more effective in normalizing hematocrit values than vivonex (Sallam et al., 2011).

4.1.2. Hormonal effects on gastric emptying

4.1.2.1. Ghrelin. Ghrelin accelerated gastric emptying in conscious rats (Huang et al., 2017; Yeh et al., 2016), and in cases of postoperative ileus (Trudel et al., 2002) or septic ileus (De Winter et al., 2004). It normalized gastric emptying at 6 h after burn (Sallam et al., 2007; Sallam et al., 2011) but had no effect on gastric slow waves (Sallam et al., 2011). Because atropine sulfate did not fully dampen the stimulatory actions of ghrelin on either gastric myoelectrical activity or gastric emptying, ghrelin may play a physiological role in the enteric neurotransmission controlling gastric contractions in rats (Tümer et al., 2008). Ghrelin at the dose of 2 nmol per rat was the most effective in increasing gastric emptying at 6 h after burn (Sallam et al., 2007). Ghrelin may be a potential clinical treatment for delayed gastric emptying after burn injury.

4.1.2.2. Insulin. Blood sugar was increased after burn injury and was considerably increased (by about 50%) at 6 h after burn (Sallam et al., 2011). Hyperglycemia mediated burn-induced gastric dysrhythmias. Insulin treatment considerably normalized blood sugar levels and gastric slow waves (Sallam et al., 2011). Insulin treatment increased the gastric emptying rate by 53% as compared with saline treatment 6 h after burn (Sallam et al., 2011).

4.1.2.3. Oxytocin. Oxytocin, a neurohypophyseal nonapeptide, is synthesized in the paraventricular and supraoptic nuclei of the hypothalamus. Oxytocin has important effects on the myoepithelial cells and uterine smooth muscles. Continuous intravenous infusion of oxytocin accelerated gastric emptying and colonic peristalsis in fasted healthy women (Petricing, 1989; Ohlsson and Sjölund, 2001). However nasal administration of oxytocin had no relevant influence on constipation in healthy women (Ohlsson et al., 2005). In addition, oxytocin did not improve the burn-induced delay in gastric emptying (İşeri et al., 2008).

4.1.2.4. Brief summary. Ghrelin and insulin improve gastric emptying at 6 h after burn injury and may have potential therapeutic effects for the treatment of burn-induced delayed gastric emptying.

4.1.3. Effects of enzyme inhibitors on gastric emptying

4.1.3.1. COX inhibition. Prostaglandins, derived from COX, COX-1, and COX-2, are important responders to tissue injury that help maintain gastrointestinal integrity. Selective COX-2 inhibitors, such as nimesulide (Sallam et al., 2011) and SC-58125 (Oliveira et al., 2009), normalized burn-induced delay in gastric emptying at 6 h after burn (Oliveira et al., 2009; Sallam et al., 2011); however, they did not improve burn-induced impairment in gastric slow waves (Sallam et al., 2011). Burn-induced gastric dysrhythmias were not mediated via the COX-2 receptor pathway (Sallam et al., 2011). COX-2 inhibitor recovered burn-induced delayed gastric emptying via the

prostaglandin pathway (Oliveira et al., 2009).

4.1.3.2. Brief summary. Selective COX-2 inhibitors such as nimesulide (Sallam et al., 2011) and SC-58125 (Oliveira et al., 2009) improved burn-induced delayed gastric emptying.

4.2. Small intestinal motility after thermal injury

The geometric center of intestinal transit was considerably decreased as compared with sham models at 2 h (Alican et al., 2000; Ünlüer et al., 2000) and 6 h (Ünlüer et al., 2000; Oktar et al., 2002; Sallam et al., 2007; Oliveira et al., 2009) after burn injury, and the rate of decrease was about 24–42% (Oktar et al., 2002; Gan et al., 2007; Sallam et al., 2007).

4.2.1. Effects of various enteral fluids on intestinal transit

4.2.1.1. ORS and vivonex. In a sham model, vivonex induced faster intestinal transit than ORS did. ORS and vivonex did not delay intestinal transit at 1 h after burn, but delayed intestinal transit at 6 h after burn (Sallam et al., 2011). Compared with ORS, vivonex yielded faster intestinal transit than ORS at both 1 h and 6 h after burn (Sallam et al., 2011). ORS was superior to vivonex in increasing the post-burn hematocrit values and in expanding the plasma volume.

4.2.1.2. Brief summary. Although burn injury induced the delay of gastric emptying, ORS and vivonex expanded the plasma volume after burn injury.

4.2.2. Hormone effects on small intestinal transit

4.2.2.1. Bombesin. Bombesin is known to stimulate the secretion of almost all gut hormones, as well as the contraction of gut smooth muscle (McDonald et al., 1981; Holmgren and Jönsson, 1988). Bombesin considerably reversed the impaired intestinal transit at both 2 h and 3 days after burn injury (Alican et al., 2000).

4.2.2.2. Ghrelin. Ghrelin at doses of 2, 5, and 10 nmol per rat normalized burn-induced delayed intestinal transit, whereas the dose of 2 nmol per rat was the most effective in accelerating intestinal transit (Sallam et al., 2007). Ghrelin may serve as a potential clinical treatment for delayed intestinal transit after burn injury.

4.2.2.3. HO-1 inducer (hemin). HO is an enzyme that catalyzes the first and the rate-limiting steps in heme degradation. HO-1 plays an important role in gut protection against ischemia/perfusion injury (Attuwaybi et al., 2004). In a study by using hemin (HO-1 inducer) and SnPP-IX (HO-1 inhibitor), HO-1 was shown to considerably normalize the burn-induced delay in intestinal transit (Gan and Chen, 2007). The induction of HO-1 may provide an effective therapeutic measure for delayed gut transit at 1 day after burn injury (Gan and Chen, 2007).

4.2.2.4. Brief summary. Bombesin, ghrelin, and hemin can reverse the impaired small intestinal transit after burn injury.

4.2.3. Effects of enzyme inhibitors on small intestinal transit

4.2.3.1. COX inhibitor. Treatment with a selective COX-2 inhibitor (nimesulide) (Oktar et al., 2002; Gan et al., 2007) and a non-selective COX inhibitor (piroxicam) (Oktar et al., 2002), but not treatment with a selective COX-1 inhibitor (ketorolac) (Oktar et al., 2002) or a selective COX-2 inhibitor (SC-58125) (Oliveira et al., 2009), reversed and normalized the impaired intestinal motility. Both COX-2 and COX-1 inhibition are involved in intestinal protection against inflammatory changes after burn injury. However, the restoration of delayed intestinal transit by different COX-2 inhibitors, such as nimesulide (Oktar et al., 2002; Gan et al., 2007) or SC-58125 (Oliveira et al., 2009), is not consistent.

4.2.3.2. ET-1 receptor antagonist (PD156252). ET-1 is a 21-amino-acid peptide whose circulating blood levels are increased in patients with burn injury (Huribal et al., 1995a). There are correlations between increased ET-1 and increased prostaglandin E2 in patients with burn (Huribal et al., 1995b). PD156252 retreatment did not improve the delayed intestinal transit at 2 h after burn injury, but considerably normalized the intestinal transit at 3 days after burn injury (Unlüer et al., 2000).

4.2.3.3. iNOS inhibitor. iNOS inhibits gastrointestinal motility and plays an important role in the initiation of intestinal inflammation, especially after severe ischemic insults (Kalff et al., 2000; Hassoun et al., 2001). S-methylisothiourea (SMT), a selective iNOS inhibitor, considerably improved the burn-induced impaired intestinal transit (Gan et al., 2007).

4.2.3.4. Specific p38 MAPK inhibitor. p38 MAPK is part of the MAPK family and a regulator of the inflammatory response. SB203580 (a specific p38 MAPK inhibitor) inhibited the p38 MAPK pathway as well as the iNOS, COX-2, and IL-1 β expression, and considerably improved the burn-induced delayed intestinal transit (Gan et al., 2007). The delayed intestinal transit induced by burn is associated with the p38 MAPK pathway.

4.2.3.5. Brief summary. SB203580 and SMT improve the burn-induced delayed intestinal transit at 12 h after burn injury.

4.3. Colonic motility after thermal injury

The geometric center of colonic transit has been shown to be delayed after a burn injury (Gan and Chen, 2005; Sallam et al., 2007), and to be considerably decreased (by 34.4%) as compared with the sham model (Sallam et al., 2007).

4.3.1. Hormonal effects on colonic transit

4.3.1.1. Ghrelin. Ghrelin had no effects on colonic transit at 6 h after burn injury (Sallam et al., 2007). Ghrelin did not restore the burn-induced delayed colonic transit, although ghrelin reversed the delayed gastric emptying and small intestinal transit after burns.

4.3.2. Effects of enzyme inhibitors on colonic transit

4.3.2.1. iNOS inhibitor. SMT (a selective iNOS inhibitor) considerably normalized the delayed colonic transit in the rats with burns; however, 7-nitroindazole, a selective neuronal NOS inhibitor, did not (Gan and Chen, 2005). Neuronal NOS produced NO, which is important in mediating colonic transit (Gan and Chen, 2005). iNOS expression in neurons of the myenteric ganglia may contribute to the colonic dysmotility associated with burn injury (Gan and Chen, 2005).

4.3.2.2. COX-2 inhibitor. Nimesulide (a COX-2 inhibitor) considerably improved the delayed colonic transit in rats with burns (Gan and Chen, 2005). Prostaglandins, synthesized by COX-2, are involved in the pathogenesis of delayed colonic transit after burn injury (Gan and Chen, 2005).

5. Conclusions

Crystalloid fluid was beneficial for acute fluid resuscitation in thermal injury because the gastric emptying rate was not decreased at 6 h after burns (Sallam et al., 2011) and the absorption rate was returned to normal at 4 days after burns (Hu et al., 1993). Both semisolid and caloric meals delayed gastric emptying within the first 6 h after burn (Sallam et al., 2011). Crystalloid fluid was more effective than a caloric meal in normalizing the hematocrit value at 6 h after burn (Sallam et al., 2011).

Although ghrelin, insulin, nimesulide (COX-2 inhibitor), and SC-

58125 (COX-2 inhibitor) can improve the burn-induced delayed gastric emptying, only ghrelin was documented to recover the burn-induced delayed small intestinal transit. Unfortunately, at present there are no studies showing whether ghrelin could protect the small intestinal or colonic mucosa from burn-induced injury.

The burn-induced release of inflammatory mediators causes gastrointestinal mucosal damage. Microscopic damage scores are useful in determining the protective ability of various types of intervention. MPO activity, glutathione level, MDA level, and protein oxidation are indicators of mucosal damage. Oxytocin and β -Glucans have been shown to reduce the levels of serum inflammatory mediators, as well as histological change and mucosal damage indicators; however, there is no evidence showing that oxytocin and β -Glucans could recover gastrointestinal motility. Using a combination of the different reagents, with an emphasis on recovering motility and protecting the gastrointestinal mucosa, is an alternative treatment for thermal injury.

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References

- Ajayi, A.A., Mathur, R., Halushka, P.V., 1995. Testosterone increases human platelet thromboxane A2 receptor density and aggregation responses. *Circulation* 91 (11), 2742–2747.
- Alican, I., Coşkun, T., Yeğen, C., Aktan, A.O., Yalin, R., Yeğen, B.C., 1995. The effect of thermal injury on gastric emptying in rats. *Burns* 21 (3), 171–174.
- Alican, I., Unlüer, E.E., Yeğen, C., Yeğen, B.C., 2000. Bombesin improves burn-induced intestinal injury in the rat. *Peptides* 21 (8), 1265–1269.
- Attuwaybi, B.O., Kozar, R.A., Moore-Olufemi, S.D., Sato, N., Hassoun, H.T., Weisbrodt, N.W., Moore, F.A., 2004. Heme oxygenase-1 induction by hemin protects against gut ischemia/reperfusion injury. *J. Surg. Res.* 118 (1), 53–57.
- Baron, P., Traber, L.D., Traber, D.L., Nguyen, T., Hollyoak, M., Heggors, J.P., Herndon, D.N., 1994. Gut failure and translocation following burn and sepsis. *J. Surg. Res.* 57 (1), 197–204.
- Barrow, R.E., Jeschke, M.G., Herndon, D.N., 2000. Early fluid resuscitation improves outcomes in severely burned children. *Resuscitation* 45 (2), 91–96.
- Berlanga, J., Lodos, J., López-Saura, P., 2002. Attenuation of internal organ damages by exogenously administered epidermal growth factor (EGF) in burned rodents. *Burns* 28 (5), 435–442.
- Bradley, P.P., Priebe, D.A., Christensen, R.D., Rothstein, G., 1982. Measurement of cutaneous inflammation: estimation of neutrophil content with an enzyme marker. *J. Invest. Dermatol.* 78 (3), 206–209.
- Brown, G.D., Gordon, S., 2003. Fungal beta-glucans and mammalian immunity. *Immunity* 19 (3), 311–315.
- Buege, J.A., Aust, S.D., 1978. Microsomal lipid peroxidation. *Methods Enzymol.* 52, 302–310.
- Bunjes, D., Hardt, C., Rölinghoff, M., Wagner, H., 1981. Cyclosporin A mediates immunosuppression of primary cytotoxic T cell responses by impairing the release of interleukin 1 and interleukin 2. *Eur. J. Immunol.* 11 (8), 657–661.
- Buyse, M., Berlioz, F., Guilmeau, S., Tsocas, A., Voisin, T., Péranzi, G., Merlin, D., Laburthe, M., Lewin, M.J., Rozé, C., Bado, A., 2001. PepT1-mediated epithelial transport of dipeptides and cephalixin is enhanced by luminal leptin in the small intestine. *J. Clin. Invest.* 108 (10), 1483–1494.
- Cakir, B., Cevik, H., Contuk, G., Ercan, F., Ekşioğlu-Demiralp, E., Yeğen, B.C., 2005. Leptin ameliorates burn-induced multiple organ damage and modulates postburn immune response in rats. *Regul. Pept.* 125 (1–3), 135–144.
- Chen, C.F., Chapman, B.J., Munday, K.A., Fang, H.S., 1982. The effects of thermal injury on gastrointestinal motor activity in the rat. *Burns Incl. Therm. Inj.* 9 (2), 142–146.
- Chen, C.Y., Asakawa, A., Fujimiya, M., Lee, S.D., Inui, A., 2009. Ghrelin gene products and the regulation of food intake and gut motility. *Pharmacol. Rev.* 61 (4), 430–481.
- Chen, C.Y., Fujimiya, M., Laviano, A., Chang, F.Y., Lin, H.C., Lee, S.D., 2010. Modulation of ingestive behavior and gastrointestinal motility by ghrelin in diabetic animals and humans. *J. Chin. Med. Assoc.* 73 (5), 225–229.

- Chen, Y.C., Inui, A., Chang, E.S., Chen, S.C., Lee, W.J., Chen, C.Y., 2016. Comparison of gut hormones and adipokines stimulated by glucagon test among patients with type II diabetes mellitus after metabolic surgery. *Neuropeptides* 55, 39–45.
- Chu, K.U., Higashide, S., Evers, B.M., Rajaraman, S., Ishizuka, J., Townsend Jr., C.M., Thompson, J.C., 1994. Bombesin improves survival from methotrexate-induced enterocolitis. *Ann. Surg.* 220 (4), 570–576.
- Clements, J.A., Heading, R.C., Nimmo, W.S., Prescott, L.F., 1978. Kinetics of acetaminophen absorption and gastric emptying in man. *Clin. Pharmacol. Ther.* 24 (4), 420–431.
- Czaja, A.J., McAlhany, J.C., Pruitt, B.A., 1974. Acute gastroduodenal disease after thermal injury. An endoscopic evaluation of incidence and natural history. *N. Engl. J. Med.* 291 (18), 925–929.
- Damte, B., Marino, J.A., Fratianni, R.B., Spagnuolo, P.J., 1993. Neutrophil lipooxygenase metabolism and adhesive function following acute thermal injury. *J. Lab. Clin. Med.* 121 (2), 328–336.
- De Winter, B.Y., De Man, J.G., Seerden, T.C., Depoortere, I., Herman, A.G., Peeters, T.L., Pelckmans, P.A., 2004. Effect of ghrelin and growth hormone-releasing peptide 6 on septic ileus in mice. *Neurogastroenterol. Motil.* 16 (4), 439–446.
- Deitch, E.A., Berg, R., 1987. Bacterial translocation from the gut: a mechanism of infection. *J. Burn Care Rehabil.* 8 (6), 475–482.
- Faggioni, R., Feingold, K.R., Grunfeld, C., 2001. Leptin regulation of the immune response and the immunodeficiency of malnutrition. *FASEB J.* 15 (14), 2565–2571.
- Gan, H.T., Chen, J.D., 2005. Roles of nitric oxide and prostaglandins in pathogenesis of delayed colonic transit after burn injury in rats. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 288 (5), R1316–R1324.
- Gan, H.T., Chen, J.D., 2007. Induction of heme oxygenase-1 improves impaired intestinal transit after burn injury. *Surgery* 141 (3), 385–393.
- Gan, H.T., Pasricha, P.J., Chen, J.D., 2007. Blockade of p38 mitogen-activated protein kinase pathway ameliorates delayed intestinal transit in burned rats. *Am. J. Surg.* 193 (4), 530–537.
- Gürbüz, V., Corak, A., Yeğen, B.C., Kurtel, H., Alican, I., 1997. Oxidative organ damage in a rat model of thermal injury: the effect of cyclosporin A. *Burns* 23 (1), 37–42.
- Hashimoto, T., Ohno, N., Adachi, Y., Yadomae, T., 1997. Enhanced production of inducible nitric oxide synthase by beta-glucans in mice. *FEMS Immunol. Med. Microbiol.* 19 (2), 131–135.
- Hassoun, H.T., Weisbrodt, N.W., Mercer, D.W., Kozar, R.A., Moody, F.G., Moore, F.A., 2001. Inducible nitric oxide synthase mediates gut ischemia/reperfusion-induced ileus only after severe insults. *J. Surg. Res.* 97 (2), 150–154.
- Holmgren, S., Jönsson, A.C., 1988. Occurrence and effects on motility of bombesin related peptides in the gastrointestinal tract of the Atlantic cod, *Gadus morhua*. *Comp. Biochem. Physiol. C* 89 (2), 249–256.
- Hu, O.Y., Ho, S.T., Wang, J.J., Ho, W., Wang, H.J., Lin, C.Y., 1993. Evaluation of gastric emptying in severe, burn-injured patients. *Crit. Care Med.* 21 (4), 527–531.
- Huang, K.F., Chung, D.H., Herndon, D.N., 1993. Insulinlike growth factor 1 (IGF-1) reduces gut atrophy and bacterial translocation after severe burn injury. *Arch. Surg.* 128 (1), 47–53.
- Huang, H.H., Chen, L.Y., Doong, M.L., Chang, S.C., Chen, C.Y., 2017. α -Melanocyte stimulating hormone modulates the central acyl ghrelin-induced stimulation of feeding, gastrointestinal motility, and colonic secretion. *Drug Des. Devel. Ther.* 11, 2377–2386.
- Huang, H.H., Ting, C.H., Syu, Y.F., Chang, C.S., Chen, C.Y., 2016. Correlation between colonic secretion and colonic motility in rats: role of ghrelin. *World J. Gastroenterol.* 22 (46), 10140–10147.
- Huribal, M., Cunningham, M.E., D'Aiuto, M.L., Pleban, W.E., McMillen, M.A., 1995a. Endothelin-1 and prostaglandin E2 levels increase in patients with burns. *J. Am. Coll. Surg.* 180 (3), 318–322.
- Huribal, M., Cunningham, M.E., D'Aiuto, M.L., Pleban, W.E., McMillen, M.A., 1995b. Endothelin levels in patients with burns covering more than 20% body surface area. *J. Burn Care Rehabil.* 16 (1), 23–26.
- Işeri, S.O., Gedik, I.E., Erzik, C., Uslu, B., Arbak, S., Gedik, N., Yeğen, B.C., 2008. Oxytocin ameliorates skin damage and oxidant gastric injury in rats with thermal trauma. *Burns* 34 (3), 361–369.
- Işeri, S.O., Düşünceli, F., Erzik, C., Uslu, B., Arbak, S., Yeğen, B.C., 2010. Oxytocin or social housing alleviates local burn injury in rats. *J. Surg. Res.* 162 (1), 122–131.
- Jahovic, N., Güzel, E., Arbak, S., Yeğen, B.C., 2004. The healing-promoting effect of saliva on skin burn is mediated by epidermal growth factor (EGF): role of the neutrophils. *Burns* 30 (6), 531–538.
- Jaworska, K., Huc, T., Samborska, E., Dobrowolski, L., Bielinska, K., Gawlak, M., Ufnal, M., 2017. Hypertension in rats is associated with an increased permeability of the colon to TMA, a gut bacteria metabolite. *PLoS One* 12 (12), e0189310.
- Jeschke, M.G., Bolder, U., Chung, D.H., Przkora, R., Mueller, U., Thompson, J.C., Wolf, S.E., Herndon, D.N., 2007. Gut mucosal homeostasis and cellular mediators after severe thermal trauma and the effect of insulin-like growth factor-I in combination with insulin-like growth factor binding protein-3. *Endocrinology* 148 (1), 354–362.
- Kabasakal, L., Sener, G., Cetinel, S., Contuk, G., Gedik, N., Yeğen, B.C., 2005. Burn-induced oxidative injury of the gut is ameliorated by the leukotriene receptor blocker montelukast. *Prostaglandins Leukot. Essent. Fatty Acids* 72 (6), 431–440.
- Kalff, J.C., Schraut, W.H., Billiri, T.R., Simmons, R.L., Bauer, A.J., 2000. Role of inducible nitric oxide synthase in postoperative intestinal smooth muscle dysfunction in rodents. *Gastroenterology* 118 (2), 316–327.
- Kino, Y., Kato, M., Ikehara, Y., Asanuma, Y., Akashi, K., Kawai, S., 2003. Plasma leptin levels in patients with burn injury: a preliminary report. *Burns* 29 (5), 449–453.
- Levine, R.L., Garland, D., Oliver, C.N., Amici, A., Climent, I., Lenz, A.G., Ahn, B.W., Shaltiel, S., Stadtman, E.R., 1990. Determination of carbonyl content in oxidatively modified proteins. *Methods Enzymol.* 186, 464–478.
- Ljungman, A.G., Leanderson, P., Tagesson, C., 1998. (1 $\rightarrow$ 3)- β -D-Glucan stimulates nitric oxide generation and cytokine mRNA expression in macrophages. *Environ. Toxicol. Pharmacol.* 5 (4), 273–281.
- Lin, C.P., Chuang, W.C., Lu, F.J., Chen, C.Y., 2017. Anti-oxidant and anti-inflammatory effects of hydrogen-rich water alleviate ethanol-induced fatty liver in mice. *World J. Gastroenterol.* 23 (27), 4920–4934.
- Magnotti, L.J., Upperman, J.S., Xu, D.Z., Lu, Q., Deitch, E.A., 1998. Gut-derived mesenteric lymph but not portal blood increases endothelial cell permeability and promotes lung injury after hemorrhagic shock. *Ann. Surg.* 228 (4), 518–527.
- McDonald, T.J., Ghatei, M.A., Bloom, S.R., Track, N.S., Radziuk, J., Dupre, J., Mutt, V., 1981. A qualitative comparison of canine plasma gastroenteropancreatic hormone response to bombesin and the porcine gastrin-releasing peptide (GRP). *Regul. Pept.* 2 (5), 293–304.
- McGregor, D., 1965. The effect of sympathetic nerve stimulation on vasoconstrictor responses in perfused mesenteric blood vessels of the rat. *J. Physiol.* 177, 21–30.
- Melchiorri, D., Reiter, R.J., Sewerynek, E., Chen, L.D., Nisticó, G., 1995. Melatonin reduces kainate-induced lipid peroxidation in homogenates of different brain regions. *FASEB J.* 9 (12), 1205–1210.
- Michell, M.W., Oliveira, H.M., Kinsky, M.P., Vaid, S.U., Herndon, D.N., Kramer, G.C., 2006. Enteral resuscitation of burn shock using World Health Organization oral rehydration solution: a potential solution for mass casualty care. *J. Burn Care Res.* 27 (6), 819–825.
- Niall, M., Ryan, G.B., O'Brien, B.M., 1982. The effect of epidermal growth factor on wound healing in mice. *J. Surg. Res.* 33 (2), 164–169.
- Ohlsson, B., Sjölund, K., 2001. Oxytocin increased stool frequency in patients with chronic constipation. A preliminary report. *Int. J. Surg. Investig.* 3, 287–292.
- Ohlsson, B., Truedsson, M., Bengtsson, M., Torstenson, R., Sjölund, K., Björnsson, E.S., Simrén, M., 2005. Effects of long-term treatment with oxytocin in chronic constipation: a double blind, placebo-controlled pilot trial. *Neurogastroenterol. Motil.* 17 (5), 697–704.
- Ohno, N., Hashimoto, T., Adachi, Y., Yadomae, T., 1996. Conformation dependency of nitric oxide synthesis of murine peritoneal macrophages by beta-glucans in vitro. *Immunol. Lett.* 53 (2–3), 157–163.
- Oktar, B.K., Kadir, B., Mutlu, N., Celikel, C., Alican, I., 2002. Protective role of cyclooxygenase (COX) inhibitors in burn-induced intestinal and liver damage. *Burns* 28 (3), 209–214.
- Oliveira, H.M., Sallam, H.S., Espana-Tenorio, J., Chinkes, D., Chung, D.H., Chen, J.D., Herndon, D.N., 2009. Gastric and small bowel ileus after severe burn in rats: the effect of cyclooxygenase-2 inhibitors. *Burns* 35 (8), 1180–1184.
- Olsen, P.S., Poulsen, S.S., Kirkegaard, P., Nexø, E., 1984. Role of submandibular saliva and epidermal growth factor in gastric cytoprotection. *Gastroenterology* 87 (1), 103–108.
- Ozveri, E.S., Bozkurt, A., Haklar, G., Cetinel, S., Arbak, S., Yeğen, C., Yeğen, B.C., 2001. Estrogens ameliorate remote organ inflammation induced by burn injury in rats. *Inflamm. Res.* 50 (12), 585–591.
- Paller, M.S., 1986. Hypothyroidism protects against free radical damage in ischemic acute renal failure. *Kidney Int.* 29 (6), 1162–1166.
- Petring, O.U., 1989. The effect of oxytocin on basal and pethidine-induced delayed gastric emptying. *Br. J. Clin. Pharmacol.* 28 (3), 329–332.
- Ross, D., 1988. Glutathione, free radicals and chemotherapeutic agents. Mechanisms of free-radical induced toxicity and glutathione-dependent protection. *Pharmacol. Ther.* 37 (2), 231–249.
- Sallam, H.S., Oliveira, H.M., Gan, H.T., Herndon, D.N., Chen, J.D., 2007. Ghrelin improves burn-induced delayed gastrointestinal transit in rats. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 292 (1), R253–R257.
- Sallam, H.S., Kramer, G.C., Chen, J.D., 2011. Gastric emptying and intestinal transit of various enteral feedings following severe burn injury. *Dig. Dis. Sci.* 56 (11), 3172–3178.
- Sehirli, O., Sener, E., Sener, G., Cetinel, S., Erzik, C., Yeğen, B.C., 2008. Ghrelin improves burn-induced multiple organ injury by depressing neutrophil infiltration and the release of pro-inflammatory cytokines. *Peptides* 29 (7), 1231–1240.
- Sener, G., Sehirli, A.O., Satiroğlu, H., Keyer-Uysal, M., Yeğen, B.C., 2002. Melatonin improves oxidative organ damage in a rat model of thermal injury. *Burns* 28 (5), 419–425.
- Sener, G., Sehirli, A.O., Satiroğlu, H., Kaçmaz, A., Ayanoglu-Dülger, G., Yeğen, B.C., 2003. Octreotide improves burn-induced intestinal injury in the rat. *Peptides* 24 (1), 123–127.
- Sener, G., Sehirli, O., Velioglu-Oğünç, A., Ercan, F., Erkanli, G., Gedik, N., Yeğen, B.C., 2006. Propylthiouracil (PTU)-induced hypothyroidism alleviates burn-induced multiple organ injury. *Burns* 32 (6), 728–736.
- Sewerynek, E., Melchiorri, D., Reiter, R.J., Ortiz, G.G., Lewinski, A., 1995. Lipopolysaccharide-induced hepatotoxicity is inhibited by the antioxidant melatonin. *Eur. J. Pharmacol.* 293 (4), 327–334.
- Spindel, E.R., Giladi, E., Segerson, T.P., Nagalla, S., 1993. Bombesin-like peptides: of ligands and receptors. *Recent Prog. Horm. Res.* 48, 365–391.
- Sun, Z., Wang, X., Deng, X., Lasson, A., Wallén, R., Hallberg, E., Andersson, R., 1998. The influence of intestinal ischemia and reperfusion on bidirectional intestinal barrier permeability, cellular membrane integrity, proteinase inhibitors, and cell death in rats. *Shock* 10 (3), 203–212.
- Swaroop, A., Ramasarma, T., 1985. Heat exposure and hypothyroid conditions decrease hydrogen peroxide generation in liver mitochondria. *Biochem. J.* 226 (2), 403–408.
- Toklu, H.Z., Sener, G., Jahovic, N., Uslu, B., Arbak, S., Yeğen, B.C., 2006. Beta-glucan protects against burn-induced oxidative organ damage in rats. *Int. Immunopharmacol.* 6 (2), 156–169.
- Trudel, L., Tomasello, C., Rio, M.C., Bouin, M., Plourde, V., Eberling, P., Poitras, P., 2002. Ghrelin/motilin-related peptide is a potent prokinetic to reverse gastric postoperative ileus in rat. *Am. J. Physiol. Gastrointest. Liver Physiol.* 282 (6), G948–G952.

- Tümer, C., Oflazoğlu, H.D., Obay, B.D., Kelle, M., Taşdemir, E., 2008. Effect of ghrelin on gastric myoelectric activity and gastric emptying in rats. *Regul. Pept.* 146 (1–3), 26–32.
- Unlüer, E.E., Alican, I., Yeğen, C., Yeğen, B.C., 2000. The delays in intestinal motility and neutrophil infiltration following burn injury in rats involve endogenous endothelins. *Burns* 26 (4), 335–340.
- Venditti, P., Balestrieri, M., Di Meo, S., De Leo, T., 1997. Effect of thyroid state on lipid peroxidation, antioxidant defences, and susceptibility to oxidative stress in rat tissues. *J. Endocrinol.* 155 (1), 151–157.
- Wallace, J.L., Boichot, E., Sidoti, C., Brex, A., Paubert-Braquet, M., 1993. Protective effects of somatostatin against gastric damage induced by hemorrhagic shock, stress and PAF in the rat. *Regul. Pept.* 47 (2), 195–203.
- Wichmann, M.W., Zellweger, R., Demaso, C.M., Ayala, A., Chaudry, I.H., 1996. Enhanced immune responses in females, as opposed to decreased responses in males following haemorrhagic shock and resuscitation. *Cytokine* 8 (11), 853–863.
- Wichmann, M.W., Ayala, A., Chaudry, I.H., 1997. Male sex steroids are responsible for depressing macrophage immune function after trauma-hemorrhage. *Am. J. Phys.* 273 (4), C1335–C1340 Pt 1.
- Wilson, R.E., 1996. Care of the burn patient. *Ostomy Wound Manage* 42 (8), 16–18.
- Wolf, S.E., Ikeda, H., Matin, S., Debroy, M.A., Rajaraman, S., Herndon, D.N., Thompson, J.C., 1999. Cutaneous burn increases apoptosis in the gut epithelium of mice. *J. Am. Coll. Surg.* 188 (1), 10–16.
- Yeh, C., Ting, C.H., Doong, M.L., Chi, C.W., Lee, S.D., Chen, C.Y., 2016. Intracerebroventricular urocortin 3 counteracts central acyl ghrelin-induced hyperphagic and gastropromotor effects via GRF receptor 2 in rats. *Drug Des. Devel. Ther.* 10, 3281–3290.