Int. J. Morphol.,
40(5):1294-1299, 2022.

The Effects of L-Carnitine on Gastrointestinal Contractility and Histological Changes in Rat Intestinal Ischemia-Reperfusion Injury

Efectos de la L-Carnitina sobre la Contractilidad Gastrointestinal y los Cambios Histológicos en la Lesión por Isquemia-Reperfusión Intestinal de Rata

Ali Özant[1]; Ülfet Farisoglu[2]; Pelin Toros[3] & Emine Koç[2]

ÖZANT, A.; FARISOGLU, U.; TOROS, P.; KOÇ, E. The effects of L-carnitine on gastrointestinal contractility and histological changes in rat intestinal ischemia-reperfusion injury. *Int. J. Morphol., 40(5)*:1294-1299, 2022.

SUMMARY: Ischemia-reperfusion (I/R) of the small intestine causes serious abdominal pathologies including tissue dysfunction and organ failure. L-carnitine (L-C), a powerful antioxidant, may help lessen the severity of these pathological effects since it plays a key role in energy metabolism. In this work we aimed to study the effects of L-C on the isolated ileal and duodenal contractility and histological changes in intestinal ischemia and reperfusion injury. Twenty eight Wistar rats were divided into four groups. The first group is the control group. Second group, I/R group, had rats submitted to 45-minutes of intestinal ischemia and to 45-minutes reperfusion. The third group, I/R+ L-C group, rats were treated with L-C 5 minutes before reperfusion and than submitted to ischemia. The fourth group, included rats that were treated with L-C without ischemia or reperfusion. Intestinal ischemia was conducted by obstructing superior mesentery arteries by silk loop.The ileal and duodenal segments were isolated and suspended in tissue bath. Contractile responses were induced by acetylcholine (Ach) and relaxation was achieved with phenylephrine. At the same time the terminal ileal and duodenal segments were examined for histological changes. Ach-induced contraction responses were higher in the I/R+L-C group, the L-C group, and the control group compared to the I/R group, in both ileal and duodenal segments. On the other hand, the phenylephrine-induced relaxations were higher in the I/R+L-C and L-C groups, especially in duodenal segments. In I/R group intestinal morphology was observed to be severely damaged whereas in I/R+L-C group the damage was noticeably lower possibly due to protective properties of L-C. I/R injury caused severe cellular damage response within the muscularis resulting in decreased gastrointestinal motility. Treatment with the L-C has significantly affected the gastrointestinal contractility. Also L-C treatment reduced the damage in intestinal morphology that occurs after IR injury.

KEY WORDS: Ischemia-reperfusion; Gastrointestinal contractility; Histological damage; L-carnitine.

INTRODUCTION

Failure of blood circulation in the gastrointestinal tract causes multiple dysfunctions. Due to sensitive nature of labile cells, the intestinal tissue can be easily damaged by an I/R which may be caused by any one of many clinical conditions such as acute mesenteric ischemia, intestinal obstruction, incarcerated hernia, trauma and shock (Mallick *et al*., 2004). Intestinal I/R injury leads to functional and structural dysfunction in the gut which initiates an inflammatory cascade and cause ileus (Hierholzer *et al*., 1999). It results in severe form of circulatory shock that oxygen derived free radicals play an important role (Stroh *et al*., 1998). I/R injury of intestine is important in many situations such as the interruption of blood flow to the gut as in aortic aneurysm surgery, cardiopulmonary bypass, enterocolitis and intestinal transplantation (Collard & Gelman, 2001).

The first abnormality detected in ischemia is on the mitochondria (Jassem *et al*., 2002). The major cause of this damage is related with large amount of free oxygen radicals production, iron release, inflammatory cytokines and neutrophil infiltration at the injured area (Carden & Granger, 2000).

Hierholzer *et al*. (1999) reported that intestinal I/R injury has caused neutrophils and monocytes migration into

[1] Near East University, Faculty of Medicine, Department of General Surgery, Nicosia, Cyprus.
[2] Near East University, Faculty of Medicine, Department of Physiology, Nicosia, Cyprus.
[3] Balikesir 17 Eylül University, Faculty of Medicine, Department of Histology and Embryology, Turkey.

Received: 2022-04-19 Accepted: 2022-07-05

the intestinal muscularis, thereby causing a decrease in circular muscle contractions. I/R injury evokes to molecular and cellular inflammatory responses within the intestinal muscularis layer that is associated with decreased intestinal motility (Hierholzer *et al*., 1999). Tahir *et al*. (2018) showed that neutrophils contribute to the injuries preceded by ischemia and reperfusion. During the I/R injury the mitochondrial permeability increases due to production of transition pores, a common pathway for devastating events (Kalogeries *et al*., 2012). Yet, the mechanisms that stimulate and activate circulating neutrophils after intestinal IR injury are still not clear. Many investigators have accepted that I/R injury to the small intestine results in local production of reactive oxygen species (ROS), degranulation of intestinal mucosal mast cells, and release of inflammatory mediators (Andoh *et al*., 2001) L-C is important agent that plays a valuable role in energy metabolism.

Xie *et al*. (2016) showed that L-C exerts a protective effect by preventing energy loss through its antioxidant effect on I/R injuries in the heart. It was further shown that L-propyl carnitine has significant protective effects also on intestinal tissue suffering from I/R through its inhibiting effect on leukocyte infiltration thereby preserving endothelial function. Furthermore L-propyl carnitine also decreased micro vascular permeability maintaining tissue perfusion (Stroh *et al*., 1998). It was shown that dietary carnitine deficiency causes gastrointestinal contractility disorder, gastrointestinal discomfort and dysfunctions in hemodialysis patients (Irie *et al*., 2017). Unesterified form of L-carnitine exists in mammalian cells especially in skeletal muscle (Atila *et al*., 2002). Sources of L-C are mainly dietary products such as meat and dairy and to a limited extend, endogen biosynthesis in liver and kidney (Moghaddas & Dashti-Khavidaki, 2018). In a study of protective effects of L-C against I/R injury, Yuan *et al*. (2011) reported enhancement in IL-10, suppression in serum TNF-alfa, IL-beta, IL-6, reduction in levels of bacterial translocation and morphological damage.

There are not enough studies in I/R injury about intestinal function and gastrointestinal contractility and histological changes. Therefore, in this study, we aimed to investigate the effects of I/R injury on intestinal contractility and morphologic damage of rat ileum and duodenum and if there is any protective effects of L-C application on I/R damage. L-C is not just a cofactor in beta-oxidation, there are many unknown effects on many organs and yet to be discovered function in physiology. Also future studies are necessary to provide more information focusing on reperfusion after ischemia and the effects of L-C on gastrointestinal contractility and histologicalchanges.

MATERIAL AND METHOD

This study has received the approval by the local ethics committee of Near East University (Date 19.03.2021, reference number, 2021-128). Healthy adult female Wistar rats (250-300 g) were housed under standard conditions. They were maintained using a 12 h light/dark cycle and provided with commercially available rat chow and tap water ad libitum. The animals were anaesthetized with ketamine 90 mg/kg and ksilasine 10mg/kg i.p. and a midline incision made into the peritoneal cavity. Four experimental sets were designed. The first set of animals were the shame-operated control group (C) on which only the laparotomy was performed. The second set, the I/R group, had rats whose small bowels were exteriorized to the left on moist gauze and who were subjected to 45 min intestinal ischemia, caused by isolation and obstruction of the superior mesenteric artery with silk loop, and later the silk threads were gently removed to allow for 45 min of reperfusion. Intestinal ischemia was confirmed by the pale color of the intestine. In the third group, the I/R+L-C group, rats were experimented on as in the second group with the only exception being administration of L-C (200 mg/kg i.v) 5 min prior to reperfusion.The fourth and final group of rats, the L-C group, were operated on like the control group but were administered L-C (200 mg/kg i.v).The abdomen was sutured after the procedure in all experimental groups. Animals in the control group and the I/R group were administered sterile serum physiological solution in identical fashion and volume as an experimental control measure against the third and fourth group animals being administered L-C.

At the final stage of the experimental procedures, ileal and duodenal segments (0.3–0.5 mm long pieces) were removed for each experimental protocol. All experimental groups were sacrificed in the same way after the procedure is completed. Each of the ileal and duodenal tissue segments were suspended in isolation in tissue baths containing 15 ml of the Krebs–Henseleit solution (mM NaCl 118.9, KCl 4.6, $CaCl_2$ 2.5, KH_2PO_4 1.2, $NaHCO_3$ 25, $MgSO_4$ 1.2 and glucose 11), and a 95 % O2, 5 % CO_2 mixture at 37 ºC, pH 7.4, was passed into the solutions. The segments were brought into equilibrium for 60 min under an optimal resting tension of 1g. After equilibration, the ileum and duodenum segments were contracted with Ach and relaxed with phenylephrine. The Ach ($3x10^{-7}$ M) and phenylephrine ($3x10^{7}$ M) doses were considered as maximal doses, after the cumulative addition of Ach and phenylephrine into the control group. The acetylcholine (Sigma A6625), phenylephrine (Sigma P6126) and L-C (Carnitine; Santa Farma, istanbul) were obtained from Sigma chemical. Contraction and relaxation responses were recorded in the organ bath (May-ITBS 08).

Histological preparation: Ileal and duodenal segments were first fixed in 10 % formalin and were embedded in paraffin, sectioned (5 μm) and stained with hematoxylin and eosin (H&E) for morphological analysis in light microscopy. Histological evaluation of intestinal tissues was performed based on the modified staging method described by Hierholzer *et al*. (1999). I/R injury was scored in each animal under light microscopy. The scores obtained from each rat were summed and averaged, thus obtaining a single mean ileum and duodenum score for each rat. The injury was evaluated according to the following criteria: Grade 0- no specific pathologic changes. Grade 1- mild mucosal damage denudation of villous: epithelium, otherwise normal structure. Grade 2- moderate damage: loss of villous height and epithelial sloughing with evidence of congestion, hemorrhage, and inflammation in the mucosa. Grade 3-severe damage: loss of a large number of villous, including denudation, and sloughing in the mucosa. Villous lengths were evaluated for each group in duodenum and ileum. Villous lengths were recorded using fiji/imagej program by measuring 10 different areas in x10 objectives from each group and evaluated statistically.

Statistical Analysis. All of the contraction, relaxation and histological results were statistically evaluated with the graphpad prism 8.3.1 program. One-Way ANOVA (One-Way Analysis of Variance) was used to statistically compare the differences among the groups, with multiple comparison using Tukey's test. P≤0.05 value was accepted as significant in the statistical evaluation. Data are presented as the mean±standard error of mean.

RESULTS

In this study, the effects of L-C in I/R damaged ileum and duodenum were investigated by analyzing the ACh-induced contractions and phenylephrine-induced relaxations and the histological changes following an I/R episode.

Muscle function: The effects of L-C on Ach-induced contraction in ileal segments inI/R, I/R+L-C, and L-C groups are respectively exhibited in Figure 1.

From Figure 1, it can be observed that Ach-induced contractions were lowest in the I/R group, and second lower measures belonged to theIR+L-C group.There was significant difference in IR and I/R+L-C group($p< 0.05$). The contractile responses were highest in the L-C group when compared to I/R andI/R+L-C groups.

As shown in Figure 2, the contractile responses to ACh in duodenal segments were significantly higher in I/R+ L-C and the L-C groups compared to the I/R group($p< 0.05$, $p< 0.005$). Figure 3 illustrates the responses to the phenylephrine-induced relaxation in ileal segments. Remarkably, these responses were significantly low in all experimentally manipulated groups when compared to the control group response ($p< 0.005$, $p< 0.05$).

As shown in Figure 4, the responses to phenylephrine-induced relaxation responses were significantly decreased in the I/R group compared to the control group in duodenal segments ($p< 0.05$). The responses in I/R+L-C and L-C were observed higher as compared to I/R groups.

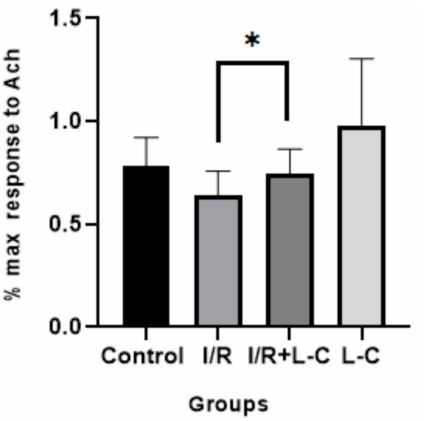

Fig. 1. The ACh-induced contractions on isolated ileum in control and experimental groups. *** P<0.001, ** p<0.002, * p<0.033.

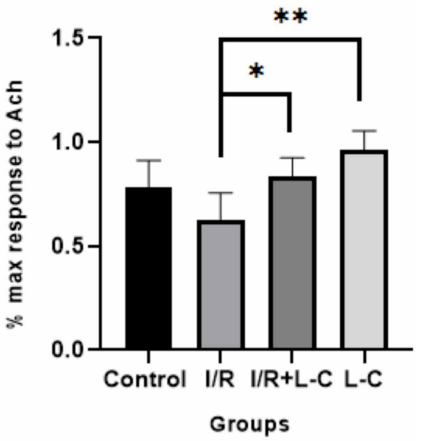

Fig. 2. The ACh-induced contractions on isolated duodenum in control and experimental groups.*** P<0.001, ** p<0.002, * p<0.033.

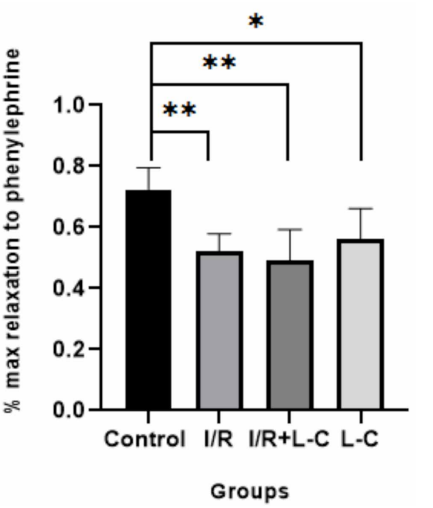

Fig. 3. Relaxations effects of phenylephrine on the control and experimental groups on isolated ileum.*** P<0.001, ** p<0.002, * p<0.033.

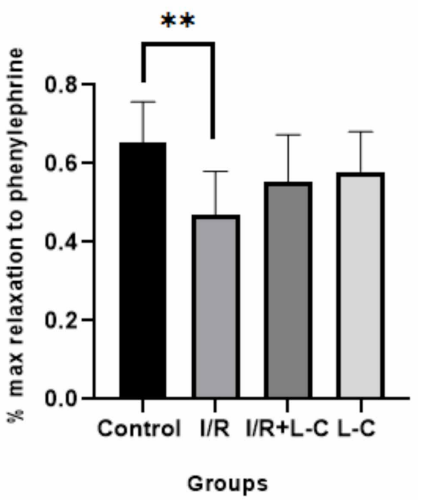

Fig. 4. Relaxations effects of phenylephrine on the control and experimental groups on isolated duodenum.*** P<0.001, ** p<0.002, * p<0.033.

Histological Results: Figures 5A and 5D shows respectively that the control groups in duodenum (Grade 0) and ileum (Grade 0) were normal in structure. No histological damage was observed in any rat in the control group. In both the duodenum (5B) and the ileum (5E) of the I/R group, intestinal morphologies were severely damaged and in both cases the villous epithelial were broken, exhibiting congestion, hemorrhage, and inflammatory cell infiltration (Grade 3) which were seen in Figure 5 B, E. In the IR + LC group, there was no congestion in the duodenum 5C (Grade 1), while some areas of the ileum were congested 5F (Grade 2) as seen in Figure 5 C, F. The most extensive changes in morphology were detected in the IR group, which was statistically different from the others; control or I/R+L-C and L-C group.

Histological scores: Histological scores in villous lengths of the groups were seen in Table I. Villous lengths in duodenum and in ileum were measured for each group using fiji/imagej program 10 different areas in x10 objectives from each group and were evaluated statistically.

Villous lengths were significantly lower in I/R group compared to the control group in both the duodenum and the ileum (p<0.001, p<0.001). In I/R+L-C group villous lengths were significantly higher for both duodenum and ileum compared to the control (p<0.033, p<0.033) and I/R group (p<0.002, p<0.002). In L-C group, the villous length was observed significantly higher than compared to IRin duodenum and ileum (p<0.001, p<0.001) and IR+L-C group (p< 0.033) in the ileum.

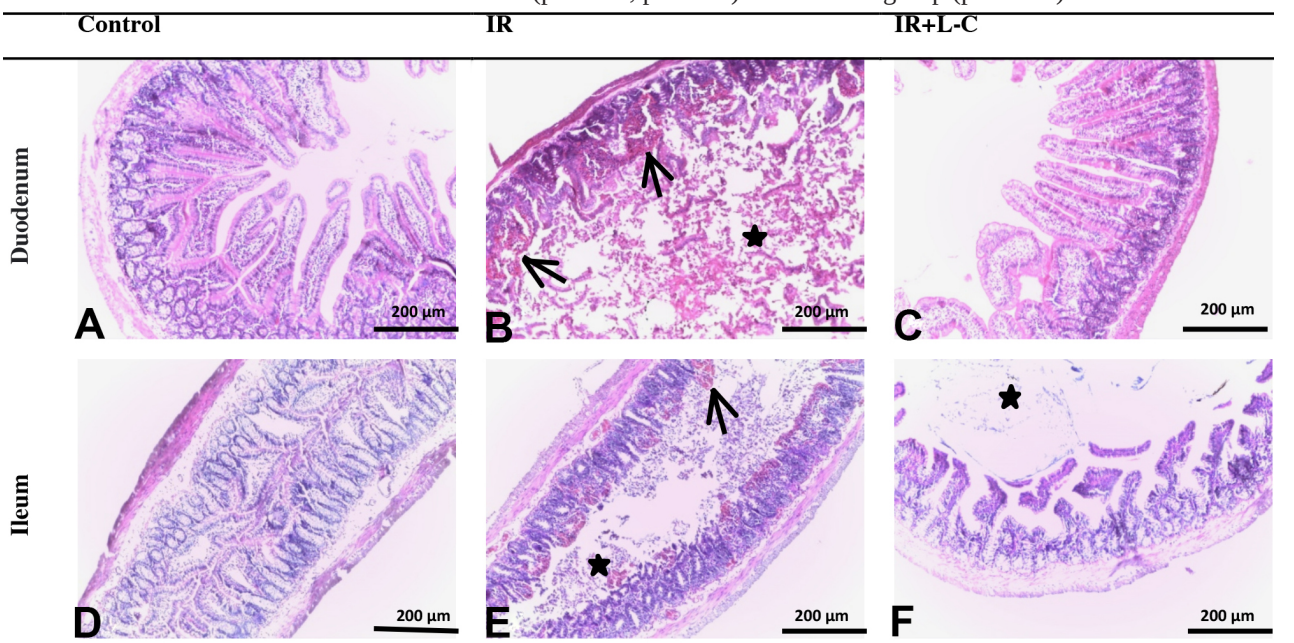

Fig. 5. Light micrographs of rat duodenum and ileum section in experimental groups. A. Control group of duodenum (Grade 0), B. IR group of duodenum (Grade 3), star: epithelial sloughing, Black arrow: congestion and hemorrhage C. IR+L-C group of duodenum (Grade 1), D. Control group of ileum (Grade 0), E. IR group of ileum (Grade 3), F. IR+L-C group of ileum (Grade 2). Haematoxylin and eosin, Scale bar=200 µm.

Table I. Histological scoring and villous lengths of the groups.

Groups	Histological score Duedonum (mm)	Histological score Ileum(mm)	Villus Lengths Duedonum (mm)	Villus Lengths Ileum (mm)
Control	0,00±0,00	0,00±0,00	619,3±75.29	286,0±22,76
IR	2,75±0,46***a	2,87±35***a	255,3±41,04***a	122,5±22,10***a
IR+L-C	1,00 ± 0,00 ***a, *** b	1,37 ± 0,51***a,** b	490,3±104,1*a, ,**b	209,8±46,79*a,**b
L-C	0,00 ± 0,00 *** b, *** c.	0,00 ± 0,00 *** b, *** c.	608,3±70,47 *** b	282,3±19,60***b, *c

*** P<0.001, ** p<0.002, * p<0.033. a. Significant compared to the control group b. Significant compared to IR c. Significant compared to the IR+L-C

DISCUSSION

This study investigated the effects of L-C on gastrointestinal contractility and histological changes in ileal and duodenal segments in the case of I/R injury in rats. Our results showed that I/R injury decreased ileal and duodenal contractility and L-C has negated to a significant extent this adverse effect of I/R injury by exerting what can be described as a protective effect. Our histological results showed that I/R caused substantial tissue damage in duodenum and ileum and L-C has similarly helped limit the extent of tissue damage through its protective or healing effect and L-C helped to prevent and reduce mucosal damage.

This study points out that ileal and duodenal contractility decreased in I/R injury groups. This is in line with Hierholzar *et al*. (1999). who show that I/R injury decreased jejunal contractility. Similar results were also observed in Ballabeni *et al*. (2002) where irregular spontaneous motor activity of the longitudinal musculature were greatly reduced in I/R injury groups. There results showed that the intestinal motor activity were decreased after I/R and there were reversible changes in contractile response to exogen acetylcholine after mild I/R with24h reperfusion, concluding that reperfusion period plays an important role in the adaptive changes of intestinal motility (Ballabeni *et al*., 2002). It was shown that prolonged ischemia caused lack of oxygen delivery, anaerobic metabolism for ATP production, ion transport system collapse and calcium accumulation in intracellular and mitochondria. All these events finally lead to cell death, as in myocardial infarction, stroke and peripheral vascular disease (Eltzschig & Eckle, 2011; Moghaddas & Dashti-Khavidaki, 2018).

Our histological results showed that there was mucosal damage in ileum and duodenum of the rats with brake down of villous epithelial which exhibited congestion, hemorrhage and inflammatory cell infiltration in I/R group.The therapeutic approaches to ischemia resolution are prompt restoration of blood flow and applying a preconditioning agent prior to I/R induction. Therefore we used L-C as free radical scavengers. Our results showed that L-C caused significant increased contractility as compared I/R groups. However, many investigators accepted that L-C plays important role to transport long-chain free fatty acids from cytosol into mitochondria. Mitochondria turn them into tricarboxylic acid cycle and as a result of many reactions in mitochondria, oxygen is reduced and ROS formation is inhibited (Moghaddas & Dashti-Khavidaki, 2016). L-C can also potentiate the activity of antioxidant enzymes and chelate ROS generation's metal ions such as ferrous (Gülçin *et al*., 2005). It is believed that the most protective effect of L-C against IR- injury arises from its antioxidant activity which can alleviate IR injury by inhibition of ROS production in aerobic metabolism.

Our results indicated that there were significant increase in Ach-induced contraction and increased in phenylephrie-induced relaxation both in ileal and duodenal segments in I/R+L-C groups compared with I/R groups. Our histological results also showed that L-C partially restored the intestinal damage. When L-C was administrated in I/R group there was no congestion in the duodenum while some areas of the ileum were congested. However in our I/R experimental group we did not detect leucocyte activation and infiltration as in the research results of Sayan *et al*. (2008). Also, the research results of Stroh *et al*. (1998) support our findings which they reported that L-C have significant protective effect by inhibiting leukocyte infiltration into intestinal tissue and thus preserving endothelial function. The study of Akin *et al*. (2007) showed that administration of L-C, partially prevented lipid peroxidation which caused the cells gain antioxidant characteristics. Thus, L-C helps to prevent and reduce mucosal damage as we have shown in our histological results.

Since the metabolic activities of the intestine were high, they were very sensitive to I/R. Although the exact mechanisms of intestinal injury have not been absolutely defined, researchers apply antioxidants to understand the events during reperfusion. In our studies, we applied L-C after I/R injury and before reperfusion as antioxidant to study the gastrointestinal motility and histological changes. Our results showed that L/C partially prevents gastrointestinal dysmotility and histological damage.

Hosgorler *et al*. (2010) had observed that on a long (3h) duration of reperfusion in intestinal organ model, L-C application was able to reduce the severity of reperfusion injury by through significant reduction in morphologic changes, perfused microvessels, and epithelial regeneration. Our results confirm the results of Hosgorler *et al*. (2010). However, Ballabeni *et al*. (2002) reported that reperfusion time plays an important role in recovery. They showed that intestinal mild ischemia/24 h reperfusion induced reversible changes in enteric motility and transient mucosal damaged of rat ileum.

Although, in the present experiments, we indicated that there were alterations in the intestinal motility and histological damage in I/R injury of intestine and the repairing effects of L-C, the exact mechanisms responsible for these changes remain unclear. Many experiments claimed that the oxidant stress increased, possibly due to an elevated reactive oxygen species production or due to a decrease in the function of natural antioxidant pathways.

ÖZANT, A.; FARISOGLU, U.; TOROS, P.; KOÇ, E. Efectos de la L-carnitina sobre la contractilidad gastrointestinal y los cambios histológicos en la lesión por isquemia-reperfusión intestinal de rata. *Int. J. Morphol., 40(5)*:1294-1299, 2022.

RESUMEN: La isquemia-reperfusión (I/R) del intestino delgado provoca graves patologías abdominales que incluyen disfunción tisular y falla orgánica. La L-carnitina (L-C), un poderoso antioxidante, puede ayudar a disminuir la gravedad de estos efectos patológicos, ya que desempeña un papel clave en el metabolismo energético. El objetivo de este trabajo fue estudiar los efectos de L-C sobre la contractilidad ileal y duodenal aislada y los cambios histológicos en la lesión por isquemia y reperfusión intestinal. Se dividieron 28 ratas Wistar en cuatro grupos. El primer grupo fue el control. El segundo grupo, grupo I/R, de ratas sometidas durante 45 minutos de isquemia intestinal y a 45 minutos de reperfusión. El tercer grupo, grupo I/R+ L-C, las ratas se trataron con L-C, 5 minutos antes de la reperfusión y luego se sometieron a isquemia. El cuarto grupo, las ratas fueron tratadas con L-C sin isquemia ni reperfusión. La isquemia intestinal se realizó obstruyendo la arteria mesentérica superior con un asa de seda. Los segmentos ileal y duodenal se aislaron y suspendieron en un baño de tejido. Las respuestas contráctiles fueron inducidas por acetilcolina (Ach) y la relajación se logró con fenilefrina. Al mismo tiempo, se examinaron cambios histológicos de los segmentos del íleon terminal y del duodeno. Las respuestas de contracción inducidas por Ach fueron mayores en el grupo I/R+L-C, el grupo L-C y el grupo control en comparación con el grupo I/R, tanto en el segmento ileal como en el duodenal. Por otra parte, las relajaciones inducidas por fenilefrina fueron mayores en los grupos I/R+L-C y L-C, especialmente en los segmentos duodenales. En el grupo I/R se observó que la morfología intestinal estaba dañada significativamente, mientras que en el grupo I/R+L-C el daño fue notablemente menor, posiblemente debido a las propiedades protectoras de L-C. La lesión por I/R causó una respuesta de daño celular severo dentro de la capa muscular que resultó en una disminución de la motilidad gastrointestinal. El tratamiento con L-C afectó significativamente la contractilidad gastrointestinal. Por otra parte, el tratamiento L-C redujo el daño en la morfología intestinal que ocurre después de la lesión por IR.

PALABRAS CLAVE: Isquemia-reperfusión; Contractilidad gastrointestinal; Daño histológico; L-carnitina.

REFERENCES

Akin, M.; Kurukahvecioglu, O.; Gulbahar, O.; Isikgonul, I.; Taneri, F.; Tezel, E. & Onuk, E. Comparison of the effects of sodium nitroprusside and L-carnitine in experimental ischemia-reperfusion injury in rats. *Transplant. Proc., 39(10)*:2997-3001, 2007.

Andoh, A.; Fujiyama, Y.; Araki, Y.; Kimura, T.; Tsujikawa, T. & Bamba, T. Role of complement activation and mast cell degranulation in the pathogenesis of rapid intestinal ischemia/reperfusion injury in rats. *Digestion, 63 Suppl. 1*:103-7, 2001.

Atila, K.; Coker, A.; Sagol, O.; Coker, I.; Topalak, O.; Astarcioglu, H.; Karademir, S. & Astarcioglu, I. Protective effects of carnitine in an experimental ischemia-reperfusion injury. *Clin. Nutr., 21(4)*:309-13, 2002.

Ballabeni, V.; Barocelli, E.; Bertoni, S. & Impicciatore, M. Alterations of intestinal motor responsiveness in a model of mild mesenteric ischemia/reperfusion in rats. *Life Sci., 71(17)*:2025-35, 2002.

Carden, D. L. & Granger, D. N. Pathophysiology of ischaemia-reperfusion injury. *J. Pathol., 190(3)*:255-66, 2000.

Collard, C. D. & Gelman, S. Pathophysiology, clinical manifestations, and prevention of ischemia-reperfusion injury. *Anesthesiology, 94(6)*:1133-8, 2001.

Eltzschig, H. K. & Eckle, T. Ischemia and reperfusion--from mechanism to translation. *Nat. Med., 17(11)*:1391-401, 2011.

Gülçin, I. Antioxidant and antiradical activities of L-carnitine. *Life Sci., 78(8)*:803-11, 2006.

Hierholzer, C.; Kalff, J. C.; Audolfsson, G.; Billiar, T. R.; Tweardy, D. J. & Bauer, A. J. Molecular and functional contractile sequelae of rat intestinal ischemia/reperfusion injury. *Transplantation, 68(9)*:1244-54, 1999.

Hosgorler, F. U.; Atila, K.; Terzi, C.; Akhisaroglu, S. T.; Oktay, G.; Kupelioglu, A.; Ergor, G. & Saydam, S. Carnitine protects the intestine against reperfusion injury in rats. *J. Surg. Res., 159(1)*:603-10, 2010.

Irie, J.; Kanno, Y.; Kikuchi, R.; Yoshida, T.; Murai, S.; Watanabe, M.; Itoh, H. & Hayashi, M. L-Carnitine improves gastrointestinal disorders and altered the intestinal microbiota in hemodialysis patients. *Biosci. Microbiata Food Health, 36(1)*:11-6, 2017.

Jassem, W.; Fuggle, S. V.; Rela, M.; Koo, D. D. H. & Heaton, N. D. The role of mitochondria in ischemia/reperfusion injury. *Transplantation, 73(4)*:493-9, 2002.

Kalogeries, T.; Baines, C. P.; Krens, M. & Korthuis, R. J. Cell biology of ischemia/reperfusion injury. *Int. Rev. Cell Mol. Biol., 298*:229-317, 2012.

Mallick, I. H.; Yang, W.; Winslet, M. C. & Seifalian, A. M. Ischemia-reperfusion injury of the intestine and protective strategies against injury. *Dig. Dis. Sci., 49(9)*:1359-77, 2004.

Moghaddas, A. & Dashti-Khavidaki, S. L-carnitine and potential protective effects against ischemia-reperfusion injury in noncardiac organs: from experimental data to potential clinical applications. *J. Diet. Suppl., 15(5)*:740-56, 2018.

Moghaddas, A. & Dashti-Khavidaki, S. Potential protective effects of l-carnitine against neuromuscular ischemia-reperfusion injury: From experimental data to potential clinical applications. *Clin. Nutr., 35(4)*:783-90, 2016.

Sayan, H.; Ozacmak, V. H.; Altaner, S.; Aktas, R. G. & Arslan, S. O. Protective effects of L-arginine on rat terminal ileum subjected to ischemia/reperfusion. *Pediatr. Gastroenterol. Nutr., 46(1)*:29-35, 2008.

Stroh, R.; Christopher, T. A.; Lopez, B. L.; Guo, L. P.; Amico-Roxas, M. & Ma, X. L. L-propionyl carnitine, an endogenous ester in fatty acid metabolism, exerts anti-shock and endothelial protective effects in rat splanchnic ischemia-reperfusion injury. *Shock, 9(3)*:216-22, 1998.

Tahir, M.; Arshid, S.; Fontes, B.; Castro, M. S.; Luz, I. S.; Botelho, K. L. R.; Sidoli, S.; Schwämmle, V.; Roepstorff, P. & Fontes, W. Analysis of the effect of intestinal ischemia and reperfusion on the rat neutrophils proteome. *Front. Mol. Biosci., 5*:89, 2018.

Xie, J.; Zeng, Q. & Wang, L. The protective effect of L-carnitine on ischemia-reperfusion heart. *J. Huazhong Univ. Sci. Technolog. Med. Sci., 26(2)*:188-91, 2006.

Yuan, Y.; Guo, H.; Zhang, Y.; Zhou, D.; Gan, P.; Liang, D. M. & Chen, J. Y. Protective effects of L-carnitine on intestinal ischemia/reperfusion injury in a rat model. *J. Clin. Med. Res., 3(2)*:78-84, 2011.

Corresponding author:
Assistant Prof. Ali Özant
Near East University, Faculty of Medicine
Department of General Surgery
Nicosia/TRNC
TURKEY

E-mail: ali.zant@yahoo.com

ORCID: 0000-0002-7746-2719

Ali Özant	ORCID: 0000-0002-7746-2719
Ülfet Farisoglu	ORCID: 000-0002-8577-291X
Pelin Toros	ORCID: 0000-0002-8733-2096
Emine Koç	ORCID: 0000-0001-8804-4937