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Concomitant L-Carnitine Supplementation and Exercise Training Affects Apoptosis in Male Rats

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Abstract

Background: Apoptosis is a defensive measure that removes dysfunctional cells. Exercise training has a broad spectrum of benefits that influence apoptosis and cell viability. L-carnitine (LCAR), a supplement nowadays, has shown beneficial effects against cell death. We investigated the simultaneous effect of exercise training (acute exercise [AE] and high-intensity interval training [HIIT]) and LCAR supplementation on the proteins involved in apoptosis. The animals were anesthetized twenty-four hours after the conclusion of the final training session.

Methods: Forty-eight male Wistar rats (210±10 g) were assigned to six groups ($n=8$) as follows: Control, LCAR (200 mg/kg/d LCAR, IP), AE, HIIT, LCAR+AE, and LCAR+HIIT. The animals were anesthetized and sacrificed twenty-four hours after the last training session; the rats' blood sample was collected, and the serum was separated. The serum Bcl-2 levels, as an anti-apoptotic factor, and caspase-3 and BAX, as proapoptotic factors, were measured using specific ELISA kits.

Results: AE increased apoptosis, but HIIT's effects were almost neutral. LCAR administration in groups that performed either AE or HIIT significantly attenuated apoptosis. However, in group 6 (LCAR+HIIT), the anti-apoptotic effects were noteworthy because LCAR+HIIT significantly increased Bcl-2 and reduced caspase-3 levels compared to the control group.

Conclusion: HIIT improved cell viability through increasing Bcl-2 levels, and LCAR strengthened HIIT's anti-apoptotic properties. AE increased proapoptotic proteins, and LCAR modified the elevated proapoptotic markers in the AE group. Therefore, LCAR may be considered a promising supplement against exercise-mediated injury. This study can be extended to humans to evaluate the beneficial effects of LCAR+HIIT and LCAR+AE.

Keywords: L-carnitine, Apoptosis, Bcl-2, Exercise

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Introduction

In multicellular organisms, every cell follows a precise program to destroy itself via apoptosis (1-3). Apoptosis is a defensive measure that omits dysfunctional cells in a controlled manner (1). The fragmentation of mitochondria during apoptosis is the result of dynamic changes in several proteins, including Bcl-2, BAK, mitofusin-2, BAX, and dynamin-related protein 1 (2, 4). Bcl-2 and BAX are the most important factors implicated in managing mitochondrial apoptosis (5). Normally, this program is suppressed by inhibitory factors. The mechanisms by which apoptosis is inhibited involve the retention of proapoptotic factors within cellular compartments such as lysosomes and mitochondria (2). The apoptotic proteins caspase-3, BAX, and BAK are crucial for predicting apoptosis related to mitochondrial membrane permeability. Interestingly, these proteins can also modulate mitochondrial morphology, because the BAX and BAK double-knockout (DKO) cells show scattered mitochondria because of reduced mitochondrial fusion (3).

The beneficial effects of exercise include mitochondrial biogenesis, which improves vascular status and heart

rate (6). Exercise increases the production of oxidants in the electron transfer chain. Oxidants can directly affect the levels of glutathione, ATP, nicotinamide adenine dinucleotide (NADH), and oxidative damage to mitochondrial DNA (7,8). Other activators, including tumor necrosis factor-α (TNF-α) and glucocorticoids, may have similar functions or work with different mechanisms to induce cell death. All these factors may affect mitochondrial proteins, including Bcl-XL, caspases, and BAX, and help release cytochrome c from the mitochondria (8,9). Cytochrome c release causes the onset of a "no-return point" and the activation of caspases, resulting in apoptosis (8,9). Training has been extensively utilized to enhance aerobic capacity and performance.

Additionally, two types of exercise training, high-intensity interval training (HIIT) and endurance training, are more important. Kwak (10) reported the anti-apoptotic properties of exercise training. The effects of exercise include increasing mitochondrial content, improving muscle oxidative capacity, and improving insulin sensitivity (11). The study by Moradi et al (12) reported that eight weeks of low-intensity interval training and HIIT both reduced BAX and increased Bcl-2 expression in the rat muscle. Regardless of its type, eight weeks of exercise positively affects apoptotic factors. The intensity of exercise also affects the number of changes (13).

L-carnitine (LCAR), also referred to as levocarnitine (beta-hydroxy-gamma trimethyl ammonium butyrate), is a naturally occurring compound (1,14,15). LCAR is absorbed through sodium-dependent active transport and inactive transport through the intestines (14). Tissues such as the liver, brain, and kidney are the source of LCAR synthesis from lysine and methionine; its synthesis also needs iron, niacin, and ascorbic acid (1). Without carnitine, the body cannot effectively utilize most dietary lipids, accumulating fatty acids that can eventually contribute to obesity and other metabolic diseases (14-16).

Carnevali et al (17) found that HIIT enhances the mitochondrial capacity for lipid transportation by elevating the carnitine palmitoyltransferase activity, which plays a crucial role in oxidative metabolism. Additionally, it has been noted that HIIT positively affects oxidative processes in the muscles of hypertensive animals (18). In general, HIIT contributes to increased energy efficiency and overall physical function (17,19). Furthermore, supplementing with LCAR alongside regular aerobic exercise has been shown to enhance liver tissue apoptosis in type 2 diabetes models (20). Mice who perform exercise training are able to maintain their LCAR store levels better than those who do not exercise. There is also evidence that individuals taking LCAR supplements while exercising experience improvements in their lipid profiles. In addition, LCAR supplementation has been associated with enhancements in athletic performance (14).

Exercise training potentially decreases apoptosis by reducing stress, which has different effects on different body systems and apoptotic processes (21). Long-term exposure to high oxidative stress can stimulate different systems to make the body more compatible in the long run. As a result, the apoptotic system is also expected to show symptoms under these conditions (13,22,23). In the present study, we aimed to investigate the simultaneous effect of exercise (acute and HIIT) and LCAR administration on the serum levels of proteins involved in apoptosis in rats.

Materials and Methods

Materials

L-carnitine (L-carnitine hydrochloride, Sigma, Cat. No.: C0283), Rat BAX kit (Cat. No.: CK-E30005, Hangzhou Eastbiopharm Co., Ltd.), Rat Bcl-2 kit (Cat. No.: CK-E30187, Hangzhou Eastbiopharm Co., Ltd.), Rat caspase-3 kit (Cat. No.: CK-E90197, Hangzhou Eastbiopharm Co., Ltd.).

Methods

All animal care and procedures complied with the European Convention for the Protection of Animals Used for Experimental and Other Scientific Purposes. Additionally, our study received formal approval from the Ethics Committee at Kerman University of Medical Sciences, under the reference code IR.KMU.REC.1400.027.

Animals

We used male Wistar rats in our current study. Forty-eight rats (aged 8 weeks and weighing 210 ± 10 g) were obtained from the Physiology Research Center. The rats were maintained at a temperature of 22 ± 2 °C and subjected to a 12-hour light/dark cycle. They had unrestricted access to food and water and were acclimatized to the lab setting for two weeks. Following this period, the rats were assigned to six groups ($n = 8$). The groups included group 1 (control) did not receive LCAR; Group 2 (LCAR), was administered 200 mg/kg/d of LCAR via intraperitoneal injections) (15,23,24); Group 3 (AE) performed acute exercise; Group 4 (HIIT) performed HIIT; Group 5 (LCAR + AE) received 200 mg/kg/d LCAR and performed AE; and group 6 (LCAR + HIIT) received 200 mg/kg/d LCAR and performed HIIT). In the morning, the rats received LCAR and then performed exercise after a few hours (24-30). Twenty-four hours following the last training session, in a CO2 chamber, the animals were anesthetized until they were unconscious. Subsequently, they were decapitated, and blood samples were taken from each rat. After 30 minutes at RT, the collected blood samples were centrifuged at 3500 rpm (15 min) to separate the serum, which was then stored at -80 °C for later analysis.

LCAR Administration

LCAR was prepared using sterile normal saline and administered via daily intraperitoneal injections at a 200

mg/kg dose for 4 weeks (15).

Exercise Protocols

High-intensity interval training (HIIT)

Familiarity of rats lasted for 2 weeks at a speed of 15 meters per minute for 15 minutes. The exercise training intensity was determined by measuring blood lactate levels following exercise (Lactometer; Lactate Scout Company/ Code: 37, Germany), with levels exceeding 6 mmol/L considered high intensity. The speed test started with a 10 m/min warm-up, and the speed increased (0.3 m/min) until exhaustion to calculate the intensity. The sessions included ten 2-minute work bouts/day (22 m/min, 29° slope) separated by 2-minute rest periods, 5 days/week. During the experiment, the control group underwent no training and remained stationary on the conveyor belt to induce treadmill stress. We determined the relative speed (high intensity) by assessing the maximum speed achieved by each rat (25-27).

Acute exercise (AE) protocol

AE was performed in one session in the relevant groups 24 hours before the animals were euthanized. After a 5-minute warm-up, the animals started on the treadmill at 15 m/min, and the speed slowly increased to 70% max speed (the above-mentioned maximum speed) until exhaustion (29-31).

Apoptosis indices measurement using ELISA

ELISA (obtained from Eastbiopharm) kits were used according to the kit instructions to quantify apoptosis indices, including anti-apoptosis (Bcl2) and pro-apoptosis (caspase-3 and BAX) levels. After preparing the reagents, standards, and samples, the serum and standards were poured into the designated wells, and an antibody labeled with enzyme was added to all wells. Then, they were incubated (37 °C) for 1 hour. The plate was washed with a washer instrument (5 times) using the wash buffer supplied in the kit. Chromogen solutions A and B were applied to the wells and were left to react at 37 °C to generate a blue color. Finally, the stop solution was used to stop the reaction, and the Optical Density (OD) of the wells was quantified using the Nanomabna ELISA reader instrument. The OD of the standards was used to obtain the standard curve and calculate the straight-line regression equation. The sample quantity of each apoptosis-related protein was calculated by the obtained equation (32).

Statistical analysis

We used SPSS software (Version 20) for data analysis. After assessing data normal distribution (Shapiro-Wilk test), we used one-way analysis of variance (ANOVA) to determine the differences in variables between groups along with Tukey's post hoc test. A significance level of $P < 0.05$ was considered significant in all statistical comparisons.

Results

Serum BAX levels were significantly elevated in the AE, LCAR + AE, and HIIT groups compared to the control group ($P < 0.001$ for both AE and LCAR + AE; $P = 0.017$ for HIIT) as well as compared to the LCAR group ($P < 0.001$ for both AE and LCAR + AE; $P = 0.008$ for HIIT). LCAR administration significantly reduced BAX levels in the LCAR + AE group compared to the AE group ($P = 0.033$) (Figure 1).

Moreover, AE significantly attenuated Bcl-2 levels compared to both the control and LCAR groups ($P < 0.003$ and $P < 0.001$, respectively). The LCAR + HIIT combination significantly enhanced Bcl-2 levels compared with controls ($P = 0.029$) (Figure 2). Both AE and the LCAR + AE combination significantly raised the BAX to Bcl-2 ratio compared to the control ($P < 0.001$) and LCAR ($P < 0.001$) groups (Figure 3).

Additionally, LCAR administration and the LCAR + HIIT combination significantly decreased caspase-3 levels

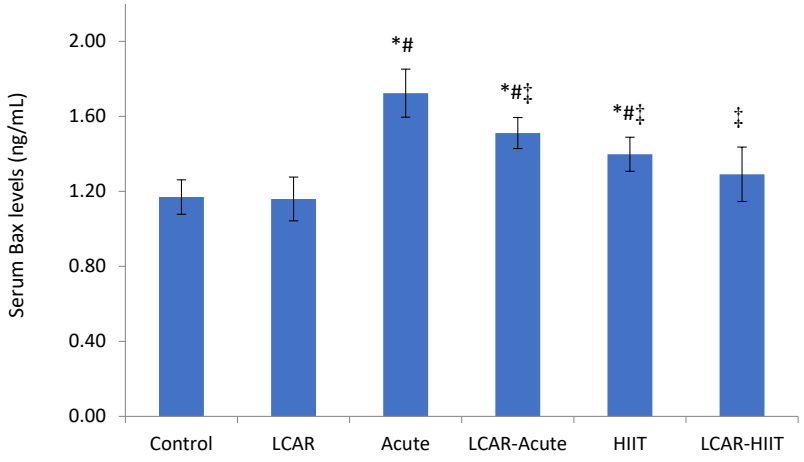

Figure 1. Serum BAX levels in the studied groups (control, L-carnitine [LCAR], acute exercise [AE], L-carnitine + acute exercise [LCAR + AE], HIIT, and L-carnitine + HIIT [LCAR + HIIT]). BAX levels were determined by a specific ELISA kit. Data are expressed as mean ± SEM, $n = 8$; $P < 0.05$ was considered significant. *Statistically significant compared to the control group, # Statistically significant compared to the LCAR group, ‡ Statistically significant compared to the acute group

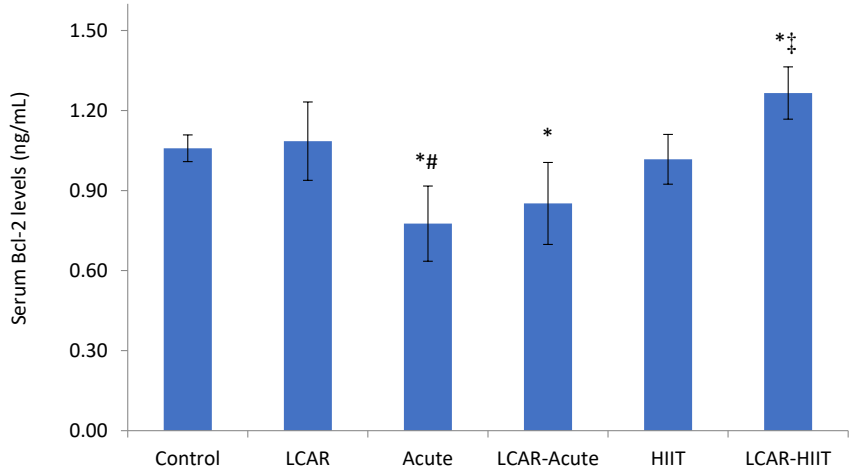

Figure 2. Serum Bcl-2 levels in the studied groups (control, L-carnitine [LCAR], acute exercise [AE], L-carnitine + acute exercise [LCAR + AE], HIIT, and L-carnitine + HIIT [LCAR + HIIT]). Bcl-2 levels were determined by a specific ELISA kit. Data are expressed as mean ± SEM; $n = 8$; $P < 0.05$ was considered significant. *Statistically significant compared to the control group, # Statistically significant compared to the LCAR group, ‡ Statistically significant compared to the acute group

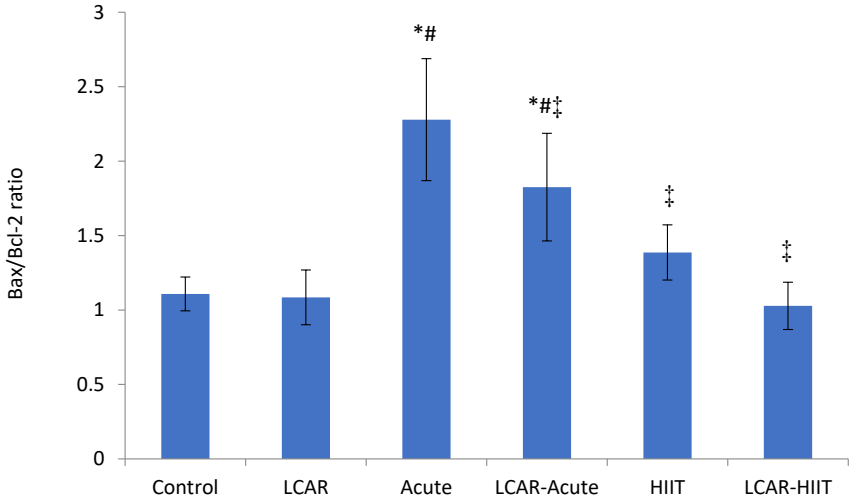

Figure 3. BAX/Bcl-2 ratio in the studied groups (control, L-carnitine [LCAR], acute exercise [AE], L-carnitine + AE [LCAR + AE], HIIT, and L-carnitine + HIIT [LCAR + HIIT]). Data are expressed as mean ± SEM; $n = 8$; $P < 0.05$ was considered significant. *Statistically significant compared to the control group, # Statistically significant compared to the LCAR group, ‡ Statistically significant compared to the acute group

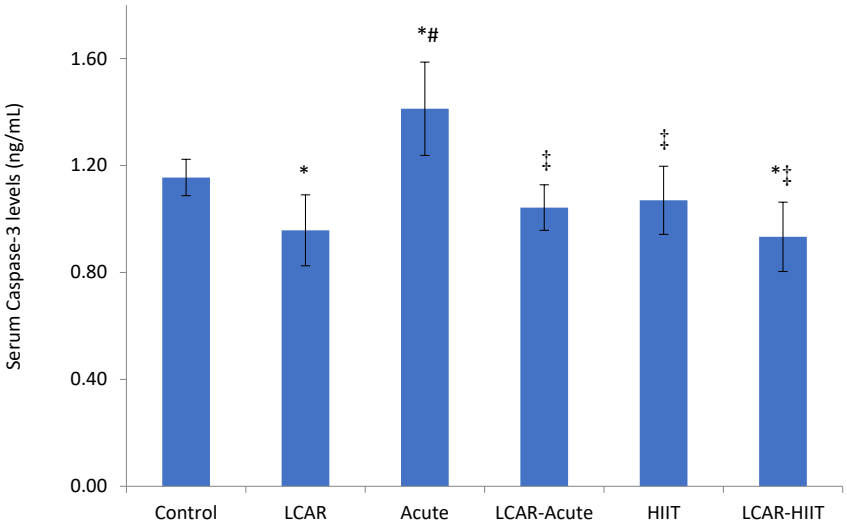

Figure 4. Serum caspase-3 levels in the studied groups (control, L-carnitine [LCAR], acute exercise [AE], L-carnitine + acute exercise [LCAR-Acute], HIIT, and L-carnitine + HIIT [LCAR + HIIT]). Caspase-3 levels were determined by a specific ELISA kit. Data are expressed as mean ± SEM; $n = 8$; $P < 0.05$ was considered significant. *Statistically significant compared to the control group, # Statistically significant compared to the LCAR group, ‡ Statistically significant compared to the acute group

compared to controls ($P = 0.03$ and $P = 0.026$, respectively) (Figure 4). In contrast, AE significantly raised caspase-3 levels compared to both the control and LCAR groups ($P = 0.011$ and $P < 0.001$, respectively). Additionally, LCAR administration significantly reduced caspase-3 levels in the LCAR + AE group compared to the AE group ($P < 0.001$) (Figure 4).

Discussion

Apoptosis is a process in which unwanted cells or cells damaged beyond repair are eliminated. Mitochondria produce energy for the cells, and some metabolic pathways are carried out in mitochondria (1,3). Additionally, it has been documented that oxidative damage or dysfunction of mitochondria can trigger apoptosis (1,3). It has been found that LCAR has an antioxidant and protective effect on mitochondria. LCAR's anti-apoptotic properties have been reported previously with LCAR administration upregulating Bcl-2 and reducing BAX levels (1). Exercise training potentially reduces apoptosis by decreasing stress-related factors. However, some apoptotic factors can increase during exercise, which helps limit tissue damage (33). HIIT has been reported to alter apoptosis-related signaling (5). In the present study, we evaluated LCAR supplementation and the performance of HIIT and AE on serum levels of factors involved in apoptosis regulation. Our data showed that AE increased apoptosis, and HIIT had no significant effects on apoptotic factors. Therefore, it seems that HIIT caused adaptations that AE could not because the increase in apoptotic indices was not corrected or reduced by performing AE in this study.

Most previous research that examined the effects of exercise training on apoptotic markers used tissues, including cardiac and skeletal muscles (5,26,28). In this study, we quantified the serum levels of proteins involved in apoptosis. Yoo et al (31) reported that a single exercise session has no significant effect on apoptotic proteins. However, we found that AE significantly enhances BAX, caspase-3, and BAX to Bcl-2 ratio. Also, in our study, LCAR administration attenuated BAX and caspase-3 levels after AE compared to the group that did not receive LCAR. HIIT significantly increased BAX compared to the control group, and on the other hand, caspase-3, Bcl-2, and BAX/Bcl-2 ratio were not increased compared to the control group. Previous studies have shown that HIIT increases Bcl-2 in cardiac and skeletal muscles (12,25,27). Kwak (10) reported exercise training's anti-apoptotic effects on the heart. Another study showed that HIIT increases BAX and caspase-3 and reduces Bcl-2 levels in hepatocytes of aged rats (11), which confirms our findings concerning BAX. Pourrazi et al (5) reported that HIIT increases Bcl-2 levels, but in the present study, HIIT caused no significant change in serum Bcl-2 levels and the ratio of BAX/Bcl-2. Also, in their study, HIIT had no effects on caspase-3, which aligns with our findings in the present study. This difference can be related to the duration of the study; in the study by Pourrazi et al (5), the animals performed HIIT for 12 weeks, while in our study, the duration was 4 weeks. The study by Moradi et al (12) reported that 8 weeks of high-intensity exercise attenuated BAX levels and enhanced Bcl-2 expression in rat muscles.

LCAR is considered an antioxidant and anti-apoptotic agent (1). The present study showed that LCAR administration attenuated AE's effects on serum BAX and caspase-3 levels. Also, LCAR significantly lowered caspase-3 levels in comparison with the control group. One study reported that 50 mg/kg/d of LCAR reduces BAX and caspase-3, which confirms our results, where 4 weeks of LCAR administration reduced caspase-3 levels. It should be noted that the present study's duration was 4 weeks, but the above study was conducted for 7 months (23). Another study on BALB/c mice showed that LCAR (100 mg/kg) significantly restores formalin-induced apoptosis (24). Mohammadi et al (34) reported that LCAR (250 and 500 mg/kg of diet) reduces caspase-3 and BAK/Bcl-2 ratio, which aligns with our results. We can conclude that LCAR administration improves redox balance and reduces proapoptotic agent levels through its considerable antioxidant properties.

We also examined the combination of training and LCAR in the present study. As mentioned before, AE increased serum BAX and caspase-3 and reduced Bcl-2 levels. LCAR administration successfully attenuated the caspase-3 and BAX levels in rats that performed AE and received 200 mg/kg/d of LCAR (4 weeks). Additionally, HIIT significantly increased BAX levels (versus the control and LCAR groups); on the contrary, the combination of LCAR + HIIT reversed HIIT's effect on serum BAX levels. Unlike our study, it has been reported that exercise training (6 weeks) and LCAR (100 mg/d) did not change BAX levels (20), while we found that HIIT (4 weeks) increased serum BAX levels. On the other hand, in line with the data obtained from the present study, other studies have reported that the combination of training + LCAR increases Bcl-2 and reduces BAX levels (20).

Unlike previous studies, this study quantified apoptotic protein in the serum, while other studies have focused on tissues to evaluate apoptotic proteins. The dose of LCAR and the duration of HIIT performance were not the same in different studies, which can explain some of the discrepancies observed in the results.

Conclusion

HIIT, especially in combination with LCAR, improved cell viability through increased Bcl-2 levels. LCAR strengthened HIIT's anti-apoptosis properties. However, AE increased the serum levels of proapoptotic proteins, and LCAR modified the elevated proapoptotic markers in the AE group. Therefore, LCAR may be considered a

promising supplementation against exercise-mediated injury. This study can be extended to humans to evaluate the beneficial effects of LCAR + HIIT and LCAR + AE.

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Authors' Contribution

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Data curation: Beydolah Shahouzehi, Yaser Masoumi-Ardakani, Banafsheh Daneshmand, Mahdieh Nazari-Robati, and Soheil Aminizadeh.
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Supervision: Beydolah Shahouzehi.
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Writing–original draft: Beydolah Shahouzehi, Yaser Masoumi-Ardakani, Banafsheh Daneshmand, Mahdieh Nazari-Robati, and Soheil Aminizadeh.

Competing Interests

The authors declare that there is no conflict of interest.

Ethical Approval

This study was approved by the Ethics Committee of Kerman University of Medical Sciences (IR.KMU.REC.1400.027).

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