The Protective Effect of Melatonin on Plasma Lipid Profile in Rats with Cerulein-induced Acute Pancreatitis

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Abstract
The objective of this study was to assessment the effect of melatonin on lipid profile in rats with experimentally induced acute pancreatitis. In this study, 32 adult, male, healthy Wistar Abino rats were used. Group I animals was no applied. Group II animals was intraperitoneally administered 50 mg/kg melatonin per rat twice for two hours intervals. Animals of group III received two intraperitoneal injections of cerulein (50 µg/kg and 25 µg/kg bw, respectively) at two hours intervals. Animals of group IV received two intraperitoneal injections of cerulein (50 µg/kg and 25 µg/kg bw, respectively) at two hours intervals and the rats received an intraperitoneal injection of 50 mg/kg melatonin 30 min before each cerulein injection. After 12 hours from the last cerulein injection, total cholesterol, triglyceride, LDL, HDL levels was determined. In this study, experimentally induced acute pancreatitis resulted in significantly increase in levels of total cholesterol, triglyceride and LDL (p<0.05), while HDL level significantly decreased compared with control group level (p<0.05). Pretreatment of melatonin to the rats with acute pancreatitis importantly reduced triglyceride and LDL levels compared to pancreatitis group (p<0.05). In conclusion, melatonin pretreatment may alleviate the abnormalities in plasma lipid profile caused by acute pancreatitis.

Key words: Cerulein, melatonin, acute pancreatitis, lipid profile, rats

INTRODUCTION
Acute pancreatitis (AP) is noninfectious inflammatory disorder of pancreas representing variable severity ranging from mild to severe inflammatory cascade associated with multiple-organ failure. (38, 45). The incidence of this disease is increasing in the worldwide(11). Acute pancreatitis is characterized with parenchymal edema, tissue necrosis, hemorrhage and inflammatory cell infiltration (2, 11, 24, 29, 35, 43, 59, 60). A number of pathophysiological processes of acute pancreatitis include inflammation, apoptosis, necrosis and oxidative stress (28). Researches have been focused on dyslipidemia during the course of acute pancreatitis and about relationship between hypertriglyceridemia and acute pancreatitis(13, 18, 26). Despite developments in treatment of the disease, acute pancreatitis has still high morbidity and mortality rates reaching up to 30% in severe cases(7, 49). In treatment of the disease, new approaches and use of alternative medicinal agents are continued to investigate due to its complex etiology and clinical course.

Melatonin (N-acetyl-5-methoxytrptamine) known as major pineal secretory product is also synthesized in other organs and tissues such as retina, lens, bone marrow cells, gastrointestinal tract, and skin. (48). Melatonin has several physiological functions including control of reproductive activity in seasonally reproductive animals, sleep promotion, circadian regulation and modulation of immune responsiveness. (44). In addition, melatonin effectively reduces oxidative stress via many mechanisms (44, 48, 53). Melatonin detoxifies highly toxic hydroxyl and peroxyl radicals. It has been reported that melatonin increased the synthesis of glutathione and several antioxidant enzymes. (47, 52). Numerous experimental studies have shown that melatonin is not only an important antioxidant but also an important anti-inflammatory molecule (1, 5, 9, 19, 21, 23, 37). Thus, melatonin has been clinically interest regarding these properties (21).
Also, earlier studies reported that melatonin has effects on lipid metabolism (16). It has been noted that melatonin lowered serum, hepatic, adrenal and testicular cholesterol levels. In consistent with above results, pinealectomy caused the opposite effects on lipid parameters. There are also other studies about this lowering effect of melatonin on serum cholesterol and triglyceride (20, 30, 39, 52, 56). The objective of this study was to assess the effect of melatonin on lipid profile in rats with experimentally induced acute pancreatitis.

degrees, it is considered that the knee joint causes deterioration of the extension mechanism and patella causes femoral pain with increasing tendency to slide laterally (3). It has been emphasized that it causes various pain and disability in abnormally low values (19).

MATERIAL AND METHOD

In the study, 32 adult (6 weeks), male, healthy Wistar Abino rats were used. The animals were divided into four groups. All animals were fasted before at the beginning of study, while it allowed to drink water. The study protocol was approved by The Ethical Committee of Selçuk University Experimental Medicine Research and Application Center (Report no. 2017-16).

Group I animals (n=6) was no applied. Group II animals (n=6) was intraperitoneally administered 50 mg/kg melatonin (Sigma-Aldrich, St. Louis, MO, USA) per rat twice for two hours intervals. Animals of group III (n=10) received two intraperitoneal injections of cerulein (Sigma-Aldrich, St. Louis, MO, USA) (50 µg/kg and 25 µg/kg bw, respectively) at two hours intervals. Animals of group IV (n=10) received two intraperitoneal injections of cerulein (50 µg/kg and 25 µg/kg bw, respectively) at two hours intervals and the rats received an intraperitoneal injection of 50 mg/kg melatonin 30 min before each cerulein injection. After 12 hours from the last cerulein injection, blood samples were taken from all animals. It was determined total cholesterol, triglyceride, LDL, HDL levels in the Abbott C8200 autoanalyzer using Abbott kits in these blood samples.

The data obtained from the study were analyzed by one-way ANOVA (SPSS 19). Differences among the groups were determined by Duncan’s multiple range test. Differences were considered significant at p<0.05.

RESULTS

The effect of melatonin on lipid profile in experimentally induced acute pancreatitis was summarized in Table 1. In this study, experimentally induced acute pancreatitis resulted in significantly increase in levels of total cholesterol, triglyceride and LDL (p<0.05, Table 1), while HDL level significantly decreased compared with control group level (p<0.05, Table 1). Melatonin administration to intact animals caused some fluctuations in all parameters but these changes were not important. Pretreatment of melatonin to the rats with acute pancreatitis importantly reduced triglyceride and LDL levels compared to pancreatitis group (p<0.05, Table 1). Occurred changes in total cholesterol and HDL levels with melatonin treatment to the rats with acute pancreatitis were not important.

DISCUSSION

In this study, the changes in lipid parameters in acute pancreatitis are consistent with some studies which reported severe acute pancreatitis can alter lipid profile (6, 32). In acute pancreatitis cases, high triglyceride level is most common data. In generally, low HDL level, high LDL and cholesterol levels accompanied to hypertriglyceridemia in acute pancreatitis (6, 57). It has been reported that high concentration of triglycerides and low HDL level are associated with severity of acute pancreatitis (14, 54). It was suggested that HDL has anti-inflammatory and antioxidant properties (6, 12, 34, 46, 55) and low HDL level may be associated with an increase in severity of the disease due to decrease in anti-inflammatory and antioxidant activity of HDL (57). Carpentier and Scruel (8) reported that production of triglycerides increased in the liver and lipoprotein lipase activity decreased during acute pancreatitis. It was noted that these events might lead to higher serum triglycerides concentration (8, 32).

Bonjoch et al. (4) have previously reported that inflammatory mediators promoted the progression of inflammation in acute pancreatitis. It was stated that the activation of macrophages by inflammatory cytokines from adipose tissue.
increased the inflammatory response during pancreatitis (4, 25, 36, 51). In parallel to above knowledge, it was noted that free fatty acids, oxidized lipids, halogenated lipids and bioactive lipid mediator's production increased during acute pancreatitis (4, 15, 22, 27, 41). There are notifications that inflammatory cytokines induced hepatic synthesis of acute phase proteins and low level of HDL is associated with high levels of inflammatory cytokines. It has been suggested that high levels of inflammatory cytokines impaired biosynthesis of HDL and also facilitated degradation of lipoprotein (45).

Based on antioxidant and anti-inflammatory properties of melatonin, pretreatment of melatonin to the rats with acute pancreatitis importantly reduced triglyceride and LDL levels compared to pancreatitis group (p<0.05, Table 1). Túnez et al. (56) reported that cholesterol, phospholipids, triglycerides and free fatty acids levels decreased in the brain and liver of melatonin-treated rats. Hoyos et al. (30) suggested that melatonin could promote augmenting the clearance of endogenous cholesterol. Melatonin administration to rats fed with high-cholesterol diet reduced total cholesterol and LDL and prevented a decrease in HDL (30). It also improved fatty liver induced by high-fat diets that affect serum lipids (42).

In ovariectomized rats, it has been noted that melatonin administration prevented increase in body mass and cholesterol concentration (50). A lowering effect of long term melatonin treatment on serum cholesterol has been reported in adult rats (3, 39) and hamsters (58). In another study, it was suggested that short term melatonin treatment decreased free cholesterol level in rats, presumably by augmenting lecithin-cholesterol acyltransferase-mediated cholesterol esterification (20).

Our results are consistent with above studies which have been shown improvement in lipid profile after melatonin treatment. Lipid lowering effect of melatonin were attributed to several mechanism such as decrease in intestinal cholesterol absorption (31), inhibition of cholesterol biosynthesis and LDL accumulation (10), interactions with LDL receptors (40) or inhibition of fatty acid transport via metabotropic receptors (17, 33).

| Table 1. Effect of melatonin on lipid profile in acute pancreatitis (Mean±SE) |
|-----------------|-----------------|-----------------|-----------------|
|                 | Total Cholesterol (mg/dl) | Triglyceride (mg/dl) | LDL (mg/dl) | HDL (mg/dl) |
| Group I         | 95.83±4.01abc     | 67.17±4.69b      | 51.67±1.28b  | 42.50±2.86ab |
| Group II        | 89.33±5.35bc      | 61.50±3.33b      | 45.17±3.50b  | 43.83±3.27bc |
| Group III       | 118.20±3.17a      | 86.70±3.58a      | 64.90±3.35a  | 31.40±3.57b  |
| Group IV        | 107.50±3.66abc    | 72.60±4.00b      | 53.30±3.61b  | 36.10±2.59abc |

** The difference between mean values with different superscripts in the same column is significant at the p<0.05 level.

**Conclusions**

Moved on our results, it was considered that melatonin pretreatment in rats with acute pancreatitis may be useful to alleviate the abnormalities of lipid profile caused by acute pancreatitis.
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