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Effects of Methamphetamine on the Histopathology of the Liver and Pancreas and their Enzymes in Adult Male Rats

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Abstract

Background: Methamphetamine (METH) is a widely addictive and abused psychostimulant drug that affects organs of body. In this study, the effects of METH administration for 7, 14, and 28 days on the histological and functional changes of the liver and pancreas of adult male rats were investigated.

Methods: In this experimental study, 58 adult male Wistar rats were randomly divided into seven groups including control (received no treatment), vehicle (received saline for 7, 14, and 28 days), and METH (received METH with a dose of 5 ml/kg, IP for 7, 14 or 28 days). Sampling from the liver and pancreas tissues was done after the above-mentioned times for each group, then, tissue samples were stained by H&E technique and evaluated for structural changes, as well as the evaluation of biochemical factors including SGPT, SGOT, and amylase enzymes. Data were analyzed by one-way ANOVA, using SPSS software version 20. Statistical significant level was considered at $P<0.05$.

Results: In this study, METH caused a significant structural change in the liver and pancreas in the METH-treated groups compared with the control group. Functional changes depended on the length of treatment, with the 7-day treatment group having less damage than the 14- and 28-day periods.

Conclusion: According to the results of the present study, methamphetamine administration for 7, 14, and 28 days had adverse effects on the rats liver and pancreas structure and their enzymes (SGPT, SGOT, and amylase). Therefore, underlying mechanism need further investigation.

Introduction

Amphetamines are one of the most addictive psychostimulant drugs, one of the most well-known forms of which is methamphetamine (METH). This drug has important financial, emotional, and psychological side effects on the METH abusers by producing cognitive problems. It causes increased heart rate and blood pressure, vasoconstriction, eventual organ damage, and persistent damages to the organs

of the body, such as cardiovascular (1), pulmonary (2), renal (3), and teste damages (4). This drug also causes damages to dopamine and serotonin terminals.

It is called as speed, crystal, crank, go, and ice. Currently, METH is listed as the second most abused drug after opioids with approximately 35 million users globally especially in Asia, Oceania, and North America (5).

METH often affects the central nervous system (CNS), for this reason, most studies have been focused on the CNS, neuronal function, addiction, and neural cellular damages. Previous studies have proven the relationship between the CNS and other internal and peripheral organs of the body (7,8).

The digestive system that is consisted of the gastrointestinal tract and accessory organs is one of the internal parts of the body, which plays an important role in the body's metabolic and regulatory activity. The relationship between the CNS and gastrointestinal system is controlled through neural pathways and hormonal regulated.In general, these two systems affect each other. In fact, METH causes considerable hyperthermia, which is strongly related to the neuronal damage (9-11).

The liver and pancreas are two important parts of the digestive system that play a vital role in securing the necessary enzymes for food decomposition. These organs also play an important role in the endocrine system and the blood purification. Due to the role of these two organs in regulating the metabolism of the body, damages to these organs can endanger the health of the individuals (12-14).

The aim of this study was to investigate the effects of METH administrations on the structural changes of the liver and pancreas and their enzymes (SGPT, SGOT, and amylase) in adult male rats.

Materials and Methods

Animals

Adult male Wistar rats (aged 8 weeks with a body weight of 250-300 g) were purchased from the animal center of Kerman University of Medical Sciences. Animals were kept in the standard conditions (12 h dark/light cycle, 23 ± 2°C, and free access to standard pellet food and water). All steps of this study were conducted according to the National Institute of Health (NIH) guidelines, as well as ethical guidelines for investigation of animals, which were approved by the Ethics Committee of Kerman University of Medical Sciences (Ethical code: IR.KMU.AH.REC.1396.1994).

Experimental groups

To investigate the effects of METH on the function and structure of the liver and pancreas, a total of 58 male Wistar rats were used. Animals were randomly divided into 7 groups including control (received no treatment), vehicle (received saline), and METH (received METH). The treatment was done for 7, 14 or 28 days.

METH Preparation

METH purity of 99.1% was identified by the Pharmaceutics Research Center, Kerman University of Medical Sciences. It was dissolved in normal saline (0.9% sodium chloride, 1 mg METH per 1 ml normal saline); stock solutions were prepared solutions were prepared and administered via intraperitoneal (IP) injection at the daily dose of 5 mg/kg either for 7, 14 or 28 days.

Histopathological and biochemical study

At the end of each experiment and 24 h after the last days, rats were sacrificed, blood samples were collected, and the liver and pancreas of rats were removed. For histopathological study, the samples were fixed in 10% buffered formalin for 48 h. Then, the tissues were washed with ethanol, dehydrated, cleared, and embedded in paraffin wax. The sections were cut with a rotary microtome at 5 mm thicknesses, then, stained with hematoxylin and eosin (H&E), and finally, the sections obtained were evaluated for structural changes using a light microscope. For biochemical analysis, the levels of serum glutamic oxaloacetic transaminase (SGOT) and serum glutamate-pyruvate transaminase (SGPT) in the serum and amylase enzyme were measured using ELISA kits.

Statistical analysis

All data were expressed as mean ± SEM (standard error of the mean). Data were analyzed using one-way analysis of variance (ANOVA), followed by Dunnett's post-hoc test.. Statistically significant level was considered at $P<0.05$. Statistical analysis was performed using SPSS software (version 20, IBM Corporation, Armonk, NY, USA).

Results

Biochemical evaluation

The results showed that SGPT, SGOT, and amylase levels in vehicle groups did not change significantly after 7, 14 or 28 days of treatment compared to the control group. In terms of SGPT parameter, a significant difference was observed only after treatment for a 7-day period ($P<0.001$) and no significant difference was observed after 14 and 28 days of treatment ($P>0.05$). In terms of SGOT parameter, the level of enzyme increased after 7 and 28 days of treatment, but after 14 days of treatment, the level of enzyme decreased compared to control group, this change was not statistically significant ($P>0.05$). Finally, in terms of amylase parameter, the level of enzyme decreased, although these changes were not statistically significant as in other cases ($P>0.05$) (Figure 1).

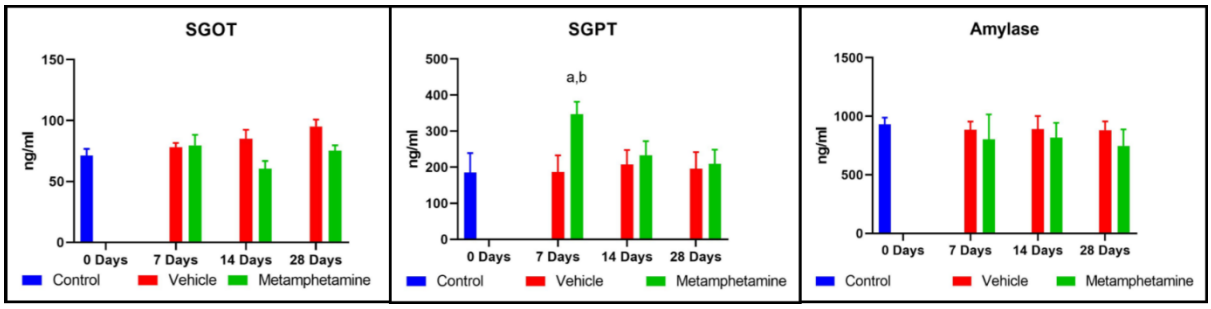

Figure 1. Effects of 7-, 14-, and 28-day METH treatment on the level of SGPT, SGOT, and amylase in different groups of male rats including METH group received methamphetamine (5 mg/kg) intraperitoneally for either 7, 14, or 28 days, vehicle group received saline, and control group received no treatment. Data are expressed as Mean ± SD (n=10 per group). a: Compared with control group, b: Compared with vehicle.

The effects of methamphetamine on histopathology of liver and pancreas

Considering the examination of the liver and pancreas tissue samples, the results showed the normal structure of these organs in control and vehicle groups. All histopathological findings also showed normal structure of the liver and pancreas in control and vehicle groups. In METH groups, damages to the liver tissue such as severe congestion in vein and lobules, steatosis, portal lymphocytic infiltration, and cytoplasmic damage (vacuolar degeneration) were observed. However, no structural changes such as necrosis or apoptosis were observed in the liver and pancreas samples (Figures 2 and 3).

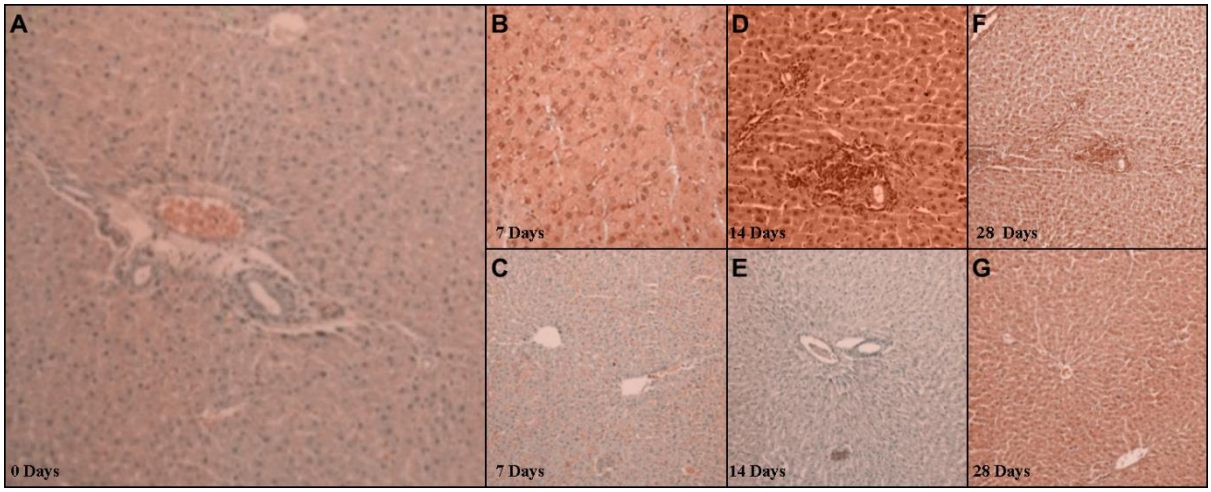

Figure 2. Effect of methamphetamine (5 mg/kg) on the structural changes of liver in adult male rats. A (control): Liver showing normal hepatocytes with normal radial arrangements around hepatic cords, B (vehicle group, 7 days), C (METH, 7 days), D (vehicle group, 14 days), E (METH, 14 days), F (vehicle group, 28 days), and G (METH, 28 days). Methamphetamine produced a trend toward increased hyperthermia and alterations in hepatocellular morphology with disarrangement in cytoplasm. With increasing the duration of drug use, the rate of this damage also increased (hematoxylin and eosin (H&E) staining ×400).

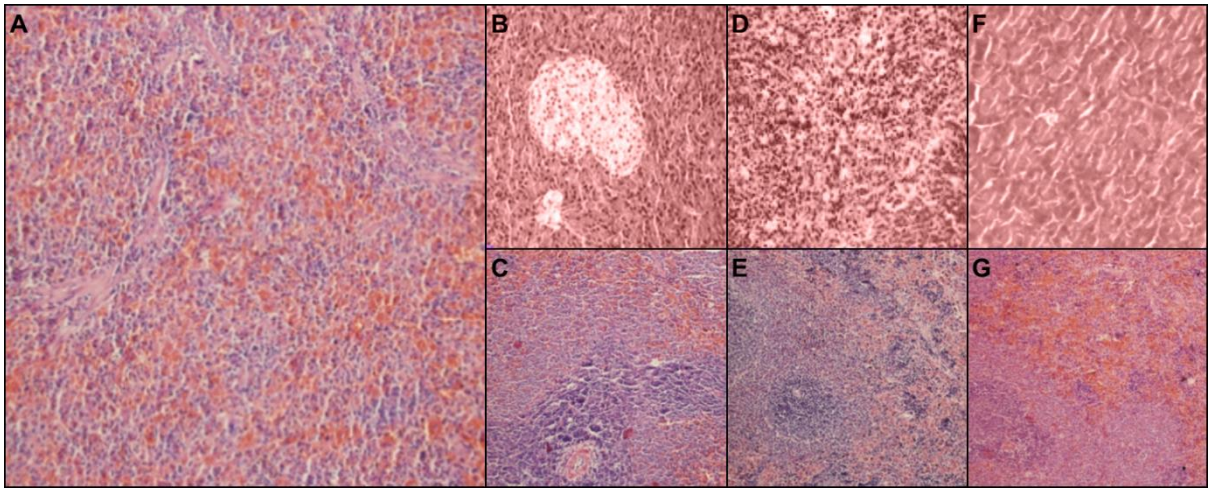

Figure 3. Effect of methamphetamine (5 mg/kg) on the structural changes of pancreas in adult male rats. A (control): Normal control rat pancreas showing normal islets of Langerhans with pale rounded and ovoid β-cells in the center, B (vehicle group, 7 days), C (METH, 7 days), D (vehicle group, 14 days), E (METH, 14 days), F (vehicle group, 28 days), and G (METH, 28 days). METH-treated groups showing shrinkage of islets of Langerhans with degeneration of components cells where its nucleus appeared densely basophilic (hematoxylin and eosin (H&E) staining ×400).

Discussion

The results of the present study indicated that consecutive administration of methamphetamine for either 7, 14 or 28 days caused structural changes in the liver and pancreas of adult male rats. These changes in the liver are mainly hypertension, deformity, and the number of hepatocytes and Kupffer cell, as is known, any broad structural changes such as necrosis or apoptosis, that lead liver function are not observed. As liver tissue, due to its nature, is responsible for cleaning blood from pesticides and drugs, it is exposed to various types of damages and its nature changes, if the external matter's toxicity is high (14).

The serum levels of SGPT and SGOT are commonly measured clinically as biomarkers of hepatic function damage, which show the liver function. In this study, it was found that the levels of SGPT and SGOT in the METH-treated rats were higher than those in control and vehicle groups. The changes in the level of enzymes in SGPT in 7 days group was statistically significant ($P<0.001$), while in other cases, the liver's compliance with the injectable METH on days 14 and 28 was less significant and the other statistically significant was not significant ($P>0.05$).

The results also demonstrated the adverse effects of METH on the structure and functions of liver and pancreas, which is consistent with the results of some previous reports (7,10,14,15).

METH has been shown to be hepatotoxic for human users and have adverse effects on the digestive system, but molecular mechanisms involved in this toxic effect have not yet been completely clarified and further studies are needed on the molecular processes affecting this drug on the organs of digestive system. Several studies have reported the implication of the increased generation of free radicals and oxidative stress in the action mechanism of METH to all organs of body (16-18). It was also shown that oxidative stress results in severe oxidative and lipoperoxidative damages to liver cells in METH abusers (19-21).

Drug use has become a global problem, which, despite numerous studies indicated its harmful effects on health, still accounts for a high population of addicts. Therefore, there is a need for a comprehensive plan for informing communities about adverse effects of drug abuse, controlling drug use, and treating addiction, including METH and its derivatives, marijuana, opioids, and alcohol.

Conclusion

According to the results, the use of METH in adult male rats can cause structural changes in the liver and pancreas and their biochemical activity and change the concentrations of SGOT, SGPT, and amylase.

Conflict of interests

The authors declare that they have no conflict of interests

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