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Histological and Histochemical Changes in the Liver Of Albino Rats Due To Methyl Alcohol Administration

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Abstract

Histological and histochemical changes in the livers of 40 adult male albino rats (Rattus norvegicus) were studied at different intervals following methyl alcohol administration. The animales were divided into three groups. Methanol was adminitrated by oral a intubation in two doses (1ml/Kg. body weight and 2ml/Kg. body weight, respectively) for twenty consecutive days. Then the animals were killed after different periods of time (5, 10 and 20 days). The changes appeared to be time and/or dose dependent. Early signs of hepatic changes were characterized by hydropic degeneration, nuclear pyknosis, erosion of the endothelial lining of the blood vessels, vascular congestion and internal haemorrhage. Degenerative hepatic cells were seen invaded by inflammatory infiltrative cells. Maximum signs of deterioration were detected when 2ml/Kg. body weight was given. The first dose of methanol (1ml/Kg. body weight) caused depletion of liver glycogen, lipids, total proteins, proteins containing NH group, nucleic acids contents, and succinate dehydrogenase (SDH). Also, it caused a significant elevation of alkaline and acid phosphatase activities. The second dose of methanol (2ml/Kg. body weight) showed stronger effects on the 10th and 20th days of administration.

Introduction

Methyl alcohol is a material which is used to denature industrial ethyl alcohol. A number of deaths have been reported as a result of drinking wine that is diluted with methanol. Its cheapness makes it popular with those heavy drinkers who are often vagrant or homeless people who can not afford

or dinary ethyl alcohol (Kaye, 1980) or due to inhalation of methanol vapours resulting from environmental pollution. It is well documented that the ingestion of methanol causes visual toxicity, metabolic acidosis, central nervous system depression and abdominal pain. The individual susceptibility for methanol damage varies widely depending on the amount ingested which causes toxic symptoms (Mc - Martin et al., 1975; Tephly et al., 1979 and Swartz et al., 1981). In regards to the changes in the liver, Upreti and Shanker (1978), Lamb et al., (1979) and Anderson et al., (1979) investigated the histological and enzymatic pattern in cases of alcoholism. In addition, Chan et al., (1988) correlated the increased alcoholic consumption with disturbances in liver and renal functions.

Succinate dehydrogenase enzyme is still perhaps the most important of all dehydrogenases (Pearse, 1972). It is an essential enzyme of Kreb's cycle in animals (Seligman and Rutenburg, 1951). Lactate dehydrogenase is particularly significant in the cell energy production under an erobic conditions (Thaler and Kissane, 1966). In addition, Chetty et al., (1980) stated that the activity of succinate dehydrogenase decreased while that of lactate dehydrogenase increased as a result of ammonia toxicity in all tissues of Tilapia mossambica. Also, methanol caused an increase in activity of liver succinate, dehydrogenase (SDH) and serum lactic dehydrogenase (LDH) in rats (El-Sayed et al., 1991). At the same time, methanol administration to monkeys, rats, and humans resulted in a significant elevation of blood glucose levels (Cattaneo, 1986 and Hanafy, 1989). Acute methanol intoxication in rats was reported to result in decreased oxidative phosphorlation in liver mitochondria (Trifonov et al., 1991).

The present work is concerned with studying the histological and histochemical changes in liver of albino rats due to methyl alcohol administration.

Materials and Methods

Forty adult albino rats (Rattus norvegicus), maintained on an ad-libitum diet of commerical ground food and water, were used in this study. The animals were randomly divided into three groups. The first and the second of these groups (15 rats each group) were given an oral daily dose of 1 ml / Kg.

body weight and 2ml/Kg. body weight of pure methanol respectively, for twenty consecutive days by oral intubation with a smooth tip to protect the interior lining of the oral and buccal cavity from injury. The rat was held between its tw ears, so that the oesophageal opening was clearly and unobstructively opened. An equal volume of distilled water was added to the methanol dose before administration to diminish the irritative effect of pure methanol on the interior lining of the stomach. The dose selected (2ml MeoH/kg b.wt.) was the subleathal dose based on the study of Kishta, O.(1993). The remaining third group (10 animals) served as a control. Five experimental and three control animals were killed at different periods of time, 5, 10 and 20 days, dissected immediatly and specimens of liver were fixed in chilled acetone for 24 hours and processed for histochemical localization of both alkaline and acid phosphatase enzymes by Gomori's method (Pearse, 1972). Other parts of liver were fixed in buffered formol or Carnoy's solution. Paraffin sections were prepared and stained with haematoxylin and eosin, methyl green pyronin (Mattar, 1980), Periodic acid Schiff reaction for the glycogen (Pearse, 1972) and mercury bromphenol blue methods (Pearse, 1972). For the detection of proteins containing NH- group, the Ninhydrin Schiff method (Yasuma and Itchikawa, 1953) was applied. A third specimen of liver was fixed in calcium formol and was cut into frozen section 20 um thick and stained with sudan black B for the demonstration of lipids and succinate dehydrogenase (Bancroft and Stevens, 1982).

Results

I. Histological Studies:

The normal rat liver was divided into the classic hepatic lobules. Each lobule was formed of cords of hepatic cells radiating from the central vein. The cell cords were separated by narrow blood sinusiods. The liver cells were polyhedral cells with acidophilic cytoplasm and each cell had a rounded pale stained nucleus. Each lobule was bound by scanty connective tissue. Outside the lobules, at certain angles, were portal islands of connective tissue. Each contained a branch of the hepatic artery, a branch of the hepatic portal vein and a bile ductule (Fig. 1). Liver cells examined 20 days after treatment with 1ml/Kg. body weight were hydropically degenerated. Few cells showed cytoplasmic vacuoles (Fig. 2) which were confirmed by sudan

Figure (1): *Section in the liver of a control rat showing the cords of Liver cells radiating from the central vein.(H & E X 400).*

Figure (2): *Section in the liver of a rat administrated with the first dose, then sacrified after 10 days, showing vacuoles in the cytoplasm of hepatic cells. (H & E X 400).*

black B stain to be fat globules. Localised masses of infiltration cells were seen in between the liver cells. Vascular congestion and haemorrhages were observed. Liver cells examined 5, 10 and 20 days after treatment with 2ml/Kg. body weight showed obvious necrotic degeneration. Most parenchymal cells had lost their regular pattern and had karyopyknotic nuclei and coagulative faint cytoplasm (Fig 3). Inflammatory infiltration was greatly inhibited (Fig. 3).

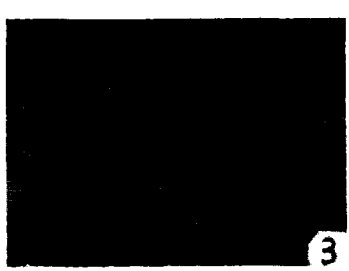

Figure (3): *Section in the liver of a rat administrated with the second dose, then sacrified after 20 days, showing fatty infiltration. (H & E X 400).*

II. Histochemical Studies:

1. Glycogen Content:

Sections stained by periodic acid Schiff demonstrated the glycogen granules in the normal liver cell cytoplasm. The granules were displaced to one side of the cell. The peripheral zonal cells showed higher glycogen content than the central zonal cells (Fig. 4). Glycogen depletion was observed in the peripheral zone of the hepatic lobule 5, 10 and 20 days after the administration of 1ml/Kg. body weight of methyl alcohol. Marked depletion was also observed after the use of 2ml/Kg. body weight of methyl alcohol (Fig. 5).

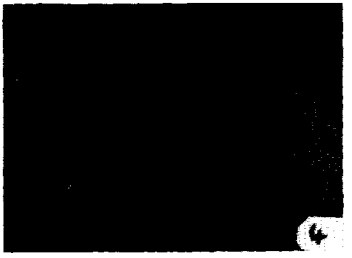

Figure (4): *Section in the liver of a control rat showing its glycogen content. The glycogen granules are seen accumulating at the sides of the liver cells (PAS X 400).*

Figure (5): *Section in the liver of a rat administrated with the second dose then sacrified after 20 days, showing a marked depletion in the glycogen content of liver cells (PAS X 400).*

2. Lipid Content:

Fat appeared occasionally in hepatic cells of control groups as fine granules scattered in the cytoplasm. Lipid depletion was observed in the liver cells 5, 10 and 20 days after the administration of 1ml/kg. Body weight of methyl alcohol. Hepatic cells surrounding the central veins were relatively rich in lipid inclusions. Some hepatic cells contained sudanophilic small granules in their cytoplasm, while others were loaded with sudanophilic granules. A marked depletion was also observed after the use of 2 ml/kg. Body weight of methyl alcohol (Fig. 6) .

Figure (6): *Section in the liver of a rat administrated with the second dose, then sacrified after 10 days, showing periportal fatty infiltration. (Sudan black BX 400).*

3. Total Protein Content:

Total proteins were visualized in the hepatic cells of control groups exhibit the form of small bluish particles distributed randomly in a weak to moderate stained cytoplasm. Both cell and nuclear membranes were intensely coloured with bromphenol blue (Fig. 7). Inhibition in total proteins was noticed starting

Figure (7): *Section in the liver of a control rat showing the total Protein contents. (Bromphenol blue X 1000).*

from the 10th day after treatment. This was detected in the cytoplasm of hepatic cells, while nuclei showed positive staining affinity (Fig. 8). By the 20th day, most hepatic cells appeared deviod of stainable proteins, more particularly the degenerative necrotic ones (Fig. 9).

Figure (8): *Section in the liver of a rat administrated with the first dose, then scarified after 20 days, showing the inhibition in total proteins in cytoplasm of hepatic cells. (Bromphenol blue X 1000).*

Figure (9): *Section in the liver of a rat administrated with the second dose, then scarified after 20 days, showing the hepatic cells devoid of proteins. (Bromphenol blue X 1000).*

Proteins containing free - amino groups (NH -): In the liver cells of normal rats, proteins containing free - amino groups were detected in the form of diffused, small - sized particles located in the cytoplasm, exhibiting a pink-red colouration after Ninhydrin - Schiff's technique (Fig. 10). A marked positive reaction to these substances was also observed in the nucleoli, whereas the nuclei showed a weak reaction. A slight diminution in the free - amino group contents in most of the liver cells examined five days after treatment with 1ml/kg. Body weight occured. The above depletion in these inclusions shown in figure (11) have reached their maximum on the 20th day after treatment with 2ml/kg. Body weight where the specific pink colouration of the amino groups became much fainter than the normal conditions.

Figure (10): *Section in the liver of a control rat showing the proteins containing NH -groups. (Ninhydrin-Schiff X 1000).*

Figure (11): *Section in the liver of a rat administrated with the first dose, then scarified after 10 days, showing the inhibition in proteins containing NH - group. (Ninhydrin-Schiff X 1000).*

4. Nucleic Acids:

RNA was demonstrated in hepatic cells of control animals as bright red particles irregularly distributed in the cytoplasm. The nucleoli were rich in RNA. DNA was noticed in hepatic cells of control animals as fine densely stained particles in the nuclei. These particles represented the chromatin particles (heterochromatin). One or two dense chromatin particles were observed attached to the nucleoli. The nucleoli appeared faintly stained as they contained a certain fraction of DNA. (Fig. 12). In liver cells examined 10 days after treatment with 1ml/kg. Body weight, RNA was appeared as intensely stained elongated particles distributed in the cytoplasm except for the perinuclear part of the cytoplasm which appeared in all liver cells as colourless deviod of any particles (Fig. 13). The outer borders of some liver cells were homogeneously stained and did not contain RNA particles. The nucleoli were rich in RNA. Liver cells examined 20 days after treatment with 2ml/kg. body weight showed that, some nuclei were enlarged while other nuclei showed pyknotic feature (Fig.13). The nucleoli were increased in number and most of them were peripherally located. Each nucleolus was attached to a chromatin particles which appeared densely stained. The other

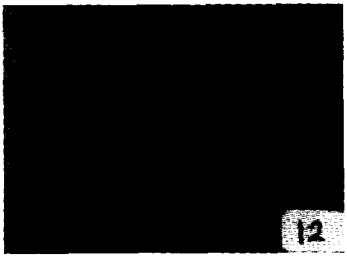

Figure (12): *Section in the liver of a control rat showing its normal RNA content. The RNA granules appear greenish blue in colour in the cytoplasm of the liver cell. The nucleoli are also distinctly red coloured. The nuclei appear greenish-blue owing to DNA inclusions. (Pyronin-methyl green stain X 1000).*

Figure (13): *Section in the liver of a rat administrated with the first dose (1ml), then sacrified after 10 days, showing the inhibition in the nucleic acids. (Pyronin - methyl green stain X 1000).*

Chromatin particles were faintly stained and adhered to the nuclear membrane leaving a clear nuclear sap at the center of the nucleus.

5. Succinate Dehydrogenase Activity:

In the normal liver, the activity appeared as purple granules in the cytoplasm of hepatic cells. The nuclei, blood vessels and bile ducts were unstained. The cytoplasmic activity was higher in the central and peripheral zonal cells (Fig. 14). Inhibition of this enzymatic activity began to appear 10 days after administration of 1ml/kg. Body weight of methyl alcohol. After 20 days, the inhibition was more evident and observed mainly in the peripheral zone of the hepatic lobules (Fig. 15). Marked depletion was also observed after the use of 2ml/kg. body weight of methyl alcohol.

Figure (14): *Section in the liver of a control rat showing succinate dehydrogenase activity. (Nachlas technique X 60).*

Figure (15): *Section in the liver of a rat administrated with the second dose (2ml), then sacrified after 20 days, showing decreased succinate dehydrogenase activity. (Nachlas technique, X 60).*

6. Alkaline and Acid Phosphatase Activities:

In the normal liver, the activity was demonstrated in the nuclei of liver cells. The cytoplasm gave a faint reaction, and the endothelial cells showed activity in their nuclei. Mild increase in the activity was observed in the cytoplasm and nuclei of liver cells 5, 10 and 20 days after the administration of 1 ml/kg. Body weight of methyl alcohol. This increase of both enzymes became marked 20 days after the administration of 2 ml/kg. body weight of methyl alcohol and was more obvious in the peripheral zone of the hepatic lobules (Fig. 16).

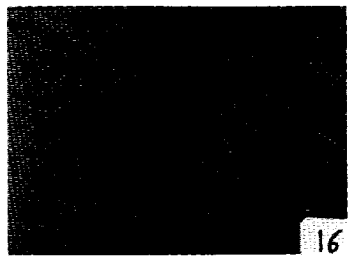

Figure (16): *Section in the liver of a rat administrated with the second dose, then sacrified after 10 days showing increased alkaline phosphates activity. (Gomori X 160).*

Discussion

In the present study, methyl alcohol administration proved to exert conspicuous effects on the histological structure of the liver. In regards to the liver, its vital function which concerned with metabolism and bile secretion is markedly affected, especially in chronic alcoholism. Vacuolization of the cytoplasm was noticed in the present material to be a common pathological feature. Ariens et al., (1976) reported that tissue toxicity usually manifests itself, especially in the histological prepration, in the form of cell degeneration accompanied by formation of large vacuoles, accumulation of fat and tissue necrosis. According to Mollendroff (1973), vascular formation is a cellular defense mechanism against substances injurious to cells. In such a case, these substances were segregated in the vacuoles and were thus prevented from interfering with cellular metabolism. Other conspicuous alterations in the liver tissue following methyl alcohol administration included pyknosis of the nuclei and erosion of the lining of the blood vessels. Inflammatory changes and lymphocyte infiltration also were noticed in the present study. Following administration of 2 ml/kg. body weight of methyl alcohol, a significant increase in the size of the hepatic lobules was noticed in the present study. The individual cells were also much larger than normal and their nuclei exhibited marked increase in size. Crampton et al., (1977) reported that a large number of chemical compounds of different chemical structures and biological activities can produce liver

enlargement in the rat. According to Greaves and Faccini (1984), this activity in the liver cell may be simply accompanied by induction of the hepatic microsomal drug metabolizing system, which enhances metabolism and thus prevents the accumulation of the repeatedly administered chemical compounds leading to distorsion of the normal liver architecture.

In the present work, the depletion of liver glycogen observed in the examined material 5, 10 and 20 days after methyl alcohol administration is in accordance with Eletskii (1965) who reported that the glycogen contetnt in the liver of treated rats exhibited variable changes at different dose levels. At higher dosage (2 ml / kg. body weight), marked depletion of glycogen following methanol treatment was observed that could be explained by direct toxic effect of the compound on the liver cells. The decreased liver glycogen can be attributed to decreasing glycogen synthetase activity which leads to inhibition of glycogenesis (Hakim et al., 1971). Supporting the a forementioned results Kereiberg et al., (1971) reported that ethanol did not significantly reduce the basal glucose turnover rate thus they concluded that inhibition of glyconeogensis might have been masked by a concomitant increase glycogenolysis.

Apparent fat infiltration and loss of cellular architecture, accompained by drop in glycogen content of liver cells, were noticed. This subject was previously discussed by Upreti and Shanker (1978). Where they described a marked decline in phosphorylating activities of liver. Moreover, Lamb et al., (1979) confirmed the occurrence of drop in hepatic glycerolipid biosynthesis in acute and chronic ethanol intake. Fatty changes were observed in the liver of treated rats. This may be due to inability of liver cells to synthesize proteins that are normally conjugated with triglycerides to form soluble lipoproteins. This resutls in accumulation of triglycerides in liver cells.

Our results and those of other authors, which reported detectable levels of methanol in animals or human subjects poisoned with methanol, are in harmony with Jeganathan and Namasivayam (1989) who concluded that methanol - induced changes in brain biogenic amines were due to methanol itself and not due to its metabolic end products viz' formaldehyde or formicacid.

In the present investigation, it was observed that daily treatment of rats for 20 consecutive days with methyl alcohol equals 1 ml/kg. body weight produced marked decrease in the total proteins and nucleic acid contents of rat liver cells examined on the 5th, 10th and 20th day. Maximum signs of protein depletion in these cells were detected when the 2 ml/kg. body weight was given. The influence of methyl alcohol on proteins containing NH - group was nearly similar th that observed in the total proteins. Such proteinic depletion could be attributed to the disturbances which took place in nucleic acids, particularly RNA in pathological conditions. Bruin (1976) added that, not only the reduction in the amount of RNA, but also lesions of its functional capacity, bring about such a failure in protein synthesis. Furthermore, De-Vellis and Schieide (1970) suggested the changes in the patterns of protein synthesis might be related to DNA damage. The decrease in RNA content in the liver cells of treated rats indicated a decrease in liver function. The decrease in the total protein and nucleic acid contents of the liver of treated albino rat may be attributed to the decreased capillary permeability and the decreased uncoupling of the oxidative phosphorlyation with complex changes in the cell metabolism. This agreed with the results obtained by Proscott (1968).

It could be suggested that the cellular metabolism depends to a greater extent on their total proteins and nucleic acids as well as their enzymatic functions and it may result in the decrease of the capillary permeability and phosphorylation processes taking place in the cell. This will be reflected on the zymogen granules synthesis of the various glands and accordingly on their secretory function. The liver of all rats receiving methyl alcohol showed a significant decrease in succinate dehydrogenase activity, especially in the periportal region, which is an indication for the change in mitochondrial activity. In accordance with several histochemical data, the distribution and arrangement of the sites of succinate dehydrogenase activity coincide with those of the mitochondria. Hence, it was concluded that the mitochondria represent the actual sites of succinate dehydrogenase activity in the cytoplasm (Gupta, 1972, Moussa et al., 1979). Mitochondrial damage was proved by the decrease in succinate dehydrogenase activity. These findings agree with the observations of Kubat & Koldovsky (1969) in the small intestine of rats. De-Robertis and his associates (1965) regarded any alteration

which occurs in the mitochondria as indicative signs of degeneration.

The inhibition of mitochondrial proteins synthesis may affect the structure and composition of mitochondrial membranes thus, affecting the integrated oxidase system or lack of intramitochondrial ATP. This factor is the main cause in inhibiting the dehydrogenase system. Disturbances in the mode of occurrence of cellular respiratory enzymes (SDH & LDH) in some organs have also been reported by some authors to be due to the effect of various factors as insecticide treatment. Sitkiewicz & his collegues (1976), found that the treatment of rat with organo-phosphories insecticides caused inhibition of SDH activity in rat liver cells but has no effect on SDH activity of brain cells. Sitkiewicz and Zalewask (1975) suggested that the highly concentrated phospholipid in the cells of the nervous system acts to protect the respiratory enzymes in the mitochondria against poisoning by or ganophosphorus insecticides. Yarbrough and Wellsin (1971) reported that endrin inhibition of succinate dehydrogenase activity occurred only after the mitochondrial membranes were disrupted.

Babu et al., (1989) found that carbamates caused metabolic diversions in the oxidative metabolism of hepatic system of rat by the following aspects: inhibition of dehydrogenase indicated disturbance in mitochondrial integrity. Reduction in cytochrome-c oxidase indicated respiratory distress and drop in ATP suggested the prevalence of energy crisis.

The present study also revealed a significant elevation of alkaline phosphatase enyzme activity after admininstration of 2 ml/kg. body weight methanol. These results are in accordance with Graham & Rennie (1990) and El-Sayed et al., (1991) who reported that alkaline phosphatase activity increases in serum of rats after chronic alcohol consumption, and with Pongpanew et al., (1981) who reported significantly higher median values of alkaline phosphatase in patients suffering from the effect of chronic alcohol consumption. From the a forementioned results, it is apparent that methanol elevates the liver function enzymes (alkaline phosphatase) which indicates a possible damage to the liver.

In this study, there was a gradual increase in acid phosphatase activity after adminstration of 1ml/kg. body weight of methyl alcohol. This findings is in agreement with Hurban et al., (1972) who found that acid phosphatase was increased as a result of increased lysosomal activity.

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التغيرات النسيجية والنسج كيميائية في كبد الجرذ الأبيض نتيجة تعاطي الكحول الميثيلي

اسماعيل ابوطه

ملخص

استخدم في هذا البحث أربعون من ذكور الجرذان البيضاء البالغة لدراسة تأثير الكحول الميثيلي على التغيرات النسيجية والنسيج كيميائية في كبد الجرذ الأبيض.

وقد قسمت الحيوانات الى ثلاث مجموعات حيث تم اعطاء جرعتين مختلفتين من الكحول الميثيلي ١ مل و٢ مل لكل كيلو جرام من وزن الجسم على التوالي - عن طريق الفم باستخدام انبوبة معدية - وذلك لمدة عشرين يوما متتالية . وتركت المجموعة الثالثة للمقارنة . وقد تم قتل هذه الجرذان على فترات فمجموعة بعد خمسة أيام ومجموعة بعد عشرة أيام والباقي بعد عشرين يوما من بدء التجربة ، وقد أظهرت الدراسة أن الكبد قد تأثر نسيجيا بصورة كبيرة نتيجة تعاطي الكحول الميثيلي فظهرت عليه علامات التحلل وغزته تجمعات من الخلايا الدموية البيضاء كما تمزقت بطانة أوعيته الدموية . أما الخلايا الكبدية فقد ظهرت بها الفجوات وتحللت الأنوية كما لوحظ وجود نقص في كمية الجليكوجين المختزن والدهون ومحتوى البروتينات والبروتينات حاوية المجموعات الأمينية الحرة والأحماض النووية والأنزيم نازع الهيدروجين السكسيني SDH هذا بالاضافة الى زيادة واضحة في نشاط انزيمي الفوسفاتيز القاعدى والحامضي وقد ازدادت الأعراض السابقة مع اعطاء الجرعة الثانية من الكحول الميثيلي بعد اليوم العاشر والعشرين من المعالجة .