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Neurotherapeutic effect of allopurinol against brain injury in hyperlipidemic rats

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Hyperlipidemia is characterized by abnormally elevated levels of lipids and positively associated with cerebrovascular diseases. The aim of the present study was the evaluation of possible effects of allopurinol against brain injury in hyperlipidemic rats. Hyperlipidemia was induced by maintaining the rats on high fat diet for 6 weeks. The diet was prepared by adding 1% cholesterol powder, 0.2% cholic acid, and 10% fat to the rat powdered standard laboratory diet., At the end of the 4th week animals were treated with fluvastatin (2.5 mg/kg, p.o) and three dose of allopurinol (50, 100 and 200 mg/kg, p.o) concomitant with hypercaloric diet for 2 weeks. Assessment of activity by grid floor activity cage was done at zero time and the end of the 6 week period. Blood was drawn for biochemical assays as serum cholesterol, triglyceride, liver transaminases and creatine kinase levels. Brains were isolated for determination of malondialdehyde (MDA) and reduced glutathione (GSH) contents as well as finally histopathological study. High fat diet -induced hyperlipidemia associated with a reduction in activity of rats and an elevation of serum cholesterol, triglyceride, and liver transaminase. The allopurinol treatment improves the elevation in serum cholesterol, triglyceride, liver transaminase, creatine kinase levels and ameliorates MDA and GSH brain contents as well as attenuates karyolysis. These results suggest that allopurinol has antihyperlipidemic properties as improves hyperlipidemia and its brain complications by modulation of lipid profile elevation and brain oxidative stress.

Key words: Allopurinol, activity, brain injury, hyperlipidemia, rats.

INTRODUCTION

Hyperlipidemia refers to elevated levels of lipids and cholesterol in the blood, and is also identified as dyslipidemia, to describe the manifestations of different disorders of lipoprotein metabolism. With the continuous improvement in the standard of living worldwide, the population of individuals with hyperlipidemia has expanded. Hyperlipidaemia is one of the predisposing factors for atherosclerosis and can be modified either by proper lifestyle changes, medical management or by the combination of both. It has emerged as the most important preventable and modifiable risk factors for coronary heart disease (CHD). Clinical signs of this condition are an increase in the fasting serum cholesterol level (hypercholesterolemia) or the fasting serum triglyceride level (hypertriglyceridemia) or both (Adekunle et al., 2013). Hyperlipidemia damages multiple organ

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systems and eventually leads to a complex vascular inflammatory disease (de Carvalho et al., 2011). Hypertriglyceridemia and hypercholesterolemia have been correlated with a higher risk of cerebrovascular diseases (Diaz-Castro et al., 2011). There are more than 15 million fatalities worldwide due to cardio-and cerebrovascular diseases every year, making these diseases the leading cause of mortality (Drechsler et al., 2011).

There is therefore a fundamental requirement to decrease the levels of lipids. The evolution of hyperlipidemia is associated with oxidative stress (Yang et al., 2008) as total serum cholesterol is really an indicator of the amount of the free radical damage in the body. Higher the free radical level, higher the body needs to produce cholesterol internally from liver to act as an antioxidant and free radical scavenger (Bansal and Jaswal, 2009). Various antioxidant strategies are currently being investigated for determination whether free radicals represent a valuable therapeutic target in brain injury. These strategies consist of inhibiting free radical production, scavenging free radicals or increasing their degradation. Xanthine oxidase (XO) inhibitor prevent the formation of free radicals and appropriate support for enhancing antioxidant supply in higher lipid subjects may help prevent the course of the disease. Allopurinol, a xanthine oxidase inhibitor, is a drug used primarily to treat hyperuricemia (excess uric acid in blood plasma) and its complications, including chronic gout (Pacher et al., 2006). However, no investigative reports exist till date pertaining to therapeutic effect of xanthine oxidase inhibitor on brain injury in hyperlipidemic rat. Hence, we decided to assess the effects of allopurinol on brain injury in hyperlipidemic rats to find new drug indication which may be useful for treatment of brain injury in hyperlipidemic rat with less adverse effects as compared with current used antihyperlipidemic drug (statin).

MATERIALS AND METHODS

Animals

Adult male albino Wistar rats, weighing 120 to 140 g each were used in the current study. They were purchased from the animal house of the National Research Center (NRC; Giza, Egypt). Animals received human care in compliance with the guidelines of the animal care and use committee of the NRC. The animals were kept in a quiet place and were allowed free access to water and standard food pellets throughout the period of investigation. Experiments were performed according to the National Regulations of Animal Welfare and Institutional Animal Ethical Committee (IAEC).

Diets

The standard laboratory diet consists of vitamin mixture 1%, mineral mixture 4%, corn oil 10%, sucrose 20%, cellulose 0.2%, casein (95% pure) 10.5%, and starch 54.3%. High fat diet was prepared by adding 1% cholesterol powder, 0.2% cholic acid, and 10% fat to the rat powdered standard laboratory diet (Abdelbaset et al., 2014).

Drugs

Fluvastatin and allopurinol were obtained from Pfizer and Sigma Co. (Egypt). Fluvastatin was given p.o. at a dose of 2.5 mg/kg (Oktem et al., 2007) and allopurinol at three doses of 50, 100 and 200 mg/kg (Aldaba-Muruato et al., 2012).

Experimental design

Hyperlipidemia was induced by maintaining the rats on high fat diet for 6 weeks. The diet was prepared by adding 1% cholesterol powder, 0.2% cholic acid, and 10% fat to the rat powdered standard laboratory diet. The rats were allocated into 6 groups of 8 animals each as follow: Group 1 received saline and served as normal control, group 2 hyperlipidemic control. After 4th week of induction of hyperlipidemia, group 3 received fluvastatin (2.5 mg/kg, p.o) and groups 4 to 6 received allopurinol (50, 100 and 200 mg/kg, p.o) concomitant with hypercaloric diet for 2 weeks.

Activity was measured by detecting rat movements using grid floor activity cage (Model no. 7430, Ugo-Basile, Italy). Rats were acclimatized for 1 h to the test room, before placing the animal in the activity cage (exposure) (Kauppila et al., 1991). The activity counts of rats were pretested in three successive sessions each was of 5 min duration before starting oral treatment to habituate them to the apparatus (Pavic et al., 2007). Then the rats were placed in the activity cage and the activity counts of rats were calculated over 5 min duration. The calculation of movements per 5 minutes for each rat was done at zero time before induction of hyperlipidemia and the end of experiment.

Preparation of blood samples and brain for histopathological examination

Rats were fasted for 14 h, blood samples were collected from the retro-orbital plexus of veins of all rats. Samples were left to clot at room temperature then centrifuged at 1500 rpm for 10 min for serum separation. Serum samples were stored at -20°C for analysis of triglyceride, cholesterol, alanine transaminase (ALT), aspartate transaminase (AST), as well as creatine kinase levels. Animals were then sacrificed by cervical dislocation and the brain was dissected and stored at -80°C for histopathological examination.

Biochemical assays

Determination of serum cholesterol and triglycerides were done according to Reitman and Frankel (1957) and Fossati and Prencipe (1982) respectively using Biodiagnostic kits, Egypt. Serum ALT and AST were determined according to Reitman and Frankel (1957) using Biodiagnostic kits, Egypt. creatine kinase was determined according to Szasz et al. (1976) using Stanbio kits, USA. Reduced glutathione (GSH) and lipid peroxidation (TBARS production) in brain tissue were determined according to the method of Beutler et al. (1963) and Mihara and Uchiyama (1978), respectively.

Histopathological study

Brain of all animals were dissected immediately after death, washed thoroughly with saline and fixed in 10% neutral-buffered formal saline for 72 h at least. All the specimens were washed in tap water for half an hour, dehydrated in ascending grades of alcohol (70 , 90 and 95% absolute), cleared in xylene and then embedded in

paraffin wax. Serial sections of 6 µm thick were cut and stained with haematoxylin and eosin for histopathological investigation (Carleton, 1976).

Statistical analysis

Data analysis was done using one way analysis of variance (ANOVA) followed by Dunnt's test. A percent (%) of change of movements per 5 min for each rat was calculated (considered 100%), for which square root transformed % was done according to (Jones et al., 2006) (considered 1), these calculations were done in order to avoid normal biological variations in movements of rats in all groups (provided that each group contains rats with approximately similar activity). Later on the square root transformed % of change of movements of each rat was compared to its base line activity at every transitional step throughout the whole experiment.

Evaluation of chemical parameters

Data are expressed as mean ± SE. Data analysis was done using one way analysis of variance (ANOVA) followed by least significant difference (LSD) test for multiple comparisons. Difference was considered significant when p is less than 0.05. SPSS (version 11) program was used to carry out these statistical tests.

RESULTS

Effect of allopurinol (50, 100 and 200 mg/kg, p.o) on behavioral stress test in hyperlipidemic rats

Rats maintained on high fat diet exhibited a dramatic decrease in activity level by 51.36% of their basal value after 6 weeks. Oral administration of fluvastatin and allopurinol (50 mg/kg), also, produced a diminution of activity level by 35.68 and 12.51%, while, treatment of allopurinol (100 and 200 mg/kg) resulted in increase of activity level by 16.65 and 22.23%, respectively, of their basal value after 6 weeks (Figure 1).

Effect of allopurinol (50, 100 and 200 mg/kg, p.o) on serum lipid profile in hyperlipidemic rats

Rats maintained on high fat diet exhibited a dramatic elevation of serum triglyceride and total cholesterol levels by 94.56 and 165.03%, respectively, after 6 weeks as com-pared to normal control. Oral administration of fluvastatin produced a reduction of serum triglyceride and total cholesterol levels by 25.88 and 39.48%, respectively, Similarly, treatment of allopurinol in three doses resulted in diminution of serum triglyceride level by 10.80, 14.71 and 16.01% as well as total cholesterol level by 35.21, 37.58 and 42.64%, respectively, after 6 weeks as compared to the hyperlipidemic control (Figure 2A and B).

Effect of allopurinol (50, 100 and 200 mg/kg, p.o) on serum liver function and creatine kinase levels in hyperlipidemic rats

Rats maintained on high fat diet exhibited a significant elevation of serum AST only by 12.34% and oral administration of fluvastatin produced a significant elevation of serum ALT levels by 10.63% as compared to normal control. Treatment of allopurinol (50 mg/Kg) orally tends to decrease serum AST and ALT as compared to hyperlipidemic control and fluvastatin group, allopurinol (100 mg/Kg) orally tends to decrease serum AST as compared to hyperlipidemic control and significantly decreased serum ALT by 9.11% as compared to fluvastatin group, while allopurinol (200 mg/Kg) orally significantly decreased serum AST by 11.71% as compared to hyperlipidemic control and ALT by 9.18% as compared to fluvastatin group (Table 1). Creatine kinase serum level did not change in hyperlipidemic rats, while oral administration of fluvastatin and allopurinol (50 mg/Kg) produced a significant elevation of serum creatine kinase level by 36.80% and 71.85%, respectively, as compared to normal control. Treatment of allopurinol (100 and 200 mg/Kg) orally significantly decreased serum creatine kinase level by 34.88% and 39.21%, respectively, as compared to fluvastatin group (Table 1).

Effect of allopurinol (50, 100 and 200 mg/kg, p.o)on brain MDA and reduced GSH contents in hyperlipidemic rats

Brain MDA content exhibited a significant elevation in rats maintained on high fat diet by 20.75 % while brain reduced GSH content exhibited a significant decrease by 35.39% as compared to normal control. Oral administration of allopurinol (50 mg/Kg) significantly decreased brain MDA content by 10.31% and tends to increase brain reduced GSH content while allopurinol (100 and 200 mg/Kg) significantly decreased brain MDA content by 12.19 and 13.13%, respectively, as well as increased brain reduced GSH content by 63.13 and 64.63%, respectively, as compared to hyperlipidemic control (Figure 3A and B).

Effect of allopurinol (50, 100 and 200 mg/kg, p.o) on brain histopathological changes in hyperlipidemic rats

Brain tissue section obtained from a normal rat receiving saline showing normal (Figure 4A). A hyperlipidemic rat shows many dark cells in the cerebral cortex and some cells in the hippocampus region show karyolysis (arrow) and others show reduction of size Figure 4B and C). A fluvastatin treated rat shows some dark cells in the cerebral cortex, while most of the cells are normal pyramidal cells (arrow) and a section of the cerebellar

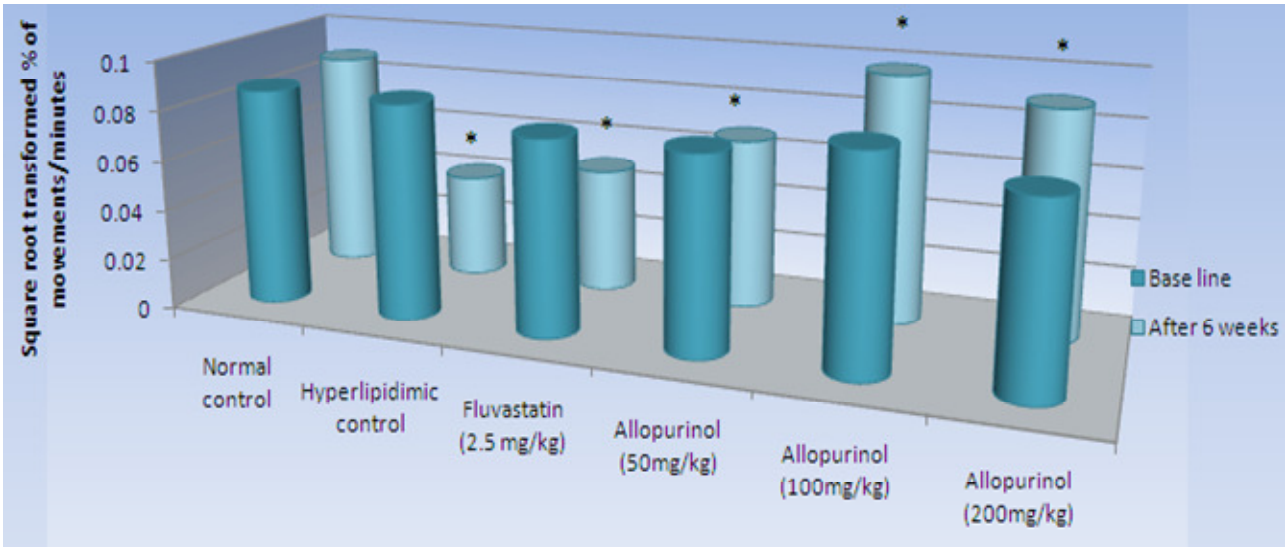


Figure 1. Effect of allopurinol (50, 100 and 200 mg/kg, p.o) on behavioral stress test in hyperlipidemic rats. Hyperlipidemic rats were maintained for 6 weeks on a special diet containing 1% cholesterol, 0.2% cholic acid, and 10% fat. After 4 weeks of induction of hyperlipidemia, tested drugs were orally administered daily for 2 successive weeks concomitant with hypercaloric diet. Data are expressed as mean ± SE (n=6). Data were analyzed by one-way ANOVA followed by Dunnt's test comparison test. * P<0.05 drug effect vs its basal value.

Table 1. Effect of allopurinol (50, 100 and 200 mg/kg, p.o)on serum liver function and creatine kinase levels in hyperlipidemic rats.

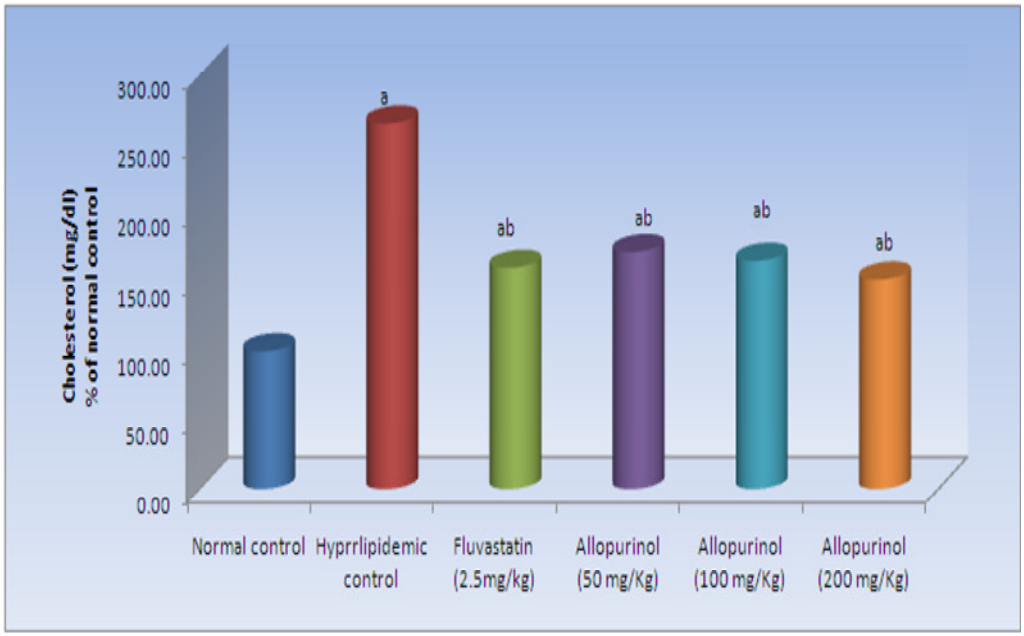
Parameter	Normal control	Hyperlipidemic control	Fluvastatin (2.5 mg/kg)	Allopurinol (50 mg/Kg)	Allopurinol (100 mg/Kg)	Allopurinol (200 mg/Kg)
AST (U/L)	61.59 ± 5.09	68.84 ± 1.90[a]	66.36 ± 2.10	65.05 ± 5.42	63.70 ± 5.96	61.09 ± 0.48[b]
ALT(U/L)	83.66 ± 2.55	87.44 ± 1.15	92.56 ± 4.85[a]	85.32 ± 2.06	84.12 ± 2.78[c]	84.05 ± 3.52[c]
Creatine kinase (mg/dl)	263.33 ± 0.87	264.00 ± 1.58	360.26 ± 7.15[ab]	452.55 ± 15.56[abc]	234.61 ± 6.27[abc]	219.00 ±1.16[abc]

Hyperlipidemic rats were maintained for 6 weeks on a special diet containing 1% cholesterol, 0.2% cholic acid, and 10% fat. After 4 weeks of induction of hyperlipidemia, tested drugs were orally administered daily for 2 successive weeks concomitant with hypercaloric diet. Rats were fasted for 14 h before blood sampling which was performed after 6 weeks. Data are expressed as mean ± SE (n=6). Data were analyzed by one-way ANOVA followed by LSD comparison test. [a] p < 0.05 vs normal control. [b]p< 0.05 vs hyperlipidemic control .[c]p< 0.05 Fluvastatin group

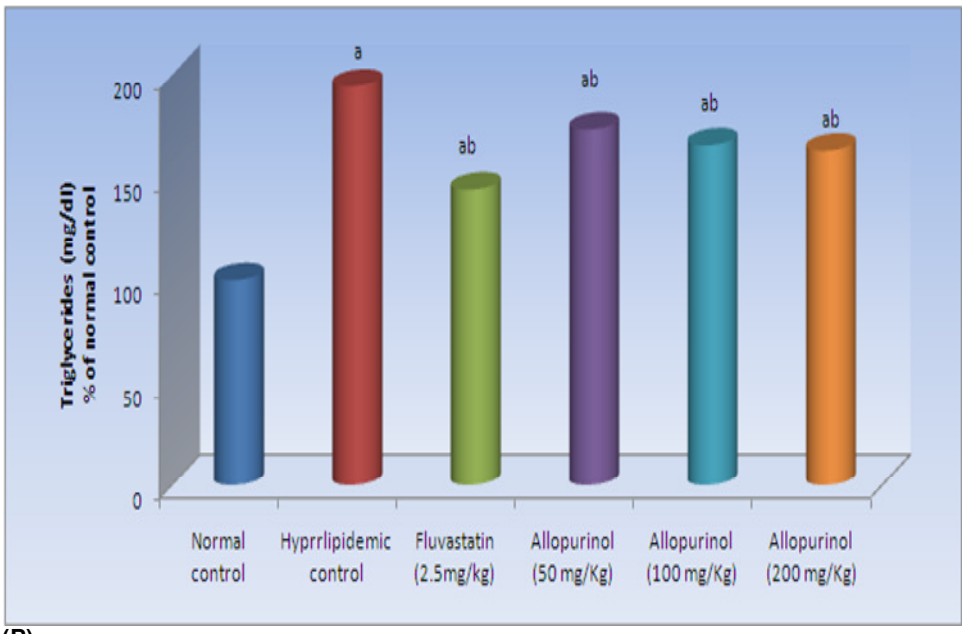
cortex shows that most of the Purkinje cells are normal (arrow) and only few cells show abnormality in shape and size (arrowhead) (Figure 4D and E); Allopurinol (50 mg/kg) treated rat shows very slight amelioration as many dark cells appear in both cerebral cortex and in hippocampal region (Figure 4F and G); Allopurinol (100 mg/kg) treated rat shows noticeable amelioration as only very few dark cells appear in cerebral cortex and in hippocampal region as well as the cerebellar cortex shows normalization of Purkinje cells (Figure 4H, I and J); Allopurinol (200 mg/kg) treated rat shows marked normalization of cells in cerebral cortex, hippocampal region and in cerebellar cortex (Figure 4K, L and M).

DISCUSSION

The present study states that hyperlipidemia has serious complications on nervous system as evidenced in experimentally induced hyperlipidemia, functionally by reduction in rat activity when tested by grid floor activity cage, this was confirmed by the laboratory investigation which revealed association of elevated serum triglyceride and total cholesterol levels with enhanced oxidative stress (MDA test) and decreased GSH content in the brain homogenates The observed results are in agreement with those of Adekunle et al. (2013) that showed increased concentrations of serum total cholesterol and triglyceride, kidney malondialdehyde in the rats given atherogenic diet than control. Moreover Minhajuddin et al. (2005) reported that the formation of thiobarbituric acid reactive substances was significantly higher in these rats compared to normals. Also histopathological examination, in current work, showed the presence of many dark cells in the cerebral cortex and karyolysis in the hippocampus region which together



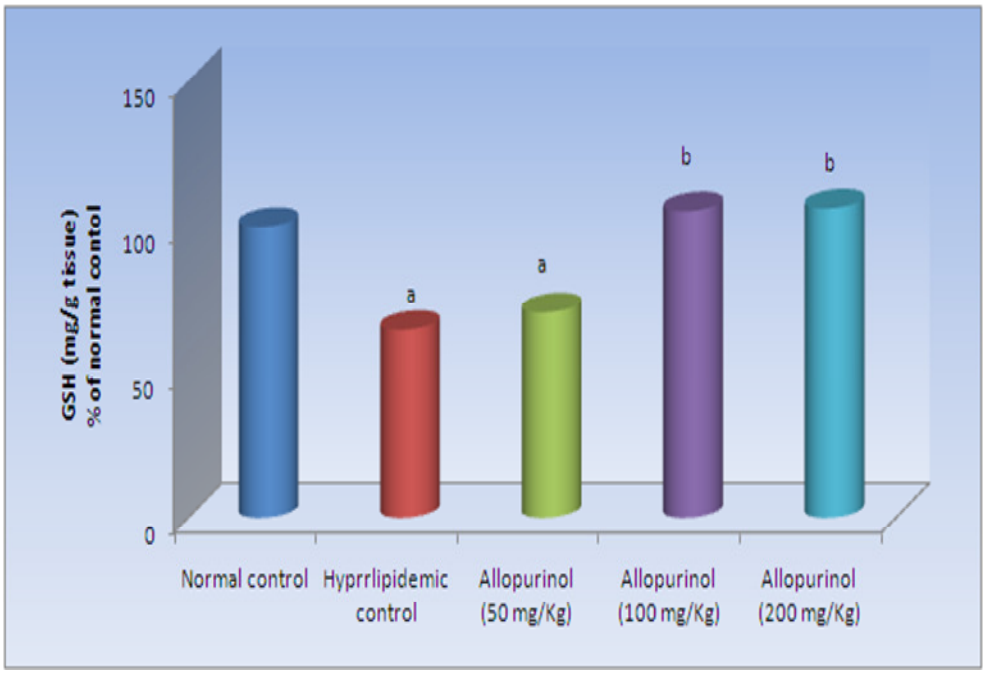
(A)



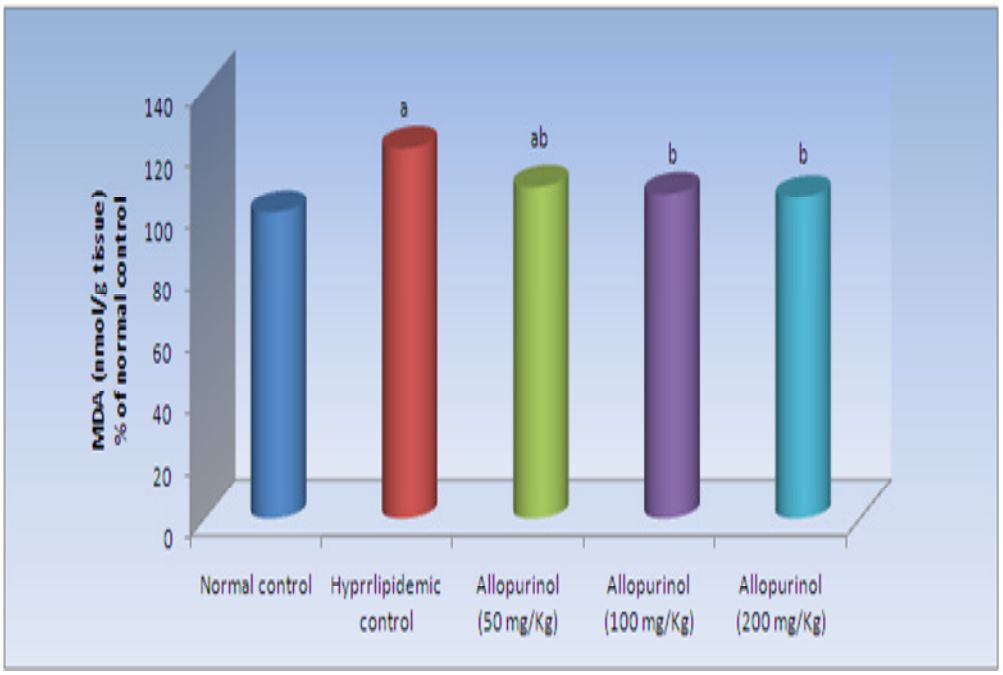
(B)

Figure 2. (A) and (B) showed Effect of allopurinol (50, 100 and 200 mg/kg, p.o)on serum triglyceride and total cholesterol levels in hyperlipidemic rats Hyperlipidemic rats were maintained for 6 weeks on a special diet containing 1% cholesterol, 0.2% cholic acid, and 10% fat. After 4 weeks of induction of hyperlipidemia, tested drugs were orally administered daily for 2 successive weeks concomitant with hypercaloric diet. Rats were fasted for 14 h before blood sampling which was performed after 6 weeks. Data are expressed as mean ± SE (n=6). Data were analyzed by one-way ANOVA followed by LSD comparison test. [a] $p < 0.05$ *vs* normal control. [b]$p< 0.05$ *vs* hyperlipidemic control .

with reduction of its cells size are consistent with the functional and biochemical changes caused byhyperlipidemia. The elevation of brain MDA level and decreased brain GSH content, obtained in current work, indicated that the effect of hyperlipidemia on central nervous system is through ROS dependant pathway



(A)



(B)

Figure 3. Effect of allopurinol (50, 100 and 200 mg/kg, p.o) on brain MDA and reduced GSH contents in hyperlipidemic rats. Hyperlipidemic rats were maintained for 6 weeks on a special diet containing 1% cholesterol, 0.2% cholic acid, and 10% fat. After 4 weeks of induction of hyperlipidemia, tested drugs were orally administered daily for 2 successive weeks concomitant with hypercaloric diet. Rats were fasted for 14 h then brain tissue homogenates were performed. Data are expressed as mean ± SE (n=6). Data were analyzed by one-way ANOVA followed by LSD comparison test. $^{a}p < 0.05$ vs normal control. $^{b}p< 0.05$ vs hyperlipidemic control .

which gave rise to the idea of use allopurinol- a xanthine oxidative inhibitor to counteract the oxidative stress

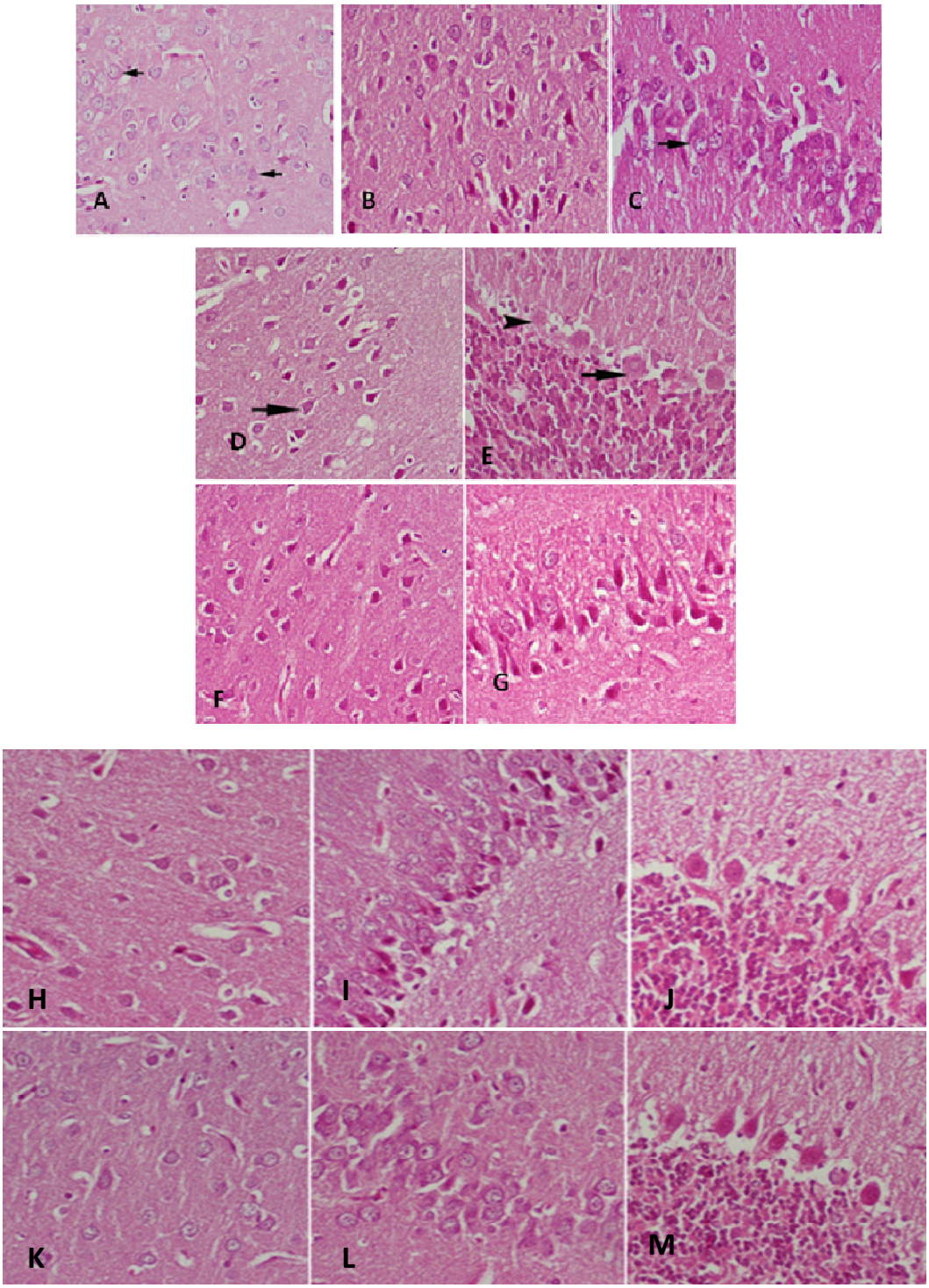


Figure 4. Photomicrographs of sections of the brain tissue of: A control rat showing normal histological structure of the hippocampus (A); A hyperlipidemic rat shows many dark cells in the cerebral cortex and Some cells in the hippocampus region show karrhyolysis (arrow) and others show reduction of size (B&C); A fluvastatin treated rat shows some dark cells in the cerebral cortex, while most of the cells are normal pyramidal cells (arrow) and a section of the cerebellar cortex shows that most of the Purkinje cells are normal (arrow) and only few cells show abnormality in shape and size (arrowhead) (D&E); Allopurinol (50 mg/kg) treated rat shows very slight amelioration as many dark cells appear in both cerebral cortex and in hippocampal region (F&G); Allopurinol (100 mg/kg) treated rat shows noticeable amelioration as only very few dark cells appear in cerebral cortex and in hippocampal region as well as the cerebellar cortex shows normalization of Purkinje cells (H, I & J); Allopurinol(200 mg/kg) treated rat shows marked normalization of cells in cerebral cortex, hippocampal region and in cerebellar cortex (K, L &M).

damaging effect of hyperlipidemia on central nervous system (CNS). Atherogenic diet elevated the lipid peroxides that are postulated to be the end products from membrane damage in rats. These elevated levels of peroxides could result from the hyperlipidemic state in relation with auto oxidation of plasma glucose and other small autooxidizable molecules (Nourooz-Zadeh et al., 1997). The antioxidant effect of allopurinol was evidenced by significant improvement of rat activity tested by grid floor activity cage, reduction in brain MDA and elevation of GSH contents and supported by histopathological findings that showed normalization of cells in cerebral cortex, hippocampal region and in cerebellar cortex when compared to the effect of hyperlipidemia. These results are in harmony with vivo study of Rodrigues et al. (2014) who showed that allopurinol administration prevented most alterations in GSH, CAT, SOD caused by hypoxanthine induces oxidative stress in kidney of rats.

Fluvastatin had been used in this study as a potent cholesterol biosynthesis inhibitor (Liao and Laufs 2005). The overall benefits observed with statins appear to be greater than what might be expected from changes in lipid levels alone, suggesting effects beyond cholesterol lowering. Indeed, recent studies indicate that some of the cholesterol-independent or “pleiotropic” effects of statins involve improving endothelial function, decreasing inflammation, and inhibiting the thrombogenic response (Liao et al., 2005). However statins have side effects as elevation in liver transaminases which was confirmed in the current work by elevation of serum ALT level as compared to normal control, in addition, Myopathy occurs in 0.1 to 0.2% of patients receiving statins in clinical trials. This adverse effect is shared by all statins; the risk of myopathy is increased by: the use of high doses of statins, concurrent use of fibrates, concurrent use of hepatic cytochrome P450 inhibitors, acute viral infections, major trauma, surgery, hypothyroidism and other conditions. Serum creatine kinase levels should be checked and monitored (Hamilton-Craig, 2001). These trials are in agreement with this study which showed elevation of serum creatine kinase level as compared to normal control.

In the current work, there is a significant elevation of serum AST level was observed in rats maintained on high fat diet. Hyperlipidemia is a major risk factor for liver disease (Ma and Li, 2006). The spectrum of hyperlipidemia-induced liver disease, also known as non-alcoholic fatty liver disease (NAFLD), ranges from “simple” steatosis to non-alcoholic steatohepatitis, which is characterized by oxidative stress, inflammation, and liver damage as well as fat deposition (Brunt, 2004). In addition, keeping rats on high fat diet for 12 weeks resulted in hepatic damage and fibrosis probably due to the infiltration of immune cells to the hepatocytes in an inflammatory milieu (Kyaw et al., 2013). The effects of allopurinol (200 mg/kg) when used as antihyperlipidemic in the present study showed promising results as it increases the rat activity, decreases serum triglyceride and total cholesterol levels, has suppressive effects on the serum levels of AST, ALT and creatine kinase, as compared to hyperlipidemic control and fluvastatin group. These data are in agreement with previous study of Aldaba-Muruato et al. (2012) who stated that there is a protective effect of allopurinol against acute liver damage and cirrhosis induced by carbon tetrachloride. In addition allopurinol reduces thioredoxin-interacting protein to alleviate liver inflammation and lipid accumulation in diabetic rats (Wang et al., 2013). Moreover, the pattern obtained, in this study, in the brain tissue MDA and GSH contents in rats fed with high fat diet is an indicator of scavenging of MDA and increasing GSH with allopurinol (100 and 200 mg/kg), these observations may be responsible for lowering the incidence of brain injury induced by hyperlipidemia. So hyperlipidemia may alter the levels of XO activity, lipid peroxidation, and GSH/GSSG ratio, while these improved with allopurinol administration. These results are in harmony with in vivo study of Rodrigues et al. (2014) who showed that allopurinol administration prevented most alterations in GSH, CAT, SOD caused by hypoxanthine induces oxidative stress in kidney of rats.

Conclusion

Hyperlipidemia is a highly prevalent risk factor for brain injury. Various antioxidant strategies are currently being a valuable therapeutic target in many disorders. So allopurinol might serve as an adjuvant therapy to avoid progression of brain damage through abolishing a decrease in activity level and elevation of serum levels of triglyceride, total cholesterol and creatine kinase as well as decrease serum AST, ALT levels which are fluvastatin side effects. Moreover allopurinol scavenges free radicals and inhibits karyolysis leading to improvement in brain injury induced by hyperlipidemia

Conflict of Interest

The authors have not declared any conflict of interest.

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