Research Article

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Degeneration of Granule Neurons In The Dentate Gyrus (Dg) Area In The Hippocampus In Male Rats Under The Influence of Simvastatin

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Abstract

Background: *Simvastatin is a lipophilic statin used to prevent and treat hypercholesterolemia.*

This study aimed to evaluate the effect of simvastatin on the appearance specifications of the DG region Hippocampus.

Method: *For the experiment, 36 male Wistar rats with an average weight of 300-250 g were divided into six groups (each group comprised six heads). Groups: 1): Control group, 2): Vitamin D dose 5 µg/kg, 3): Simvastatin group dose 1 mg/kg, 4): Simvastatin group dose 10 mg/kg, 5): Simvastatin group dose 1 mg/kg + vitamin D dose 5 µg/kg, 6): Simvastatin group dose 10 mg/kg + vitamin D dose 5 µg/kg. The duration of drug use was 28 days. At the end of the drug administration period, the animals were slaughtered, and then the brain tissue of the animals was extracted to prepare microscopic sections. Results: Microscopic studies show a negative effect of 10 mg/kg simvastatin on DG neurons.*

Conclusion: *The microscopic studies in the present study indicate that high doses of simvastatin cause degeneration of neurons in the DG region of the hippocampus.*

Keywords: Cholesterol, Dental Gyrus, Granule Neurons, Neurodegeneration, Hippocampus, Simvastatin

Background

Statins are the most significant output of microbiological research on a new target of antibacterial activity [1]. Compacting was a breakthrough discovery made by Dr. Akira Endo of Sankyo Co., Ltd. Its discovery enabled the creation of a class of drugs (statins) for hyperlipidemia [2]. Statins (HMG-CoA reductase inhibitors) are used widely for the treatment of hypercholesterolemia [3]. They are known as plasma cholesterol-lowering drugs and are widely used in patients with blood cholesterol disorders [4].

HMGCR is the primary enzyme involved in cholesterol synthesis. Statins are mainly absorbed in the liver and reduce serum cholesterol levels by inhibiting HMGCR [5]. Statins inhibit HMG-CoA reductase in the liver by regulating hepatocyte LDL receptors, increasing circulating LDL-C clearance, and decreasing plasma LDL-cholesterol levels [6].

Statins are amphiphilic drugs. They need to enter cells, be it directly by membrane interactions in the case of lipophilic agents (simvastatin, fluvastatin, atorvastatin) or by carrier proteins in the case of hydrophilic agents such as pravastatin. Rosuvastatin has an intermediate behavior [7]. Simvastatin (epistatin; synvinolin; MK 733), an HMG-CoA reductase inhibitor, acts by decreasing cholesterol synthesis and by increasing low-density lipoprotein (LDL) catabolism via increased LDL receptor activity [8]. Simvastatin is a member of the lipophilic family of statins [9]. Lipophilic statins can cross the blood-brain barrier and, as a result, can affect most high-cholesterol organs such as the brain [10].

Statins have been shown to have positive properties other than lowering atherogenic lipids, known as pleiotropic effects. The most important positive pleiotropic effects of statins are anti-inflammatory, antiproliferative, and antithrombotic ones, improving endothelial dysfunction and reductions in inflammation in the vasculature, kidney, and bone [11, 12]. The results of studies emphasize the positive effects of statins on latent molecular mechanisms on endothelial function and Antioxidant effects [13].

In addition to the positive effects, the side effects of statins have also been reported. Side effects of statins include muscle myopathy

[14] and severe liver toxicity [15]. The effects of statins on the central nervous system (CNS) have been extensively studied [16]. Some studies show that Simvastatin has protective effects on the nervous system [17, 18]. In addition to positive reports of the impact of Simvastatin [19, 20], there are adverse reports of this drug on the central nervous system [21-23].

The predominantly lipophilic statins include Simvastatin, fluvastatin, Lovastatin, Pitavastatin, and Atorvastatin [24]. Lipophilic drugs such as Simvastatin can cross the blood-brain barrier and affect brain cholesterol [25]. The obtained data indicate that cholesterol biosynthesis could be differently modulated in each brain region in adult male rats and emphasize marked differences in HMGR and low-density lipoprotein receptor regulation [26]. In this regard, the results of Ranaiy et al. show the degeneration of pyramidal neurons in areas CA1, CA2, and CA3 [23]. The results of a study by Segato et al. Show that the level of HMGR protein levels in the hippocampus is the highest, followed by the brain cortex; the lowest ones are expressed in the cerebellum and brain stem [26]. Due to the importance of statins, in the present study, the effect of Simvastatin at a dose of 1 mg/kg and 10 mg/kg for 28 days on neurons in region DG of the hippocampus in healthy male rats without Brain damage was assessed. It should be noted that the use of vitamin D supplements in some groups was done because, in some cases, vitamin D was used as a supplement with statins [27].

Materials and Methods

Thirty-six male Westar rats weighing 250-300g were purchased from the animal house of Urmia University. All procedures were followed according to the National Institute of Health guide for the care and use of Laboratory Animals (NIH Publications No. 8023, revised 1978) and local guidelines for compassionate use of animals in research; Rats were kept in cages with open access to standard tap water and compact chow. The animals were held in the same laboratory conditions (18°C to 23°C room temperature and controlled humidity) with alternating 12-h light and dark cycles. The Ethics Committee has approved the proposal of this study of Urmia University (Ethics Code: IR-UU-AEC-3/1033 / DA).

Animal Grouping

1. Healthy control group who received normal water and food and were not injected (C).
2. Vitamin D group who received only vitamin D at a dose of 5 µg/kg (200 IU) by intraperitoneal injection (VD) [28].
3. Simvastatin group with a dose of 1 mg/kg received a low dose of Simvastatin orally (SimL) [29].
4. Simvastatin group with a dose of 10 mg/kg [30] received high doses of Simvastatin orally daily (SimH) [30].
5. Simvastatin group with a low dose of 1 mg/kg with vitamin D supplement 5 µg/kg (SimL + VD).
6. Simvastatin group with a high dose of 10 mg/kg with vitamin D supplement VD 5 µg/kg (SimH + VD).The drugs were administered once daily for 28 days.

The drug simvastatin used in the present study was produced by Timova Pharmaceutical Company (Denmark).

Tissue Study Method

The brains of mice were transferred to 10% formalin for fixation and then subjected to dehydration, clarification, paraffin, and molding; then, six micron-thick sections were prepared by microtome. After staining with hematoxylin and eosin, they were examined and photographed with a light microscope. The DG region of the hippocampus neurons (granule cell layer) was explicitly studied. Degeneration of neurons (degeneration: abnormal changes in cell appearance including cell shrinkage, membrane uniformity, cytoplasm density) were examined by light microscopy [31].

Discussion

Cholesterol is probably the best-known steroid because of its association with atherosclerosis. However, biochemically it is also of significance because it is the precursor of a large number of equally essential steroids that include the bile acids, adrenocortical hormones, sex hormones, D vitamins, cardiac glycosides, sitosterols of the plant kingdom, and some alkaloids. Cholesterol is widely distributed in all body cells but particularly in nervous tissue. It is a significant constituent of the plasma membrane and plasma lipoproteins. It is often found as cholesteryl ester, where the hydroxyl group on position three is esterified with a long-chain fatty acid. It occurs in animals but not in plants [32]. Cholesterol is an essential sterol synthesized by most human cells, majorly in the liver. It is a necessary constituent of cell membranes; it acts as a precursor for synthesizing steroid hormones, vitamin D, and bile acids [33]. Cholesterol is carried in the blood by molecules called lipoproteins. A lipoprotein is a complex consisting of lipid (fat) and protein [34]. Cholesterol is transported in plasma primarily in the form of low-density lipoproteins (LDL); the principal route for its removal from tissues to the liver is in high-density lipoproteins (HDL), followed by excretion in the bile [33].

The pathway for cholesterol synthesis involves many intermediates, beginning with acetyl-coenzyme A (CoA) and some side branches along the way. The steps for Cholesterol synthesis are as follows:1. Acetyl-coenzyme A is converted to Mevalonic acid by HMG CoA (The effect of statins is at this stage), 2. Malonic acid is converted to Squalene, 3. Squalene is converted to lanosterol, 4. Lanosterol can be converted to Cholesterol in two ways. One is the Bloch route, and the other is the Kandouch-Russell route. In the Bloch route, Lanosterol is converted to 7-dehydrodesmosterol. 7-dehydrodesmosterol is converted to Desmosterol, and eventually, Desmosterol is converted to Cholesterol. In the Kandouch-Russell pathway, Lanosterol is converted to Lathosterol, Latosterol is converted to 7-dehydrocholesterol, and finally, 7-dehydrocholesterol is converted to Cholesterol [35].

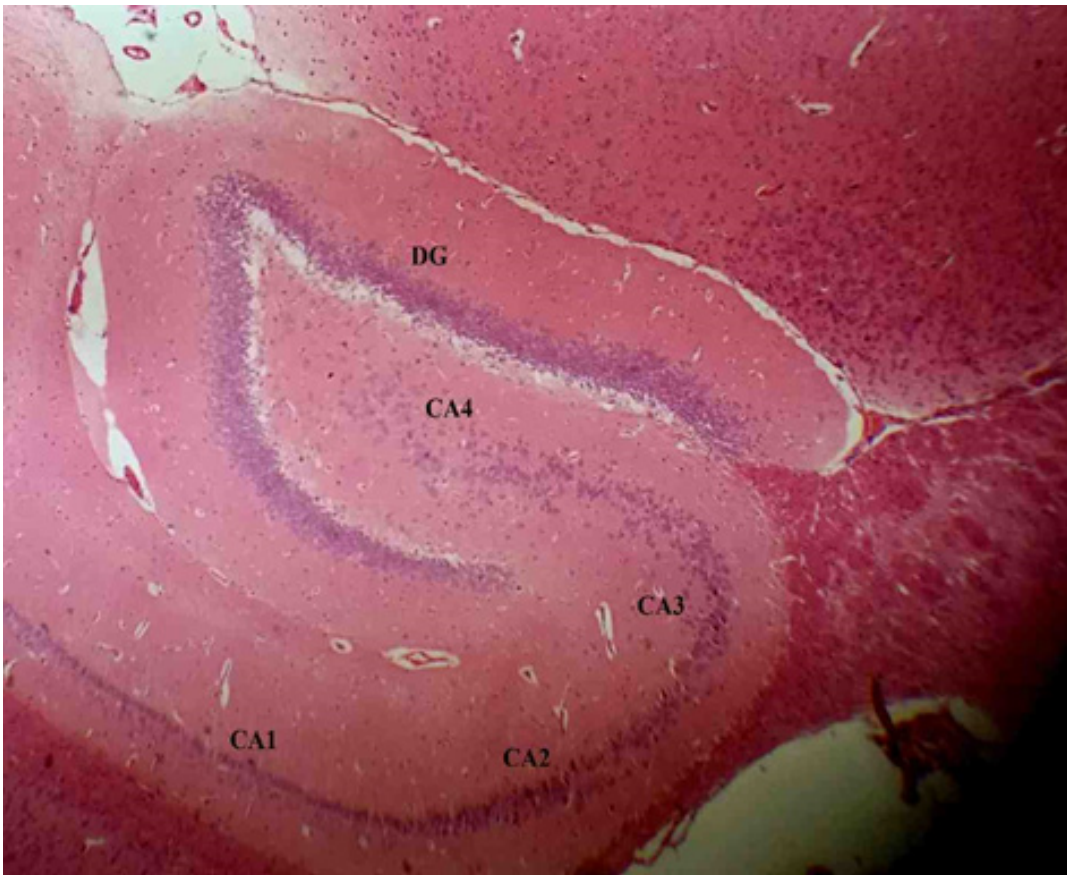

Figure 1: Longitudinal Microscopic Images of Hippocampal Tissue (X100)

Statins have an impact on serum cholesterol concentration. Treatments with statins reduce LDL-C levels [36]. Statins competitively bind to the catalytic domain of HMG-COA reductase. This family of drugs prevents HMG-CoA from reaching the active site of the LDL-C receptor. As a result, it enhances the reabsorption of LDL-C and LDL-C precursors from the systemic circulation. Proteins that bind to the sterol regulatory unit (SREBP) sense changes in cholesterol levels and subsequently increase the expression of LDL-C receptors to reabsorb LDL-C from serum to compensate for the decrease in cellular cholesterol [37]. Simvastatin, like other statins, is used to lower serum cholesterol levels [37]. Simvastatin is inactive as a prodrug and is converted to active beta-hydroxyl derivatives in the gastrointestinal tract. The most significant effect of this drug is on the liver [38-41]. Simvastatin, a member of the lipophilic statin family, can cross the blood-brain barrier, thereby affecting cholesterol synthesis in the brain. Most likely, this drug reduces the synthesis of cholesterol in the brain [10, 25].

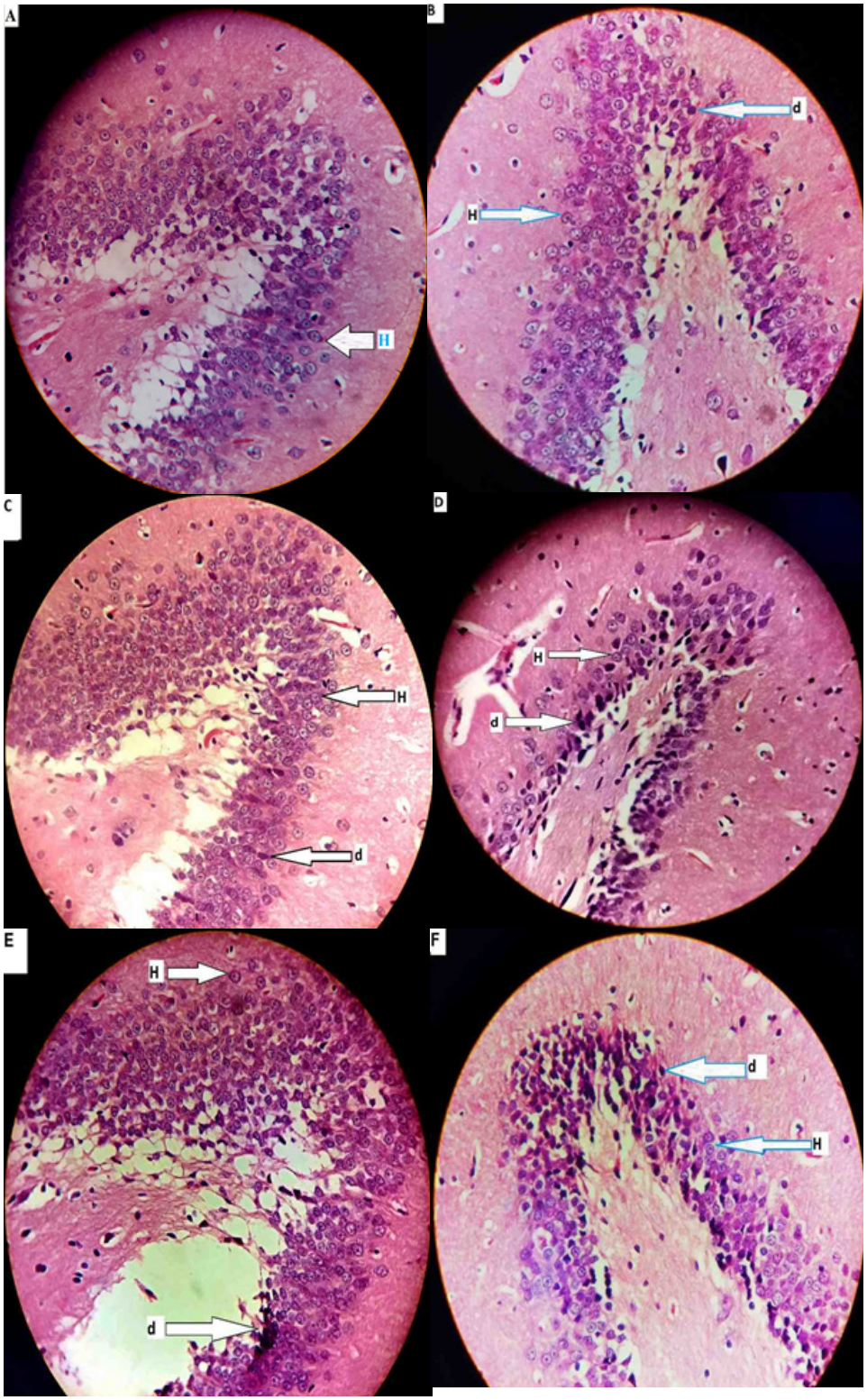

Figure 2: Longitudinal microscopic images of DG hippocampal tissue (X400). Groups (A): Control group, (B): Vitamin D dose 5 µg/kg, (C): Simvastatin group dose 1 mg/kg, (D): Simvastatin group dose 10 mg/kg, (E): Simvastatin group dose 1 mg/kg + vitamin D dose 5 µg/kg, (F): Simvastatin group dose 10 mg/kg + vitamin D dose 5 µg/kg. The H tag indicates a healthy cell in all images, and the D tag indicates a degenerate cell

The results of histological studies in the present study showed that the drug simvastatin causes degeneration of neurons in the hippocampal region DG in male rats that received simvastatin at a dose of 10 mg/kg (Figure 2-D and F). The results of this part of the present study align with the study of Ranaiy et al. published in 2021; they reported that simvastatin at a dose of 10 mg/kg degenerated neurons in regions CA1, CA2, and CA3. This adverse event was not observed in male rats receiving simvastatin at a dose of 1 mg/kg [23]. It should be noted that the presence of vitamin D supplementation did not affect preventing the degeneration of neurons in the group receiving 10 mg of simvastatin + vitamin D (Figure 2-F). In the present study, no visible tissue degeneration was observed at a dose of 1 mg/kg simvastatin on cells in the DG area (Figure 2-C and E). This lack of adverse effect at a dose of 1 mg indicates that this dose of the drug is safe. In general, in the study of this part of the hippocampus in the present study, a high percentage of neurodegeneration in neurons in the groups receiving 10 mg of simvastatin compared to the control group and other groups is clearly observed. This indicates that male rats do not tolerate a dose of 10 mg simvastatin during the 28-day treatment period. In the present study, vitamin D supplementation could not prevent the degeneration of neurons in rats receiving simvastatin 10 mg/kg (Figure2-F). These results confirm the research of Segatto, M. et al. In a study they published in 2012, they reported that statins had the most significant effect on the hippocampus and cortex and had a minor impact on the cerebellum and brainstem. The results of Segatto, M., et. Showed that differences in HMGR and LDLr regulation are present in brain areas. They also reported that these variations seem to be related to cholesterol turnover, regional myelin content, and synaptic plastic modulation. These data emphasize marked functional differences in HMGR and LDLr regulation in brain regions [26]. The results of studies show that the brainstem has the highest cholesterol level compared to other areas of the brain [42]. The main cholesterol metabolic pathways seem to be nearly suppressed in the brain stem because of the low HMGR activation and protein levels and the minimal LDLr expression. Results do not necessarily indicate that a low cholesterol content is present in these regions, rather than that cholesterol turnover is very low" [26].

Clinical evidence suggests that statins, independent of their effects on serum cholesterol levels, may also play a potential role in preventing and treating cancer. Specifically, statins have been shown to exert several beneficial antineoplastic properties, including decreased tumor growth, angiogenesis, and metastasis [43]. Evidence shows that statins impair the proliferation of breast cancer cells and reduce the risk of breast cancer recurrence. The strongest discriminants between the breast cancer cells associated with statin sensitivity at the transcriptional level were the expression of the estrogen receptor and a gene set enriched for genes involved in the cholesterol biosynthesis pathway [44]. The mechanism of action of statins on breast cancer cells may be similar to the observed effect of simvastatin on hippocampal cells in the present study. Discovering the main mechanism between this degeneration of hippocampal cells in the present study with the mechanism of action of statins on cancer cells can be an essential key in the production of anticancer drugs. This issue needs further study in the future.

Cholesterol is an essential factor in the animal's cell membrane [38], and without cholesterol, there is no such thing as a cell membrane. Cholesterol does not cross the blood-brain barrier, and brain cholesterol is produced in this organ [46]. Therefore, the passage of simvastatin through the blood-brain barrier affects brain cholesterol in this organ [6]. In the present study, high doses of simvastatin significantly affected cerebral cholesterol, causing degeneration of neurons in region DG of the hippocampus. Although the present study was performed on rats, this can be a challenge for pharmaceutical companies. The results of the present study need further research in the future.

Conclusion

The current study results indicate the adverse effect of high-dose simvastatin on the granule neurons in the DG region of the Hippocampus in male rats.

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