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Simvastatin does not Affect the Brain Weight and Body Weight of Rats

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Abstract

Background: Simvastatin is a lipophilic statin and can cross the blood-brain barrier. This study aimed to investigate simvastatin's effect on the brain weight ratio to body weight in male rats.

Method: For the experiment, 36 Wistar male rats with an average weight of 250 g to 300 g were divided into six groups (each group comprised six heads). Group (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. After the end of the treatment period, the animals were weighed, and their brain tissue was completely removed after euthanasia. Then their brains were weighed. The data were analyzed using SPSS19 software. $P<0.05$ was considered a significant level. Examining the ratio of brain weight to body weight showed that simvastatin in doses of 1 mg and 10 mg does not significantly affect the ratio of brain weight to body weight of rats.

Discuss: Lipophilic statins such as simvastatin have great effects on the nervous system, and brain cholesterol synthesis is significantly affected by treatment with high doses of simvastatin.

Conclusion: Simvastatin drug, neither in low dose nor in high dose, has any effect on the ratio of brain weight to body weight of rats.

Keywords: Body weight; Brain weight; Male rat; Simvastatin; Vitamin D

Abbreviations

HMGCR: Hydroxy Methyl Glutaryl CoA-Reductase; VD: Vitamin D; Sim: Simvastatin; SimL: Low dose of Simvastatin (1 mg/Kg); SimH: High doses of Simvastatin (10 mg/Kg); mcg: Micrograms (1 mcg = 0.0001); mg: Milligram; kg: Kilogram

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Introduction

Cardiovascular Disease (CVD) remains the leading cause of death worldwide. Research has implicated LDL-C (Low-Density Lipoprotein Cholesterol) as a factor in the development of atherosclerotic CVD [1]. Statins, the inhibitor of 3-Hydroxy-3-Methylglutaryl CoA (HMG-CoA), are known as plasma cholesterol-lowering drugs and are widely used in patients with blood cholesterol disorders [2]. HMG-CoA combines Acetyl-CoA and Acetoacetyl-CoA, converted to mevalonate by HMG-CoA reductase and NADPH cofactors. The primary function of statins is to lower cholesterol by competitively and reversibly inhibiting the enzyme HMG-COA reductase in the rate-limiting stage of cholesterol production [3]. Statins inhibit HMG-CoA reductase in the liver by regulating hepatocyte LDL receptors, increasing circulating LDL-C clearance, and decreasing plasma LDL-cholesterol levels [4].

Statins have effects other than their effect on cholesterol, called pleiotropic effects [5]. Statins have multiple pleiotropic effects, some of which also affect the cardiovascular system [6]. In addition to the cardiovascular impacts, statins also profoundly affect the nervous system. When they penetrate the brain parenchyma, they affect not only cholesterol biosynthesis but also neuronal and glial cells, the levels of neurotransmitters, neurotransmitter receptors in the synapse, and cell viability, arborization of neural dendrites, oligodendrocyte-mediated myelination, etc. affect selective manifestations [7]. Also, epidemiological studies show that long-term treatment with statins is significantly effective in treating cancer [8]. New research results suggest that statins may potentially be adjunctive therapy to reduce endothelial dysfunction and dysregulated inflammation in patients with COVID-19 infection [9].

Simvastatin is a member of the lipophilic family of statins [10]. Lipophilic statins can cross the blood-brain barrier and, as a result, can affect most high-cholesterol organs, such as the brain [11]. Statins simultaneously affect cholesterol concentration in the brain [12,13]. Due to the passage of simvastatin through the blood-brain barrier and the effect of this drug on brain cholesterol, and possible subsequent effects, in the current study, the effect of simvastatin on the ratio of brain weight to body weight in rats was investigated in two doses of 1 mg/kg and 10 mg/kg.

Materials and Methods

Thirty-six male Westar rats weighing 250 g to 300 g 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) [14]. By intraperitoneal injection (VD).

3. Simvastatin group with a dose of 1 mg/kg [15]. Received a low dose of Simvastatin orally (SimL).

4. Simvastatin group with a dose of 10 mg/kg [16]. Received high doses of Simvastatin orally daily (SimH).

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).

After the end of the drug administration period (28 days), the animals were weighed. After weighing, the animals were euthanized, their brains were completely extracted, and a digital precision balance checked their brain weight. After weighing and checking the brain weight of the rats, the ratio of the brain weight of the rats to the weight was checked. It should be noted that body weight and brain weight were measured separately for each animal.

Ratio of brain weight to body weight = Brain weight/Body weight

Statistical analysis

Data were analyzed using SPSS19 software using one-way analysis of variance and Tukey test. The results were presented as mean ± standard error. $P<0.05$ was considered as a significant level.

Results

Results related to the ratio of brain weight to body weight.

The statistical results of the ratio of brain weight to body weight of mice in the gavage group showed that there is no significant difference between the groups in the ratio of brain weight to total body weight compared to the control group ($P>0.05$) (Figure 1).

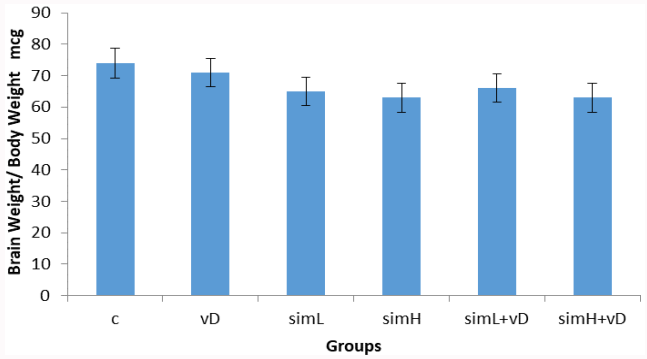

Figure 1: Comparison of the effect of treatments on ratio of brain weight to body weight, Meane ± SEM the ratio of brain weight to body weight (1) Control group (C), (2) VD (Vitamin D dose 5 µg/kg), (3) SimL group (simvastatin dose 1 mg/kg), (4) SimH group (simvastatin dose 10 mg/kg), (5) SimL + VD group (simvastatin dose 1 mg/kg + vitamin D dose 5 µg/kg), (6) SimH + VD group (simvastatin dose 10 mg/kg + vitamin D dose 5 µg/kg).

Discussion

Hydroxymethylglutaryl Coenzyme A (HMG-CoA) reductase inhibitors are known as statins. These drugs inhibit cholesterol biosynthesis, which reduces the amount of intracellular cholesterol in liver cells and then regulates the number of LDL-C (Low-Density Lipoproteins) receptors on the cell surface [17]. Statins decrease LDL-C levels [18] and increase HDL-C (High -Density Lipoproteins) levels and decrease TG levels [19]. The effects of lipophilic statins such as simvastatin on the nervous system include helping to improve the treatment of concussion, improving learning in the rat, increasing protein synthesis and differentiation of cells into adult neurons in mice, and increasing the expression of BDNF (Brain-Derived Neurotrophic Factor) and VEGF (Vascular Endothelial Growth Factor) [20]. The results of the studies indicate that brain cholesterol synthesis is significantly affected by short-term treatment with high doses of simvastatin.as a result, since a lipophilic drug such as simvastatin can affect various brain factors, there is a possibility that it can also affect brain weight.

Due to the importance of statin drugs on cholesterol levels, many studies have studied the effect of these drugs on blood sugar levels and weight. Daniel I Swerdlow and David Preiss proved in their research that weight gain along with type 2 diabetes occurs due to statins [21], as well as the results of the study by Nahal El Bayar et al. [22] this is confirmed. The potential effect of statins on blood glucose metabolism is debatable [23,24]. Some studies have reported that statins increase the risk of diabetes in non-diabetic patients [25,26], and weight gain and the risk of type 2 diabetes are new side effects of statins reported [27]. Weight gain with the use of statins is not well explained, some studies show that statins increase the accumulation of body fat and liver in obese rats [28], also the results of a study indicated a significant increase in body weight after one year of atorvastatin use [29]. Statins penetrate the blood-brain barrier with different efficiencies, depending on their lipophilicity [30,31] and since lipophilic statins such as simvastatin can cross the blood-brain barrier, they can affect most organs with high cholesterol concentrations such as the brain [11]. It should probably be kept in mind that using lipophilic statins such as simvastatin in high doses may affect brain cholesterol

synthesis in humans [32]. Among other effects of simvastatin on the nervous system: (1) Improvement of treatment concussion with simvastatin, (2) improving learning in rats, (3) increasing protein and cell differentiation into mature neurons in rats, (4) The expression of BDNF and VEGF has been reported along with the activation of the Akt signaling pathway [20].

Since the results of the research show weight loss as a result of the use of statin drugs [33], and that simvastatin is a lipophilic statin and can cross the blood-brain barrier [11], the basis of this research is based on the premise of the effect of simvastatin on brain weight and body weight due to the effect the drug was simvastatin. The present study investigated the ratio of brain weight to body weight of rats. However, the results of this research in relation to the ratio of brain weight to total body weight did not show any significant difference in the increase or decrease of the ratio of brain weight to total body weight in the test groups compared to the control group, in accordance with previous research on the use of statins (Figure 1). In general, in the present study, when simvastatin was administered to rats in two doses of 1 and 10 mg/kg for 28 days, no significant effect was observed on the ratio of brain weight to body weight in rats. These data are essential from the point of view that if any of the factors of brain weight or the body weight of rats underwent significant changes, the ratio of brain weight to body weight would probably decrease or increase. But in the present study, no significant effect was observed. And the doses used and even the length of the treatment period can affect the results of the effect of these drugs. It should be noted that the presence of supplemental vitamin D did not significantly reduce or increase the ratio of brain weight to body weight.

Based on the research done by our team, this is the first article specifically devoted to this topic. The results of the present study confirm the safety of simvastatin drug on brain weight and body weight of rats. It is shown that this part of the current research is one of the limited research's in the field of using statins and due to the value of these drugs, more research is needed in the future. It is necessary to investigate other doses of this drug in the future. Based on the research conducted in the present study, no article specifically deals with this issue.

Conclusion

The present study showed that simvastatin does not affect reducing or increasing the ratio of brain weight to body weight in rats. In general, simvastatin drug has no effect on rats' brain weight and body weight.

Declaration

Statins are at the forefront of the fight against atherosclerosis, as they effectively lower LDL-C, thus their pleiotropic effects suggest a valuable role for statins in preventing cardiovascular diseases. Considering the effects of simvastatin on the nervous system and other body organs, it is necessary to conduct more detailed research on this drug.

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