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ALTERATIONS OF NEUROBEHAVIORAL PERFORMANCE, BLOOD AND BRAIN CHOLINESTERASE ACTIVITIES AND CHOLESTEROL LEVELS BY REPEATED STATIN TREATMENTS IN MICE

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Hypolipidemic statins are characterized by a wide margin of safety, but with adverse effects. The purpose of this study was to further examine and ascertain effects of repeated administrations of atorvastatin, simvastatin and rosuvastatin on neurobehavioral performance, cholinesterase (ChE) activity and cholesterol level in mice. Male Swiss mice were treated orally with each statin at 200 mg/kg of body weight/day for 14- and 28 consecutive days. Control mice were treated with distilled water. Twenty four hours after the last 14- or 28-day dosing, each mouse was tested for 5-min open-field activity, negative geotaxis performance at an angle of 45°, 5-min head pocking and forced swimming endurance. Plasma, erythrocyte and whole brain ChE activities, and plasma and whole brain cholesterol levels were measured. Treatments with each statin for 14 and 28 consecutive days significantly decreased open-field activities and head pocking, and increased the durations of negative geotaxis and forced swimming endurance with reduction of immobility duration. Plasma, erythrocyte and whole brain ChE activities were significantly reduced. The most prominent effect was seen with atorvastatin. Brain ChE activity highly correlated with those of the plasma and erythrocytes. The statins significantly decreased plasma and brain cholesterol levels. The results ascertain adverse behavioral and neuronal cholinergic effects after repeated statin treatments in mice. Considering potential pleiotropic effects, further pharmacological studies are needed to explore values of these changes.

Key words: *atorvastatin, simvastatin, rosuvastatin, open-field activity, swimming behavior*

INTRODUCTION

Statins are hypolipidemic drugs that inhibit the target rate-limiting enzyme 3-hydroxy-3-methylglutaryl-coenzyme A in the liver to reduce blood cholesterol level[1-3]. In spite of the relative safety of statins, current evidences indicate adverse effects of these drugs on many organ systems such as the liver, kidney, skeletal muscles and the brain[4-7]. Pleiotropic effects of statins have also been reported on several organ systems, such as inhibition of brain cholinesterase effect that could be beneficial in dementia [3,8,9]. In experimental laboratory animals, statins given as single or repeated doses were reported to cause many biochemical alterations such as increased malondialdehyde level (an index of lipid peroxidation), reduced glutathione level (an antioxidant peptide) in mice[10], reduced blood and/or brain cholinesterase (ChE) activities in mice[11], chicks [12] and rats[13,14]. In the light of these statin effects, aside from their hypolipidemic actions, the current evidence suggests involvement of the central nervous system (CNS) in the adverse/pleiotropic effects of statins.

Considering statin intolerance that affects many systems[15,16] and their actions on the brain, experimentally, these studies were found to cause behavioral alterations in the form of reduced general locomotor activity in mice and rats[11], reduced neuromuscular activity in rats[17], cognitive impairment in rats[14,18], memory

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dysfunction in mice[19], depressive behaviors in mice [20], impaired swimming performance and antiepileptic effects in mice[11,21], and modulation of social behavior (autism) in rats[22]. The CNS involvement in the actions of statins was further verified by pharmacological and toxicological challenges reports that showed reductions in the onset and duration of xylazine-ketamine anesthesia in chicks [23] and propofol anesthesia in mice [24], as well as reductions in the toxicity outcomes of centrally and peripherally ChE inhibiting insecticides carbaryl in chicks [23] and dichlorvos in mice[24].

In the light of recent reports, though of limited scope in chicks [12,23] and single dose effects in mice [11], that considered ChE inhibiting properties of statins and neurobehavioral outcomes as adverse effects, as well as the oxidative effects of repeated doses of statins in mice [10], the purpose of the present study was to undertake, collectively, additional warranted experiments in mice, to examine and ascertain effects of three statins (atorvastatin, simvastatin and rosuvastatin) after extended daily repeated administration for 14- and 28 days, taking into account the targeted neurobehavioral performance, blood and brain cholinesterase activities as well as cholesterol levels.

MATERIALS AND METHODS

Animals and ethics

A total of 80 male mice of Swiss-origin (age 100-125 days and body weight 30-37 g) were used. They were housed in animal housing quarter at temperatures between 20 to 24 ºC and a 12-h light/dark cycle, with water and laboratory food ad libitum. This research project was approved by the Departmental Scientific Committee on Research and Animal Care and Use and the Committee of Postgraduate Studies at the College of Veterinary Medicine, University of Mosul, Iraq. The Institutional Review Board approval was by College of Veterinary Medicine, University of Mosul (No. 2144, November 2, 2022) and the Presidency of the University of Mosul (No. 4S/29927, October 30, 2022). The use of mice as experimental animals in the presents study was according to the institutional regulations and ethics in compliance with guidelines of Animal Research: Reporting of In Vivo Experiments (ARRIVE) (https://www.nc3rs.org.uk/arrive-guidelines) and the Guide for the Care and Use of Laboratory Animals[25]. Human participants or tissues were not used in the present study.

Statins used

Atorvastatin, simvastatin and rosuvastatin were the courtesy of the State Company for Drugs Industry and Medical Appliances, Samarra, Iraq. The required dose of each statin was freshly prepared on the day of administration as 2% solution in distilled water to be administered orally by a gavage needle at a volume of 10 mL/kg of body weight (200 mg/kg of body weight/day for 14 and 28 consecutive days). Mice treated with distilled water at 10 mL/kg of body weight accompanied all statin treatments as control counterparts. **Fig. 1** outlines the experimental protocol and distribution of a total 80 mice randomly into 8 groups of statin and control (distilled water) treatment regimens. The final number of mice for behavioral measurements was 10 per statin or control group, whereas it was 8 per statin or control group (because it involved animal sacrifice) for the determination of ChE activity and cholesterol level. According to a previous study the repetitive dose of each statin (200 mg/kg of body weight) we applied in the present study was not obviously toxic in mice[10].

Behavioral measurements

Twenty four hours after the last repetitive 14-day or 28-day dosing of each statin and distilled water **(Fig. 1)**, each mouse was separately tested for the neurobehavioral performance that included 5-min open-field activity in an open box (35 cm x 35 cm x 25 cm with 25 equal squares arena), which involved the numbers of squares crossed and rearing activity in the arena [26], negative geotaxis performance at an angle of 45° to complete 180° after placing the mouse in a head down position within 60 seconds [27], 5-min head pocking behavior in a 30-cm diameter circular arena which contained 8 holes (2 cm in diameter each)[28], and a single session of forced swimming endurance at a temperature of 24 ± 1 °C, which is an indication of despair test, to measure the durations of initial swimming attempts and immobility in a cylindrical water

tank (30 cm in height and 15 cm in diameter with water level at the 20 cm mark) [29]. Thereafter, the mice were dried off and allowed to rest in their home cages for about one hour before the start of blood sampling.

Samples obtained

After conclusion of the behavioral tests, a blood sample was withdrawn from retro-orbital plexus of each statin or control mouse under terminal anesthesia with ether into heparinized capillary tubes. Blood samples were centrifuged at 1000 g for 15 min to separate the plasma and erythrocytes. The whole brain was dissected out and homogenized with an electric homogenizer (OMNI Bead Ruptor, OMNI International, USA) at a speed of 400 rounds/s using sodium chloride-phosphate buffer solution (1:9)[24].

Determination of ChE activity and cholesterol level

ChE activities in the plasma, erythrocytes, and whole brain were determined, 24 h after the last repetitive 14-day or 28-day dosing of each statin and distilled water, spectrophotometrically using commercial kits (Elabscience Biotechnology Inc., Houston, TX, USA). Plasma and brain cholesterol levels were determined, 24 h after the 28th dosing (taken as a target treatment endpoint) of each statin and control group, using a commercial spectrophotometric kit (Biolabo SA, Maizy, France).

Statistics

The data were presented whenever appropriate as mean ± standard error (SE). They were statistically analyzed by the analysis of variance followed by the least significant difference test, using the statistical software package SPSS version 20 (IBM). Linear regressions analyses were also performed to correlate and report r^2 values of brain and blood ChE activities. The level of statistical significance was at $p < 0.05$.

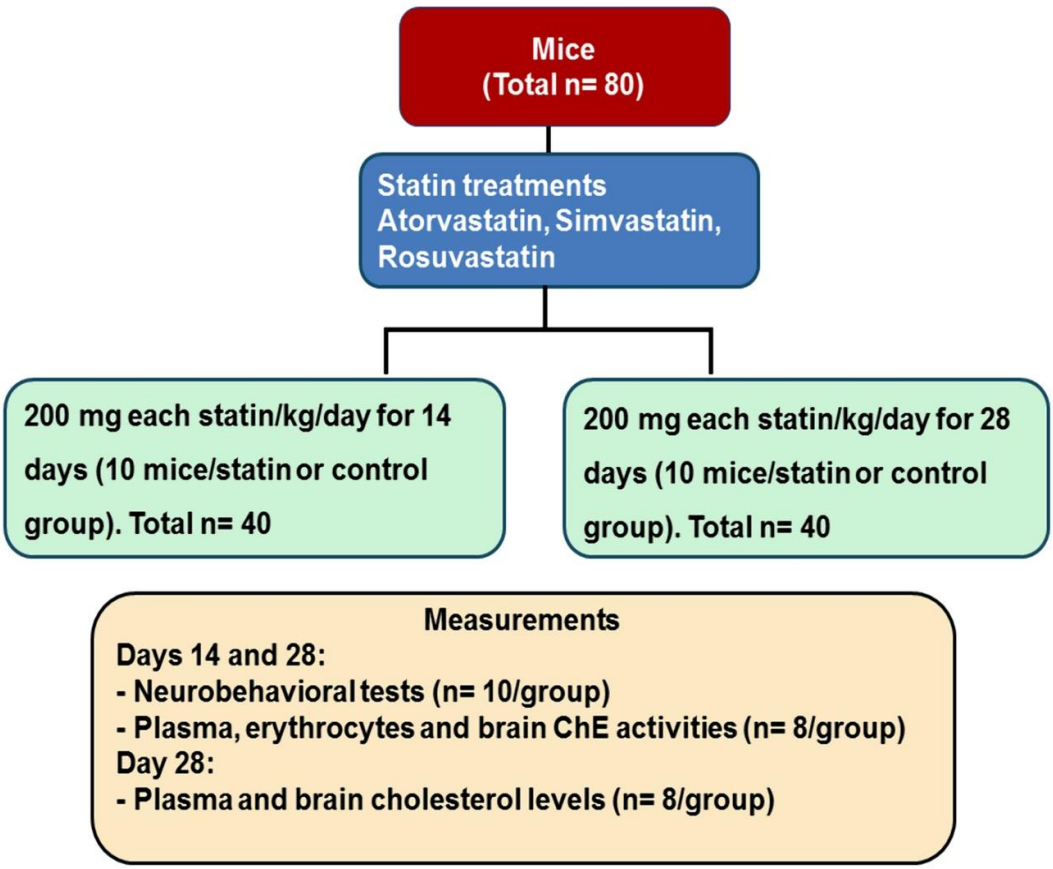

Fig. 1: The study design, repeated statin treatments, and allocation of mice into groups for neurobehavioral measurements and determinations of cholinesterase activity and cholesterol level.

RESULTS AND DISCUSSION

Results

Neurobehavioral assessments

Repeated treatment of mice with each of the three statins (atorvastatin, simvastatin, and rosuvastatin) for 14 and 28 consecutive days significantly ($P < 0.05$, in comparison with respective control values) decreased open-field activities manifested as delays in the latency to onset of movement from the central square in the open-field arena, decreases in squares crossed for 5 min (general locomotion), and reductions in the frequency of 5-min rearing **(Table 1**). In consonance with the depressed open-field behavioral performance, statin-treated mice suffered from significant reductions in head pocking activity behavior and slowed negative geotaxis performance at an angle of 45° in comparison with control mice **(Table 1)**. However, in contrast with the depressant actions of statins described above, the hypolipidemic drugs significantly increased the duration of forced swimming behavior and decreased the duration of immobility in the swimming tank when compared with respective control values **(Table 1)**.

Table 1: Neurobehavioral performance in mice dosed orally with statins at 200 mg/kg of body weight/day for 14- or 28 consecutive days.

Behavioral measurement	Duration of statin treatment			
	14 days		28 days	
	Control	Atorvastatin	Control	Atorvastatin
Open-field activity				
Latency to move (sec)	0.19±0.03	0.59±0.03*	0.25±0.13	0.78±0.02*a
Squares crossed/5 min	128.40±0.73	67.40±1.45*	122.32±0.89	47.50±1.35*†
Rearing/5 min	24.60±0.56	2.70±0.37*	19.50±0.68	1.20±0.25*†
Head pocking/5 min	23.20±0.66	4.30±0.37*	18.40±0.78	2.00±0.26*†
Negative geotaxis (sec)	2.40±0.43	30.50±0.45*	4.60±0.62	48.80±1.33*†
Forced swimming				
Duration of initial swimming (min)	2.22±0.05	4.03±0.07*	2.10±0.09	4.28±0.06*
Duration of immobility (sec)	32.30±3.36	3.10±0.41*	26.20±1.54	1.70±0.21*
	Control	Simvastatin	Control	Simvastatin
Open-field activity				
Latency to move (sec)	0.13±0.015	0.62±0.02*	0.27±0.23	0.68±0.02*†
Squares crossed/5 min	129.90±1.85	83.40±2.19*	130.76±1.62	53.20±1.37*†
Rearing/5 min	20.50±0.54	4.90±0.38*	21.30±0.61	1.90±0.28*†
Head pocking/5 min	24.20±0.76	6.30±0.37*	27.34±0.87	3.30±0.37*†
Negative geotaxis (sec)	18.0±0.25	51.00±1.02*	23.10±0.59	55.7±0.79*†
Forced swimming				
Duration of initial swimming (min)	2.34±0.08	4.31±0.09*	2.16±0.32	5.10±0.11*
Duration of immobility (sec)	34.20±0.61	4.90±0.50*	45.20±0.60	2.00±0.21*
	Control	Rosuvastatin	Control	Rosuvastatin
Open-field activity				
Latency to move (sec)	0.14±0.02	0.62±0.02*	0.20±0.46	0.65±0.03*
Squares crossed/5 min	128.50±0.09	87.50±2.03*	120.40±0.80	38.60±1.57*†
Rearing/5 min	24.30±0.58	4.80±0.42*	20.50±0.75	3.70±0.34*
Head pocking/5 min	24.00±0.79	7.00±0.39*	21.72±1.20	3.6±1.15*†
Negative geotaxis (sec)	1.40±0.16	50.70±0.99*	3.22±0.25	49.30±0.92*
Forced swimming				
Duration of initial swimming (min)	2.35±0.06	4.32±0.07*	2.31±0.52	4.83±0.09*
Duration of immobility (sec)	34.70±0.62	11.70±0.76*	29.57±0.85	4.30±0.47*

Values are mean ± SE of 10 mice/group.

*Significantly different from the respective control value, $p < 0.05$.

† Significantly different from the respective 14-day treatment value of the same statin, $p < 0.05$.

Blood and brain ChE activities

Plasma, erythrocyte and whole brain ChE activities were significantly reduced to various extents (26%-53%, 13%-48% and 24%-49%, respectively) following 14- and 28-day statin treatments in comparison with respective control values **(Table 2)**. Considering ChE inhibition values in the plasma, erythrocytes and the brain after the 28th day statin treatments, the most prominent effect was seen with atorvastatin (53%, 48%, 49%), followed by simvastatin (41%, 40%, 44%) and then rosuvastatin (32%, 31%, 36%), respectively **(Table 2**). Regression analyses of brain ChE activity vs. plasma ChE and erythrocyte ChE activities, using the individual animal data of control and statin treatment groups, revealed high level of correlation with r^2 values of 0.92 and 0.93, respectively **(Fig. 2)**. Similarly erythrocyte ChE activity highly correlated with that of the plasma with an r^2 value of 0.91.

Table 2: Plasma, erythrocyte and brain cholinesterase (ChE) activities in mice dosed orally with statins at 200 mg/kg of body weight/day for 14- or 28 consecutive days.

	14 days		28 days	
Plasma ChE activity				
Statin groups	ChE activity (U/mL)	% reduction from control	ChE activity (U/mL)	% reduction from control
Control	55.81±0.84	-	54.04±1.04	-
Atorvastatin	30.69±0.81*	45	25.18±0.65 *†	53
Simvastatin	36.65±0.47 *a	34	32.04±0.39 *a†	41
Rosuvastatin	41.42±0.34 *ab	26	36.51±0.42 *ab†	32
Erythrocyte ChE activity				
Statin groups	ChE activity (U/mL)	% reduction from control	ChE activity (U/mL)	% reduction from control
Control	77.57±0.76	-	77.70±0.54	-
Atorvastatin	52.36±0.53 *	33	40.66±0.81 *†	48
Simvastatin	59.70±0.62 *a	23	46.71±0.44 *a†	40
Rosuvastatin	64.65±0.95 *ab	13	53.47±0.66 *ab†	31
Brain ChE activity				
Statin groups	ChE activity (U/mg protein)	% reduction from control	ChE activity (U/m protein)	% reduction from control
Control	75.52±0.71	-	77.33±0.67	-
Atorvastatin	45.96±0.78 *	30	39.67±0.57 *†	49
Simvastatin	53.97±0.63 *a	40	43.12±0.80 *a†	44
Rosuvastatin	57.26±0.57 *ab	24	49.29±0.56 *ab†	36

Values are mean ± SE of 8 mice/group. The mice were sacrificed 24 hours after the last 14- or 28-day consecutive statin treatments.

*Significantly different from the respective control group, $p < 0.05$.

[a]Significantly different from the respective atorvastatin dose group, $p < 0.05$.

[b]Significantly different from the respective simvastatin dose group, $p < 0.05$.

†Significantly different from the respective 14-day treatment value of the same statin, $p < 0.05$.

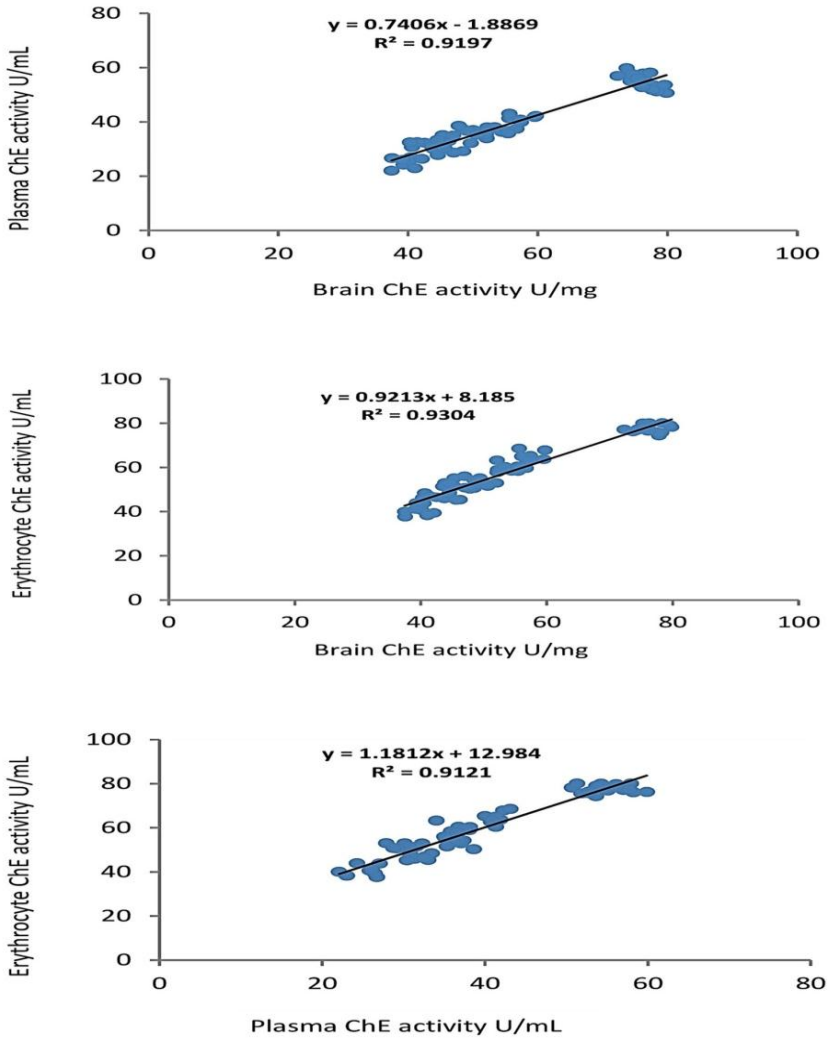

Fig. 2: Regression and correlation analyses of brain and blood cholinesterase (ChE) activities.

Cholesterol level

As a control measure of the pharmacological effects of the three statins, repetitive statin (atorvastatin, simvastatin, and rosuvastatin) treatments for 28 consecutive days significantly decreased plasma and brain cholesterol levels by 33% and 42%, 31% and 31%, and 12% and 14%, respectively in comparison with the respective control values **(Table 3)**. Atorvastatin had the most prominent effect among the statin treatment groups in reducing plasma and brain cholesterol levels, and rosuvastatin had the least effect.

Table 3: Plasma and brain cholesterol levels in mice dosed orally with statins at 200 mg/kg of body weight/day for 28 consecutive days.

Statin groups	Plasma cholesterol level (mg/100 mL)	% decrease from control	Brain cholesterol level (mg/g)	% decrease from control
Control	116.38±1.37	-	33.38±0.68	-
Atorvastatin	78.50±0.87*	33	19.50±0.57*	42
Simvastatin	80.50±0.96*[a]	31	23.00±0.53*[a]	31
Rosuvastatin	102.25±1.25*[ab]	12	28.63±0.38*[ab]	14

Values are mean ± SE of 8 mice/group. The mice were sacrificed 24 hours after the last 28-day consecutive statin treatments.

[*]Significantly different from the respective control group, $p < 0.05$.

[a]Significantly different from the respective atorvastatin dose group, $p < 0.05$.

[b]Significantly different from the respective simvastatin dose group, $p < 0.05$.

Discussion

The present study demonstrated adverse behavioral effects characterized by reduced open-field activity measures, head pocking and negative geotaxic performance following repeated statin ((atorvastatin, simvastatin, and rosuvastatin) treatments for 14 or consecutive 28 days in mice. These effects are in accordance with similar findings following single, but higher doses of the same statins in mice [11]. The repeated treatment regimens we applied in the present study were found in a recent report to be a cause for oxidative stress (increased malondialdehyde and reduced glutathione level) in the brain and plasma and probably with a liver injury in mice [10]. Considering the latter effects and our present findings of reduced brain and blood ChE activities we can deduce that relatively high doses of statins induce adverse effects in the mouse model which are characterized by behavioral abnormality coupled with neuronal changes at the cholinergic oxidant/antioxidant level. This could an initial step for developing an animal model (mice) for adverse statin intolerance. Furthermore, it was found that statin pretreatments predispose young chicks [23] and mice [24] to inadequate response to general anesthetics. Within this context, and in support of the notion of adverse effects (intolerance) of statins, several studies have documented neurochemical changes, behavioral alterations and shifts in oxidant/antioxidant balance at cellular and many organ levels in laboratory animals as well as clinically [4-7,10-13,23,30].

In the light of pleiotropic effects of statins, there are suggestions of possible beneficial effects of statin in cases of dementia [3,8,9]. Indeed, the present results of reduced brain ChE activity in mice as well as the results of others in rats [13,14,31], chicks [12] and mice [11,24] support such a beneficial outcome. To this end, further in depth studies are needed to explore effects of statin in dementia animal models. An additional beneficial effect of reduced brain ChE activity of statins, which correlated well with those of the plasma and erythrocytes in the present study, was the reported reductions in the toxicity outcome of centrally and peripherally acting ChE inhibiting insecticide carbaryl in chicks [23]. We have to, however, outweigh such a beneficial effect of statin-induced ChE inhibition and its possible interaction with antiChE insecticides, because of the oxidative stress-induced adverse effects of statins [10] and it was reported that oxidative stress produced by hydrogen peroxide might potentiate the toxicity of ChE inhibiting organophosphates in chicks [32] and dichlorvos in mice[24]. Considering the end effect on ChE activity after the 28th day statin treatment, the most effective statin in reducing blood and brain ChE activities was atorvastatin and the least effective one was rosuvastatin **(Table 2)**. This difference among the statins of the present study could be attributed to variations in pharmacokinetic, pharmacodynamics and pleiotropic profiles of statins [1-3,16]. Further studies are also needed to explore this avenue of statin interactive, but differential effects.

A word of caution is necessary herewith as the statin treatment regimens could cause liver injury, kidney damage, neuromuscular adverse effects, oxidative stress; as well as adverse psychiatric reactions 4-6,10,15,26,33. Statin-induced adverse effects and involvements of many organ systems could quite possibly predispose statin treated subjects to additional burdens of drug interaction and/or toxicity [34].

Interestingly we observed in the mice of the present study that statin treatments in contrast to the exploratory depressed activities (open-field and head pocking) produced prolongation of swimming endurance and reduced immobility response. This effect has been found in animal models (mice) of antidepressant drugs [35]. The benefit of this effect of statins awaits further studies, specially, in the light of suggestions of potential psychotropic effects of statins [22,36].

Conclusions

The data suggest and ascertain adverse behavioral effects of repeated statin treatments in mice. In accordance with potential pleiotropic effects of these statins, further studies are needed to explore in animal models, preferably the mice, values of anti-ChE action in the brain for dementia and swimming behavioral outcome for anti-depression.

Declarations

Authors' Contributions

RFA: Performed experiments in mice and conducted laboratory assays, literature search,

performed statistical analyses, and shared in drafting the manuscript. FKM: Conceptualized, designed and supervised the study; participated in the literature search, performed statistical analyses, and drafted the manuscript. Both authors have read, reviewed, and approved the final version of the manuscript for publication.

Ethical considerations

This research project was approved by the Departmental Scientific Committee on Research and Animal Care and Use and the Committee of Postgraduate Studies at the College of Veterinary Medicine, University of Mosul, Iraq. The Institutional Review Board approval was by College of Veterinary Medicine, University of Mosul (No. 2144, November 2, 2022) and the Presidency of the University of Mosul (No. 4S/29927, October 30, 2022). The use of mice as experimental animals in the presents study was according to the institutional regulations and ethics in compliance with guidelines of Animal Research: Reporting of In Vivo Experiments (ARRIVE) (https://www.nc3rs.org.uk/arrive-guidelines).

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التغييرات في أداء السلوك العصبي ونشاط إنزيم الكولين إستراز ومستوى الكولسيترول بالعلاج المتكرر لأدوية الإستاتينات في الفئران

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تتميز الإستاتينات الخافضة لدهون الدم بهامش أمان واسع، ولكن مع تأثيرات ضارة. كان الغرض من هذه الدراسة هو إجراء مزيد من الفحص والتأكد من آثار العلاج المتكرر لأتورفاستاتين وسيمفاستاتين وروسوفاستاتين على أداء السلوكي العصبي ونشاط إنزيم الكولين إستراز ومستوى الكوليسترول في الفئران. تم علاج ذكور الفئران السويسرية عن طريق الفم بكل من الإستاتينات بمعدل ٢٠٠ ملغم / كغم من وزن الجسم / يوم لمدة ١٤ و ٢٨ يومًا متتاليًا. عولجت الفئران الضابطة بالماء المقطر. بعد أربع وعشرين ساعة من آخر جرعة من العلاج المتكرر لمدة ١٤ أو ٢٨ يومًا، تم اختبار كل فأر للنشاط الحركي في الميدان المفتوح لمدة ٥ دقائق، وأداء الإمنحاء الأرضي السالب بزاوية ٤٥ درجة، وإدخال الرأس في الثقوب لمدة ٥ دقائق، والتحمل القسري للسباحة. تم قياس أنشطة إنزيم الكولين إستراز في البلازما وكريات الدم الحمر والدماغ الكلي، فضلا عن قياس مستويات الكوليسترول في البلازما والدماغ الكلي. أدت العلاجات باستخدام كل عقار إستاتين لمدة ١٤ و٢٨ يومًا متتاليًا إلى انخفاض ملحوظ في النشاط الحركي في المجال المفتوح وإدخال الرأس في الثقوب، وزيادة المدة اللازمة لإنجاز الإنتحاء الأرضي السالب والتحمل القسري للسباحة مع تقليل مدة عدم الحركة. تم تقليل أنشطة إنزيم الكولين إستراز في البلازما وكريات الدم الحمر والدماغ الكلي بشكل ملحوظ. وقد لوحظ التأثير الأبرز مع أتورفاستاتين. وكان معامل إرتباط نشاط إنزيم الكولين إستران في الدماغ عاليًا مع نشاطه في البلازما وكريات الدم الحمر. أدت الإستاتينات إلى خفض مستويات الكوليسترول في البلازما والدماغ بشكل ملحوظ. تؤكد النتائج وجود تأثيرات سلبية كولينية الفعل في السلوك العصبي والتأثير العصبي بعد علاجات الإستاتينات المتكررة في الفئران. وبالنظر إلى التأثيرات غير العلاجية المحتملة، هناك حاجة إلى مزيد من الدراسات الدوائية لاستكشاف قيم وأهمية هذه التغييرات.