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Statins modify the response of chicks to challenges with xylazine-ketamine and carbaryl

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ABSTRACT

Statins are known to affect brain function in a manner not related to their dyslipidemic effects. The purpose of the present study was to assess the behavioral response of a chick model (7-14 days old) after single treatments with the statins atorvastatin, fluvastatin or simvastatin at 100 mg/kg, orally, to a pharmacological challenge with an anesthetic regimen of xylazine (5 mg/kg)-ketamine (20 mg/kg), intramuscularly, and a toxicological challenge with the reversible cholinesterase inhibiting insecticide carbaryl (250 mg/kg, orally). Only simvastatin significantly reduced the duration of xylazine-ketamine anesthesia by 47%. Carbaryl at 250 mg/kg, orally induced signs of cholinergic poisoning (57.1 - 100%) in chicks within 3.14 min, and 57.1% death occurred within 85 min. Toxicological challenge of statin-treated chicks with carbaryl also induced signs of cholinergic poisoning, but with varying percentages of reductions compared to the control (carbaryl) group. The reductions in 4 h carbaryl-induced lethality in chicks pre-treated with atorvastatin, fluvastatin and simvastatin were 43, 57 and 29%, respectively, below that of the control value. Correspondingly, their toxicity scores decreased by 18, 18 and 11%, respectively. These data suggest that statins might modulate the functional status of the brain in a manner that affects the impact of centrally acting drugs or toxicants, and hence the behavioral outcomes in chicks. Further studies are warranted on the behavioral effects of statins after prolonged therapy.

Key words: anesthesia; carbamate; cholinesterase; dyslipidemia; statin

Introduction

Statins are used to treat dyslipidemias which are risk factors for the occurrence of atherosclerosis and coronary heart diseases (CLIMENT et al., 2021; FAN et al., 2021). The hypolipidemic effects of statins are mediated through inhibition of the hydroxyl-methyl-glutaryl-CoA reductase (BUTTERFIELD et al., 2011; SIRTORI, 2014). However, statins vary widely in their pharmacokinetics, pharmacodynamics and pleiotropic properties (BOCAN, 2002; BUTTERFIELD et al., 2011; SIRTORI, 2014). Most statins pass the blood brain barrier and thus

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exert central nervous system (CNS) effects not related to their main therapeutic application to lower hyperlipidemia (HAI-NA et al., 2020; DE GIORGI et al., 2021). Several reports have indicated that statins reduce the oxidative stress status, affect the pathophysiology of dementia, and modulate the activity of brain cholinesterase (ChE) activity (SPARKS et al., 2006; MOZAYAN and LEE, 2007; ROENSCH et al., 2007; SHARMA et al., 2008; CIBIČKOVÁ et al., 2007, 2009; GHODKE et al., 2012; SHINOHARA et al., 2014). These neuronal effects of statins appear to be differential depending on the type of the statin, the dosages used and the duration of the therapy (SIRTORI, 2014; LEPPIEN et al., 2018). It is also speculated that statins may beneficially affect the outcome of Alzheimer's disease through modulation of central cholinergic pathways (SMALL 2005; SPARKS et al., 2006; MOZAYAN and LEE, 2007; ROENSCH et al., 2007; KANDIAH and FELDMAN, 2009; MCGUINNESS et al., 2016; SHARMA, 2019; VECCHIO et al., 2021). Several studies have also reported that statins may cause some behavioral effects (e.g. aggression) in patients on hypolipidemic therapy following changes in neuronal functions initiated by decreased cholesterol levels in the brain (TATLEY and SAVAGE, 2007; LEPPIEN et al., 2018). They might affect brain function in a manner not related to cholesterol biosynthesis and metabolism (LAUFS and LIAO, 2003; RAHOLA, 2012). In rats, brain-penetrating statins reduce the risk of relapse to cocaine addiction (CHAUVET et al., 2016), in mice they were reported to affect memory function (GHODKE et al., 2012), whereas oral administration of atorvastatin at 10 or 20 mg/kg for 3 weeks in mice ameliorated diabetic-induced depressive behaviors (HAI-NA et al., 2020). Others suggested a promising role for statins in the treatment of depression (DE GIORGI et al., 2021). Further, in an experimental model of young chicks (7-14 days old), statins were reported to differentially modulate ChE activity in the brain, raising the possibility of modulation of functional aspects of the brain (RASHEED, 2009).

The behavioral outcomes of statin therapeutic manipulations are not known in chicks. The purpose of the present study was to assess the behavioral response of chicks, after statin treatments with atorvastatin, fluvastatin or simvastatin at 100 mg/kg, to a pharmacological challenge with an anesthetic regimen of xylazine-ketamine and a toxicological challenge with the reversible ChE inhibiting insecticide carbaryl. Xylazine-ketamine anesthesia (MOHAMMAD and FARIS, 2006) and carbaryl toxicity (BRIFKANI, 2009) have been reported in young chicks. Pharmacological and toxicological challenges have been applied to uncover the rather subtle effects of drugs that are not usually apparent unless a stressful condition in the form of such challenges is imposed on laboratory animals (VORHEES et al., 1994; FRANKEL et al., 2007; CHIANG et al., 2010). The young chick model (7-14 days old) used in the present study, has been found to be suitable in the behavioral assessment of various pharmacological and toxicological manipulations (MOHAMMAD et al., 2012; AL-ZUBAIDY, 2021).

Materials and methods

Animals. Cobb broiler chicks of both sexes were obtained at the age of one day from a local hatchery in Duhok, Iraq. They were housed in batches of 20-30 chicks at a temperature of 25-30 ºC with 24 h lighting and wood shavings as floor litter. The supply of water and feed were *ad libitum*. Experiments were conducted on 76 chicks (body weight 75-120 g) when their ages were between 7-14 days. We obtained official approval for the study protocol from the Committee of Postgraduate Studies at the College of Medicine, University of Duhok, Iraq, according to the institutional regulations on humane animal handling and use in research.

Experimental protocol. Fig. 1 outlines the experimental protocol and allocation of chicks to different treatment regimens. The statins and their suppliers (manufacturers) were as follows: atorvastatin (Kolestor, Eczacibasi Co., Turkey), fluvastatin (Lescol, Novartis, Switzerland) and simvastatin (Alpharma, U.K.). Each statin was prepared freshly as a suspension in distilled water and dosed orally by a gavage needle in a volume of 10 ml/kg of body weight. The chicks were

dosed orally with single doses of statins (active ingredient) at 100 mg/kg of body weight. The choice of the statin dose was based on preliminary experiments in chicks which did not produce overt signs of toxicosis (RASHEED, 2009).

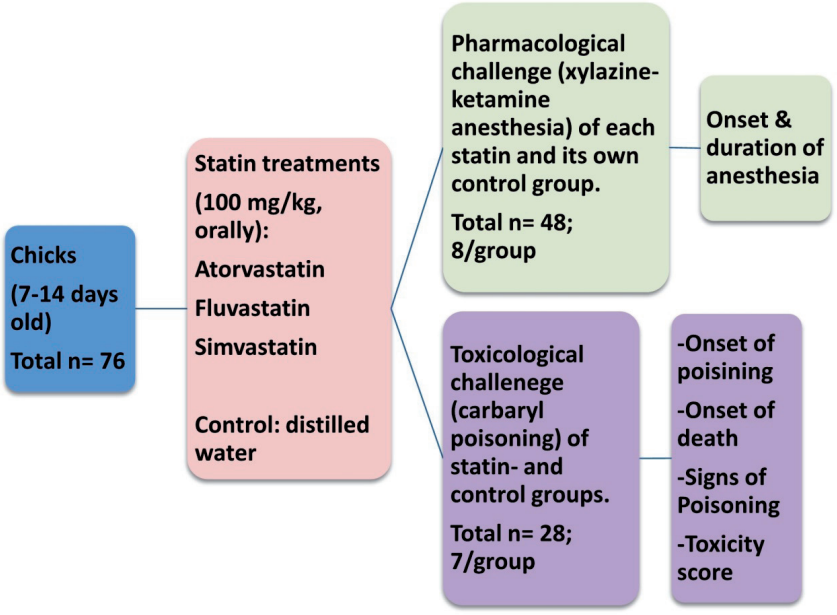

Fig. 1. The integrated experimental design of the study and allocation of young chicks treated with statins to pharmacological and toxicological challenges

Pharmacological challenge. Two hours after the administration of distilled water (control) or statins, each chick (8/treatment group) was injected intramuscularly (i.m.) with the anesthetic mixture of xylazine (5 mg/kg)-ketamine (20 mg/kg) as the pharmacological challenge reported earlier (MOHAMMAD and FARIS, 2006). The latencies to onset of loss of righting reflex after placing the chick on their lateral side (sleep) and the duration of sleep were recorded.

Toxicological challenge. For the toxicological challenge, chicks (7/treatment group) were dosed orally with distilled water (control) or with each of the statins at 100 mg/kg. Two hours thereafter, the chicks were dosed orally with the carbamate insecticide carbaryl (85%, Ferasin 85wp, Fertil, Turkey) at 250 mg-active ingredient/5 ml distilled water/kg, which had been predetermined to be toxic in chicks (BRIFKANI, 2009). After the carbaryl dosing, each chick was observed within 4 h for the occurrence of signs of acute cholinergic poisoning (salivation, lacrimation, gasping, frequent defecation, tremor and convulsions), and any delay in the onset of signs of acute poisoning, as well as any 4- and 24 h deaths were recorded (MOHAMMAD et al., 2012). The severity of carbaryl-induced poisoning was assessed by calculating the total toxicity score from the grades (1-4) assigned to the percentage of occurrence of signs of cholinergic poisoning, as well as 4- and 24 h lethalities as described earlier (MOHAMMAD et al., 2012). Briefly, the distinct signs of cholinergic poisoning mentioned above and the 4- and 24 h lethalities were graded as follows: 1 (1-25%), 2 (26-50%), 3 (51-75%) and 4 (>75%). The highest toxicity score would be 8X4= 32 in a group, when all the signs of poisoning and death occurred in the chicks.

Statistics. The statistical software package SPSS (IBM) was used for statistical analysis of the data. Parametric data were analyzed by one way analysis of variance followed by the least significant difference test, whereas frequency data were analyzed by the one-tailed Fisher's exact probability test, and the scores of the severity of poisoning were analyzed by the Wilcoxon signed rank test (RUNYON, 1977; PETRIE and WATSON, 2013). The level of statistical significance was at $P<0.05$.

Results

Pharmacological challenge. The results of xylazine-ketamine anesthesia (onset and duration of sleep) are presented in Table 1. Among the three statins, only simvastatin significantly reduced the duration of xylazine-ketamine sleep by 47%, in comparison with the respective control value (Table 1). However, none of the statins significantly affected the onset of anesthesia (Table 1). Furthermore, the anesthetic parameters (the onset and duration of anesthesia) were not significantly different among the control groups (Table 1).

Table 1. Xylazine (5 mg/kg)-ketamine (20 mg/kg) intramuscular anesthesia 2 h after the oral dosing of chicks with statins (100 mg/kg)

Statin treatment	Latency to onset of sleep (min)	Duration of sleep (min)
Control (distilled water)	1.4 ± 0.15	45.0 ± 3.0
Atorvastatin	1.7 ± 0.20	52.0 ± 6.0
Control (distilled water)	1.9 ± 0.20	54.0 ± 4.0
Fluvastatin	1.9 ± 0.12	58.0 ± 5.0
Control (distilled water)	1.7 ± 0.33	47.0 ± 9.0
Simvastatin	1.6 ± 0.24	25.0 ± 6.0*

Values are mean ± SE of eight chicks/group.
*Significantly different from the respective control value, $P<0.05$.

Toxicological challenge. Table 2 depicts carbaryl (250 mg/kg, orally)-induced cholinergic poisoning in the control and statin treated groups. Carbaryl induced signs of cholinergic poisoning in control chicks within 3.14 min, which consisted of salivation, lacrimation, gasping, frequent defecation, tremor and convulsions (57.1-100%); the chicks succumbed to death (57.1%) within 85 min (Table 2). Carbaryl toxicological challenge of statin-treated chicks also induced signs of cholinergic poisoning, but with varying percentages of reductions in occurrence compared to those of the control group (Table 2). The reductions in 4 h carbaryl-induced lethality in chicks pre-treated with atorvastatin, fluvastatin and simvastatin were 43, 57 and 29% below that of the control value (57.1%), respectively (Table 2). The reduction of lethality in the fluvastatin group was significant at $P<0.05$. Further, the reductions in the 24 h lethality of the statin pre-treated chicks were 29, 29 and 14%, respectively (Table 2). Correspondingly, in relation to the scoring of the occurrence of signs of poisoning and the 4- and 24 h lethalities (grades of 1-4), the total toxicity score of carbaryl in the three statin groups decreased by 18, 18 and 11%, respectively, in comparison with that of the control group (Table 2).

Table 2. Carbaryl (250 mg/kg, orally) poisoning 2 h after the oral dosing of chicks with statins (100 mg/kg)

Variable	Control	Atorvastatin	Fluvastatin	Simvastatin
Latency to onset of signs of poisoning (min)	3.14 ± 0.50	2.28 ± 0.35	2.42 ± 0.20	1.42 ± 0.20
Latency to onset of death in 4 h (min)	85 ± 18	82[†]	No death	105 ± 15
% occurrence of signs of poisoning				
Salivation	85.7	85.7	85.7	85.7
Lacrimation	71.4	85.7	85.7	85.7
Gasping	100	100	100	100
Frequent defecation	100	100	100	100
Tremor	85.7	28.6	71.4	71.4
Convulsions	57.1	28.6	42.9	42.9
4 h death (%)	57.1	14.3	0[*]	28.6
24 h death (%)	57.1	28.6	28.6	42.9
Total toxicity score (maximum 32)	28	23	23	25

Latency values are mean ± SE, n= seven chicks per group.
[†]Measurement for one chick (no statistical analysis).
[*]Significantly different from the corresponding control value, $P<0.05$.

Discussion

Pharmacological and toxicological challenges of laboratory animals treated with drugs or toxicants are biological tools used to uncover the supposed subtle effects of treatments that might be seen only after stressful conditions induced by such challenges (VORHEES et al., 1994; FRANKEL et al., 2007; CHIANG et al., 2010). The drug or toxicant-induced challenges in question may be depressants or stimulants (VORHEES et al., 1994). In the present study, we used two different types of challenges, a pharmacological challenge with xylazine-ketamine anesthesia, and a toxicological one with carbaryl. The mechanisms of action of these drugs differ from each other. Xylazine is mainly a central alpha-2 adrenergic agonist causing a decrease in catecholamine release (GREENE and THURMON, 1988), whereas ketamine antagonizes NMDA receptors in the brain (PELTONIEMI et al., 2016). On the other hand, carbaryl is a reversible ChE inhibitor which produces signs of poisoning characterized by a toxidrome of nicotinic, muscarinic and CNS effects (GUPTA and DOSS, 2022). Both of the challenges used in the present study revealed differential effects in the chicks treated with statins. The first challenge (xylazine-ketamine) revealed a shortening of the duration of anesthesia in chicks pretreated with simvastatin, whereas in the second one (carbaryl) there were noticeable reductions in carbaryl-induced toxidrome in chicks pretreated with statins, especially those treated with atorvastatin and fluvastatin, which manifested 18% reductions in their total toxicity scores (Table 2).

Statins were reported to modulate several behavioral outcomes in patients and laboratory animals such as memory function, aggression, depression and addiction (LAUFS and LIAO, 2003; TATLEY and SAVAGE, 2007; GHODKE et al., 2012; RAHOLA, 2012; CHAUVET et al., 2016; LEPPIEN et al., 2018; HAI-NA et al., 2020). Furthermore, statins were reported to affect

differentially brain and plasma ChE activities in laboratory animals and plasma ChE activity in patients (ROENSCH et al., 2007; SHARMA et al., 2008; CIBIČKOVÁ et al., 2007, 2009; SHINOHARA et al., 2014). In chicks, it was found that statin treatments (atorvastatin, fluvastatin and simvastatin) inhibited plasma and brain ChE activities in vitro, whereas simvastatin inhibited brain ChE activity in vivo (RASHEED, 2009). In the context of the studies cited above, the findings of the present study, which is one of the same type reported using the 7-14 day-old chick model, suggest that statins, apart from their lipid lowering effects, might modulate the functional status of the brain in a manner that affects the impact of CNS drugs and toxicants, and hence possibly the behavioral outcome.

Conclusions

In conclusion, the present findings of pharmacological and toxicological challenges, reported for the first time, further extend and ascertain the notion that statins might modulate behavior in a differential manner. Further, studies are warranted on the CNS functional and behavioral effects of various statins after prolonged therapy.

Conflicts of Interests

The authors declare that they have no competing interests.

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SAŽETAK

Poznato je da statini utječu na moždanu funkciju na način koji nije povezan s dislipidemijskim učincima. Svrha ovog istraživanja bila je procijeniti bihevioralni odgovor pilića (starih 7 - 14 dana) nakon liječenja statinima atorvastatinom, fluvastatinom i simvastatinom u dozi od 100 mg/kg, peroralno. Za procjenu su korištena 2 testa: farmakološki test primijenjen s kombinacijom anestetika ksilazina (5 mg/kg) i ketamina (20 mg/kg), apliciranih intramuskularno, i toksikološki test s reverzibilnim inhibitorom kolinesteraze, insekticidom karbarilom (250 mg/kg, peroralno). Samo je simvastatin znakovito skratio trajanje anestezije inducirane ksilazin-ketaminom za 47 %. Karbaril u dozi od 250 mg/kg, primijenjen peroralno, izazvao je znakove kolinergičkog otrovanja (57,1 – 100%) u pilića unutar 3,14 minuta i smrt u 57,1% pilića unutar 85 minuta. Toksikološki test s karbarilom u pilića liječenih statinima također je izazvao znakove kolinergičkog otrovanja, ali s različitim postocima smanjenja u usporedbi s kontrolnom (karbaril) skupinom. Smanjenje smrtnosti uzrokovane karbarilom unutar četiri sata u odnosu na kontrolnu skupinu iznosilo je 43% u pilića liječenih atorvastatinom, 57% u pilića liječenih fluvastatinom i 29% u pilića liječenih simvastatinom. Sukladno tome, toksičnost je smanjena za 18%, 18% i 11%. Ovi podaci upućuju na to da statini mogu modulirati funkcionalno stanje mozga utječući na učinak lijekova koji djeluju centralno ili toksikanata, te time i na ponašanje pilića. Potrebna su daljnja istraživanja učinaka statina na bihevioralni odgovor pilića nakon produljene terapije.

Ključne riječi: anestezija; karbamat; kolinesteraza; dislipidemija; statin