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The effects of simvastatin and fenofibrate on malondialdehyde and reduced glutathione concentrations in the plasma, liver, and brain of normolipidaemic and hyperlipidaemic rats

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The objective of study was to investigate the effects of different doses of simvastatin and fenofibrate on malondialdehyde (MDA) and reduced glutathione (GSH) in the plasma, liver, and brain tissue of male normolipidaemic and hyperlipidaemic rats. Normolipidaemic (Wistar) rats were receiving 10 or 50 mg/kg a day of simvastatin or 30 or 50 mg/kg a day of fenofibrate. Hyperlipidaemic (Zucker) rats were receiving 50 mg/kg/day of simvastatin or 30 mg/kg/day of fenofibrate. Control normolipidaemic and hyperlipidaemic rats were receiving saline. Simvastatin, fenofibrate, and saline were administered by gavage for three weeks. In normolipidaemic rats simvastatin and fenofibrate showed similar and dose-independent effects on plasma and brain MDA and GSH concentrations. Generally, plasma and brain MDA decreased, while brain GSH concentration increased. In hyperlipidaemic rats simvastatin did not affect plasma and brain MDA and GSH concentrations but significantly decreased liver GSH. Fenofibrate decreased plasma and liver MDA but increased brain MDA. In both rat strains fenofibrate significantly decreased liver GSH concentrations, most likely because fenofibrate metabolites bind to GSH. Our findings suggest that simvastatin acts as an antioxidant only in normolipidaemic rats, whereas fenofibrate acts as an antioxidant in both rat strains.

KEY WORDS: lipid peroxidation; lipid-lowering drugs; oxidative stress; Wistar rats; Zucker rats

Statins are usually used to treat patients with elevated cholesterol to prevent cardiovascular diseases (1, 2) and fibrates to treat patients with elevated triglyceride. Regardless of their antilipid effects, both groups of drugs have additional pleiotropic effects such as anti-inflammatory, antiplatelet, improved glucose tolerance, reduced vascular smooth muscle inflammation, and lower plasma fibrinogen (3–6). There are adverse effects too. Statin side effects include muscle pain and damage, liver damage, increased blood sugar, or type 2 diabetes (7). Additionally, according to Okuyama et al. (8), statins may stimulate atherogenesis by suppressing vitamin K2 synthesis and cause heart failure by depleting the myocardium of coenzyme Q10. Fibrates can also cause side effects such as high liver enzymes and serum creatinine, myopathy, and less commonly rhabdomyolysis. These side effects can be serious if fibrates are co-administered with statins (4).

Many of these positive and negative pleiotropic effects are mediated by the interaction of statins and fibrates with peroxisome proliferator-activated receptors (PPARs), especially PPAR-α (9, 10). PPAR-α receptors are expressed in the brain, heart, liver muscle, and other organs and play a significant role in oxidative stress, energy homeostasis, mitochondrial fatty acid metabolism, and inflammation (11). According to new data, PPAR-α receptors in the brain are important for statins and fibrates to act as neuroprotectors and treat various neurodegenerative disorders, such as multiple sclerosis, stroke, and Parkinson's and Alzheimer's disease (12–15). Animal studies have also shown neuroprotective effects of fenofibrate alone or in combination with simvastatin in animals with traumatic brain injury (16, 17).

Both antilipid drugs also affect two important parameters of oxidative stress, namely malondialdehyde (MDA) and reduced glutathione (GSH) (18, 19). GSH is synthesised in the liver but also in the brain, where it plays an important role maintaining the homeostasis of cell functions (19, 20). However, studies of the effects of simvastatin and fenofibrate on MDA and GSH report

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inconsistent findings. Macan et al. (21) and Mohamadin et al. (22) reported that simvastatin reduced MDA concentrations in normolipidaemic and diabetic rats, whereas Zeng and Liu (23) reported a prooxidative effect of atorvastatin. Fenofibrate, in turn, was reported to significantly reduce plasma MDA in rats (24), whereas gemfibrozil was reported to increase it significantly in the plasma, liver, and kidney in Wistar and Fisher rats (25). Ciriolo et al. (26, 27) reported that clofibrate or fenofibrate caused lipid peroxidation in rat liver homogenates.

As far as reduced glutathione is concerned, simvastatin has been reported to significantly deplete its cellular reservoirs and to increase the levels of its oxidised form (28, 29), whereas fenofibrate has been reported to increase GSH in experimental animals with diabetic nephropathy (30).

In view of these inconsistent reports of preclinical and clinical studies about simvastatin and fenofibrate effects on MDA and GSH, we decided to investigate how two different doses of simvastatin and fenofibrate would affect plasma, liver, and brain MDA and GSH concentrations in normolipidaemic rats and if the effects would be dose-dependent. We also wanted to see if the same doses of simvastatin or fenofibrate would have the same or comparable effects in normolipidaemic and hyperlipidaemic rats.

MATERIAL AND METHODS

Test substances and dose selection

Simvastatin and fenofibrate were chosen for this investigation, because both agents cross the blood-brain barrier (31, 32). Simvastatin (CAS-79902-63-9) (Lipex®, Merck Sharp & Dohme, Haarlem, The Netherlands) (simvastatin) and fenofibrate (CAS-49562-28-9) (Tricor®, Recipharm Fontaine, Fontaine-lès-Dijon, France) (fenofibrate) tablets were suspended in 5 mL/kg saline and administered daily (at 9.00–10.00 a.m.) by gavage. Our choice of fenofibrate doses of 30 and 50 mg/kg/day and of simvastatin doses of 10 and 50 mg/kg/day is based on literature data (33–36) from different experiments on rats.

Treatment of animals

This study included male 10-week-old normolipidaemic (N=72) and hyperlipidaemic rats (N=21). The normolipidaemic rats were the Wistar strain and weighed 250–300 g (University of Zagreb School of Medicine, Department of Pharmacology, Zagreb, Croatia). The hyperlipidaemic rats were the HsdOla: Zucker-Lepr fa-fa strain (Harlan Laboratories srl, Udine, Italy) and weighed 270–300 g. The animals were kept in macrolone cages at controlled room temperature (22 °C) and 12:12 h day/night cycles and had free access to standard pellet diet. Animal handling and treatment followed the national (37) and European (38) guidelines and recommendations for the use of laboratory animals. The experiments were approved by the ethics committee of the University of Zagreb School of Medicine (approval No. 380-59-10106-23-111/33).

The experiment lasted 21 days (3 weeks). Normolipidaemic rats were randomly divided into four experimental (N=10) and four control groups (N=8). The first experimental group was receiving simvastatin 10 mg/kg/day and the second simvastatin 50 mg/kg/day. The third experimental group was receiving fenofibrate 30 mg/kg/day and the fourth fenofibrate 50 mg/kg/day. Corresponding control groups were given saline (0.9 % NaCl solution) 5 mL/kg b.w. daily by gavage.

Hyperlipidaemic Zucker rats were divided in two experimental and one control group. The first experimental group (N=7) was receiving simvastatin 50 mg/kg/day and the second (N=8) fenofibrate 30 mg/kg/day. The control group (N=6) was receiving saline as described above.

On day 22 of the study, after an overnight fast of 12 h, all rats were sacrificed under diethyl ether anaesthesia. Blood samples were taken by cardiac puncture and frozen at -20 °C immediately after sampling. Liver and brain tissues were also taken immediately after sacrifice. Liver was rinsed with saline *in situ* via the superior vena cava to remove blood. The brain was also rinsed with saline. The whole brain and a part of the liver were homogenised in saline in the 1:4 ratio and centrifuged at 3500 *g* for 20 min. The separated supernatants were frozen at -80 °C.

Measurement of malondialdehyde in plasma

The samples were prepared by pipetting 100 μL of plasma and 500 μL of precipitation reagent into labelled, light-protected vials, which were vortexed and then centrifuged at 8125 *g* for 5 min. The obtained supernatant (500 μL) was then transferred to a labelled derivatisation vial and added 100 μL of derivatisation reagent. The vials were capped, briefly vortexed, and incubated at 95 °C for 60 min. Followed abrupt cooling under a stream of cold water, and then we added 500 μL of neutralisation buffer to the cooled mixture and injected 20 μL of the prepared sample into the column.

Plasma MDA concentrations were determined with a high performance liquid chromatograph (HPLC) (Nexera, Shimadzu Corporation, Kyoto, Japan) using a commercially available kit (Cat. No. 67000, Chromsystems Instruments and Chemicals GmbH, Gräfelfing, Germany), according to the manufacturer's instructions. Sample preparation was based on protein precipitation followed by derivatisation. The HPLC system consisted of a fluorescent detector (RF-20AXS), isocratic pump (LC-20ADXR), column thermostat (CTO-20A), autoinjector (SIL-30AC), degasser (DGU-20A5), and control unit (CBM-20A). Chromatographic conditions were as follows: isocratic mobile phase flow 1.0 mL/min; pressure ~125 bar; wavelength 515 nm (excitation) and 553 nm (emission); column temperature 25 °C; analysis time 5 min; injection volume 20 μL.

Data from the detector were collected and processed with the Shimadzu LabSolutions software, and the measured plasma MDA concentrations are expressed in micromoles per litre (μmol/L).

Measurement of malondialdehyde in the liver and brain

Brain and liver tissue MDA concentrations were measured using a modified method described by Drury et al. (39), which is based on MDA binding to 2-thiobarbituric acid (TBA) to form a pink compound that absorbs light at the wavelength of 538 nm. For the standard calibration curve we used 1,1,3,3-tetraethoxy propane. Further oxidation was prevented by adding butylated hydroxytoluene (BHT).

The sample solution contained 50 μL of the brain or liver tissue supernatant, 5 μL of BHT (0.2 %, w/v), 750 μL of phosphoric acid (1 %, v/v), 250 μL of TBA (0.6 %, w/v), and 445 μL of ultrapure water (18 MΩ; obtained from a Thermo Scientific Smart2Pure 3 UV/UF water purification system, Thermo Fisher Scientific Inc., Waltham, MA, USA). We stirred it and incubated in a boiling water bath for 30 min, then stopped the reaction by cooling in water, and then injected 20 μL of the prepared solution into a HPLC consisting of a degasser, isocratic pump, thermostated column space, and UV detector (LC-20AD, Shimadzu). The pre-column and analytical column were C-18 reverse phases (LiChrospher, Merck, Darmstadt, Germany) with 5 μm particles. The dimensions of the pre-column were 4.0 × 4.0, and of the columns 4.0 x 125.0 mm.

Mobile phase consisted of 50 mmol/L KH_2PO_4 and methanol (60:40, v/v, pH 6.8). The flow rate was 1 mL/min. MDA was measured with a UV detector at 532 nm and column temperature was 32 °C. Under these conditions, the MDA retention time was 2.5 min. Its brain and liver tissue concentrations are expressed as micromoles per litre (μmol/L).

Measurement of reduced glutathione in plasma, liver, and brain

Rat plasma, brain, and liver GSH concentrations were measured according to the Ellman's spectrophotometric method (40), which is based on glutathione (thiol) coupling with 5,5'-dithiobis-(2-nitrobenzoic acid) (DTNB). In this rapid reaction, a disulphide bond is cleaved to form 2-nitro-5-thiobenzoate (NTB), which is ionised to NTB^{2-} and whose yellow colour is read at 412 nm. We added 100 μL of trichloroacetic acid (TCA, 5 % solution) to 300 μL of supernatant and first stirred the mixture with a shaker and then centrifuged it at 10,000 *g* for 10 min. Reaction mixtures consisted of 850 μL of phosphate buffer and 50 μL of DTNB added to100 μL H_2O for the blank sample or to 100 μL standards for standard samples or to 100 μL of tissue or plasma supernatant and were measured at 412 nm using a Cecil 9000 spectrophotometer (Cecil Instruments Limited, Cambridge, UK). All measurements were done in triplicate. The concentration of GSH was calculated from the calibration diagram and is expressed as micrograms per millilitre (μg/mL).

Statistical analysis

All data were analysed with the GraphPAD Prism software, version 6 (GraphPAD Software, San Diego, CA, USA). For normolipidaemic rats, the results are shown as arithmetic means ± standard deviations ($\bar{x}\pm SD$) and p-values. For hyperlipidaemic rats the results are shown as arithmetic means ± standard deviations and p-values of Dunnett's multiple comparison test, which is considered optimal for comparison of different drug doses with a single control group. All applied tests were two-way. P values of less than 0.05 are considered statistically significant (41).

RESULTS

MDA and GSH concentrations in normolipidaemic rats after simvastatin treatment

Table 1 shows MDA and GSH concentrations in the plasma, liver, and brain of normolipidaemic rats receiving either of the two simvastatin doses. Compared to control, only the higher dose (50 mg/kg/day) significantly lowered MDA concentrations (20 %; p=0.044) in the plasma, neither dose lowered it significantly in the liver, and only the lower dose (10 mg/kg/day) decreased it significantly in the brain 59 % (p<0.001).

GSH concentrations increased significantly (63 %; p=0.002) only in the liver of rats receiving the lower simvastatin dose (10 mg/kg/day).

MDA and GSH concentrations in normolipidaemic rats after fenofibrate treatment

Table 2 shows MDA and GSH concentrations in the plasma, liver, and brain of normolipidaemic rats receiving either fenofibrate dose (30 or 50 mg/kg/day). Both significantly lowered MDA concentrations in the plasma [39 % (p=0.017) and 42 % (p<0.001), respectively], but neither changed them significantly in the liver or brain.

The higher fenofibrate dose significantly increased plasma GSH (31 %; p=0.03), and both doses significantly lowered it in the liver [54 % (p=0.013) and 60 % (p<0.001), respectively]. Neither dose significantly affected brain GSH concentrations.

MDA and GSH concentrations in hyperlipidaemic rats after simvastatin and fenofibrate treatment

Table 3 shows plasma, liver, and brain MDA and GSH concentrations in hyperlipidaemic rats receiving either the higher simvastatin (50 mg/kg/day) or lower fenofibrate dose (30 mg/kg/day). Compared to control, simvastatin did not significantly affect MDA concentrations in any of the organs, but fenofibrate significantly lowered them in the plasma (33 %; p=0.009) and

Table 1 The effects of simvastatin (10 mg/kg and 50 mg/kg daily for 3 weeks) on MDA and GSH levels in the plasma, liver, and brain of normolipidaemic rats

Variable	Source	Control[a]	Simvastatin[a] (10 mg/kg/day)	P value[b] (95 % CI)[c]	Control[a]	Simvastatin[a] (50 mg/kg/day)	P value[b] (95 % CI)[c]
MDA (μmol/L)	Plasma	0.26±0.051 (n=8)	0.24±0.046 (n=8)	0.471 (-0.05–0.08)	0.30±0.236 (n=7)	0.24±0.036 (n=6)	**0.044** (-0.14–0.06)
	Liver	105.2±15.12 (n=6)	92.3±19.26 (n=10)	0.166 (-33.31–6.32)	103.6±17.94 (n=8)	104.8±22.54 (n=8)	0.909 (-20.65–23.04)
	Brain	2.67±0.204 (n=8)	1.11±0.231 (n=10)	**<0.001** (-1.77–1.33)	2.28±0.508 (n=8)	1.80±0.218 (n=6)	0.050 (-0.97–0.01)
GSH (μg/mL)	Plasma	57.3±17.68 (n=6)	47.4±15.81 (n=9)	0.324 (-30.81–10.96)	51.0±17.68 (n=8)	47.7±26.80 (n=7)	0.778 (-28.32–21.61)
	Liver	133.5±21.24 (n=6)	218.1±43.03 (n=5)	**0.002** (39.80–129.6)	229.0±36.05 (n=6)	258.0±135.2 (n=6)	0.623 (-96.57–43.02)
	Brain	17.2±4.61 (n=8)	22.1±9.08 (n=10)	0.179 (-2.52–12.47)	20.2±4.23 (n=8)	23.6±5.01 (n=9)	0.152 (-1.41–8.24)

GSH – reduced glutathione; MDA – malondialdehyde. Bold P values are significant at the <0.05 level. [a] mean ± SD. [b] P value of independent two-sample *t*-test. [c] 95 % confidence interval for difference between means

Table 2 The effects of fenofibrate (30 mg/kg and 50 mg/kg daily for 3 weeks) on MDA and GSH levels in the plasma, liver, and brain of normolipidaemic rats

Variable	Source	Control[a]	Fenofibrate[a] (30 mg/kg/day)	P value[b] (95 % CI)[c]	Control[a]	Fenofibrate[a] (50 mg/kg/day)	P value[b] (95 % CI)[c]
MDA (μmol/L)	Plasma	0.33±0.127 (n=5)	0.20±0.033 (n=8)	**0.017** (-0.23–0.03)	0.31±0.048 (n=8)	0.18±0.022 (n=8)	**<0.001** (-0.17–0.08)
	Liver	62.2±14.43 (n=7)	62.4±15.37 (n=10)	0.971 (-34.18–14.22)	85.0±10.70 (n=8)	71.1±11.95 (n=8)	0.188 (-23.18–7.57)
	Brain	3.51±0.596 (n=8)	3.30±0.40 (n=10)	0.404 (-0.69–0.29)	2.89±1.018 (n=8)	2.20±0.13 (n=7)	0.120 (-1.30–0.09)
GSH (μg/mL)	Plasma	69.6±20.85 (n=5)	76.5±15.63 (n=4)	0.602 (-22.93–36.68)	70.4±12.23 (n=6)	92.4±18.32 (n=7)	**0.030** (2.60–41.41)
	Liver	71.8±36.16 (n=8)	33.3±17.71 (n=9)	**0.013** (-67.33–9.57)	72.6±16.31 (n=6)	29.2±10.27 (n=10)	**<0.001** (-57.51–29.24)
	Brain	16.7±2.54 (n=7)	15.2±3.54 (n=9)	0.349 (-4.95–1.87)	20.6±5.58 (n=8)	23.5±2.57 (n=10)	0.169 (-1.34–7.03)

GSH – reduced glutathione; MDA – malondialdehyde. Bold P values are significant at the <0.05 level.[a] mean ± SD. [b] P value of independent two-sample *t*-test. [c] 95 % confidence interval for difference between means

increased them in the brain (39 %; p=0.032). It did not change MDA concentrations in the liver.

As for GSH concentrations, both drugs had a significant (lowering) effect only in the liver (45 % and 80 % vs control, respectively).

DISCUSSION

Our results show that the effects of simvastatin on either MDA or GSH concentrations are dose-independent and confirm earlier reports that simvastatin can have antioxidative properties. The effect of lowering MDA in the plasma and tissues may be owed to statins' potential to suppress specific oxidation pathways and reduce lipid peroxidation, upregulate antioxidant enzymes (catalase, glutathione peroxidase, and superoxide dismutase), or downregulate key pro-oxidant enzymes such as nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (42–44). We believe that in normolipidaemic rats this effect is owed to lower lipid peroxidation in the presence of statins. One systematic review (45) with a meta-analysis has shown that statins significantly increase glutathione peroxidase and superoxide dismutase levels in patients.

The antioxidative properties of simvastatin are also supported by our GSH findings in normolipidaemic rats, which confirm earlier reports (22, 46).

The dose-independent lowering effects of fenofibrate on plasma, liver, and brain MDA concentrations in normolipidaemic rats are similar to those of simvastatin (Table 2) and are also supported by other studies *in vivo* (24, 47–49). However, Beltowski et al. (24) report a dose-dependent effect and suggest that fenofibrate, as a peroxisome proliferator, can increase the concentrations of hydrogen peroxide and oxidative stress locally,

Table 3 The effects of simvastatin (50 mg/kg daily for 3 weeks) and fenofibrate (30 mg/kg daily for 3 weeks) on MDA and GSH levels in the plasma, liver, and brain of hyperlipidaemic rats

Variable	Source	Control[a]	Simvastatin[a] (50 mg/kg/day)	P value[b] (95 % CI)[c]	Fenofibrate[a] (30 mg/kg/day)	P value[b] (95 % CI)[c]
MDA (μmol/L)	Plasma	0.39±0.114 (n=6)	0.40±0.036 (n=6)	0.960 (-0.11–0.09)	0.26±0.036 (n=7)	**0.009** (0.04–0.24)
	Liver	92.1±30.00 (n=6)	100.4±19.45 (n=6)	0.828 (-46.89–30.43)	82.8±31.26 (n=7)	0.774 (-27.96–46.55)
	Brain	9.7±1.67 (n=6)	8.6±2.42 (n=6)	0.641 (-2.32–4.61)	13.5±3.08 (n=6)	**0.032** (-7.26–0.33)
GSH (μg/mL)	Plasma	251.7±127.4 (n=4)	224.2±57.58 (n=5)	0.845 (-117.2–172.2)	304.6±0.033 (n=4)	0.593 (-205.5–99.61)
	Liver	59.4±22.00 (n=6)	33.0±24.04 (n=5)	**0.045** (0.57–52.34)	12.2±5.98 (n=8)	**0.001** (24.13–70.30)
	Brain	8.9±1.73 (n=6)	9.1±1.80 (n=6)	0.876 (-3.26–2.28)	9.1±2.30 (n=7)	0.847 (-3.19–2.14)

GSH – reduced glutathione; MDA – malondialdehyde. Bold P values are significant at the <0.05 level. [a] mean ± SD. [b] P value of Dunnett's multiple comparison test with control. [c] 95 % confidence interval for difference between means

but without increasing lipid peroxidation products in the plasma. Aberg et al. (48) and Arnaiz et al. (49) propose that clofibrate and fenofibrate increase the concentrations of ubiquinols as the only liposoluble endogenous antioxidants in several animal tissues that inhibit lipid peroxidation (48, 49). In humans, Tkác et al. (50) reported that fenofibrate treatment increased glutathione peroxidase activity in patients with combined dyslipidaemia.

However, we have also observed a significant decrease in liver GSH in normolipidaemic rats, which begs the question if fenofibrate can also produce prooxidant effects, as some studies suggest (27, 51). We, however, believe that this drop in liver GSH has to do with its binding with one or more fenofibrate metabolites, as demonstrated by Shore et al. (52) for one metabolite (1-O-clofibryl glucuronide) of clofibrate, which belongs to the same class of antilipidaemic drugs.

As for the second aim of our study, our results show that the same doses of simvastatin and fenofibrate produce different effects on MDA and GSH concentrations in normolipidaemic and hyperlipidaemic rats. In hyperlipidaemic rats simvastatin (50 mg/kg/day) did not change MDA concentrations and significantly decreased liver GSH, which points to oxidative stress, as reported in some earlier studies (28, 29). Some recent studies, however, report antioxidant action of statins in hyperlipidaemic rats (22, 46). These discrepancies may be owed to differences in experimental methods, including rat strain, dosing, and duration of statin treatment.

Treatment with fenofibrate, in turn, yielded comparable plasma and liver MDA lowering in hyperlipidaemic and normolipidaemic rats. Its tendency to lower MDA was also reported in the plasma of rats with hypertriglyceridaemia (53). We believe that the decrease in plasma and liver MDA concentrations in hyperlipidaemic rats may be evidence that no lipid peroxidation occurs during fenofibrate treatment.

However, brain MDA concentrations in normolipidaemic rats dropped (although not significantly), whereas in hyperlipidaemic rats they significantly increased. Considering that we found no studies reporting fenofibrate effects on brain MDA *in vivo*, we find it difficult to explain our finding, especially in regard to recent studies reporting the neuroprotective, anti-inflammatory, and antioxidative effects of fenofibrate in some neurodegenerative diseases through their agonistic action mainly on PPAR-α receptors (11, 16). It is possible that higher brain MDA concentrations in hyperlipidaemic rats have something to do with changes in these receptors, as pointed out by Wójtowicz et al. (11). New preclinical studies might clear this out, especially in view of the fact that fenofibrate did not significantly increase brain GSH in either rat strain. Speaking of GSH, fenofibrate effects were similar between normolipidaemic and hyperlipidaemic rats only in the liver.

CONCLUSIONS

To conclude, our results show similar antioxidative but dose-independent effects of simvastatin and fenofibrate on MDA and GSH in the plasma and brain of normolipidaemic rats. However, these effects are not repeated in hyperlipidaemic rats, save for a significant decrease in liver GSH concentrations by fenofibrate in both rat strains, which points to GSH binding with the same fenofibrate metabolite in the liver.

Considering our findings and the current knowledge about the importance of oxidative stress parameters, GSH in particular, in different neurological and cardiovascular conditions and the widespread use of statins and fibrates, we believe that further preclinical and clinical research is needed to shed more light on their action on oxidative stress parameters.

Conflicts of interests

None to declare.

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Učinci simvastatina i fenofibrata na malondialdehid i reducirani glutation u plazmi, jetri i mozgu normolipidemičnih i hiperlipidemičnih štakora

Cilj ovog istraživanja bio je istražiti učinke različitih doza simvastatina i fenofibrata na malondialdehid (MDA) i reducirani glutation (GSH) u plazmi, jetri i mozgu mužjaka normolipidemičnih (Wistar) i hiperlipidemičnih (Zucker) štakora. Na prvim dvjema eksperimentalnim skupinama normolipidemičnih štakora simvastatin je primijenjen u dozama 10 ili 50 mg/kg dnevno, a fenofibrat na trećoj i četvrtoj skupini u dozama od 30 i 50 mg/kg/dan. Prva eksperimentalna skupina hiperlipidemičnih štakora primala je simvastatin 50 mg/kg/dan, a druga fenofibrat 30 mg/kg/dan. Kontrolne skupine normolipidemičnih i hiperlipidemičnih štakora primale su fiziološku otopinu. Simvastatin, fenofibrat i fiziološka otopina primjenjivani su oralno tijekom tri tjedna. U plazmi i mozgu normolipidemičnih štakora simvastatin i fenofibrat pokazali su slične i o dozi neovisne učinke na koncentracije MDA i GSH. Općenito, MDA je bio smanjen, a koncentracija GSH bila je povećana. U hiperlipidemičnih štakora simvastatin nije utjecao na koncentraciju MDA i GSH, ali je prouzročio značajno smanjenje GSH u jetri. Fenofibrat je smanjio MDA u plazmi i jetri te povećao MDA u mozgu. U oba soja štakora fenofibrat je značajno smanjio koncentraciju GSH u jetri, vjerojatno zbog konjugacije GSH s nekim metabolitima fenofibrata. Prema našim rezultatima, simvastatin djeluje antioksidacijski samo u normolipidemičnih štakora, a antioksidacijski učinak fenofibrata prisutan je u oba soja.

KLJUČNE RIJEČI: lijekovi za snižavanje lipida; oksidacijski stres; peroksidacija lipida; Wistar štakori; Zucker štakori