

## Butyrylcholinesterase activity and plasma lipids in dexamethasone treated rats

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The paper describes the effect of glucocorticoid dexamethasone (DM) given intraperitoneally on the catalytic activity of butyrylcholinesterase (BuChE) measured in plasma, liver and white adipose tissue of rats of both sexes. Effects of DM on the concentration of plasma lipids and lipoproteins were also tested. Rats were given multiple (2 and 4) pharmacological doses (0.4 and 3.0 mg kg<sup>-1</sup> body mass) of DM. All animals were sacrificed 48 hours after the last dose. Administration of DM significantly decreased the catalytic activity of BuChE in plasma and liver of all treated groups regardless of sex. BuChE catalytic activity in white adipose tissue differed depending on the dose and frequency of administration. In contrast to liver where both doses caused significant BuChE inhibition, the lower DM dose did not inhibit BuChE activity in adipose tissue, and the inhibition achieved by the higher dose was not as strong as in liver. This result corroborates an earlier hypothesis that BuChE is also synthesized in the adipose tissue. DM significantly increased plasma concentrations of triglycerides, total cholesterol and high-density lipoprotein (HDL) cholesterol and decreased the low-density lipoprotein (LDL) cholesterol concentration. Neither positive correlation between BuChE and triglycerides nor negative correlation between BuChE and HDL was found. Changes in lipid profile during DM treatment were not sex- and time-dependent.

**Keywords:** dexamethasone, butyrylcholinesterase, liver, white adipose tissue, protein synthesis, lipids, lipoproteins

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Diagnosis of poisoning by organophosphates (OPs) and carbamates is made on the basis of clinical symptoms and laboratory tests for plasma butyrylcholinesterase (BuChE: EC 3.1.1.8, acylcholine acylhydrolase, plasma cholinesterase) and red blood cells acetylcholinesterase (AChE: EC 3.1.1.7) catalytic activity. Butyrylcholinesterase is synthesized in the liver and is released into plasma immediately upon synthesis. Some authors pro-

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pose that BuChE synthesis is not limited to the liver alone (1, 2). This enzyme has been found in the small intestine, smooth muscle, heart, adipose tissue, and in white matter of the brain, where it plays a minor role in regulating brain acetylcholine levels. So far, BuChE has no known biological substrate in the mammals, but it hydrolyzes a variety of choline esters, including butyrylcholine, butyrylthiocholine and propionylthiocholine (3). BuChE is clinically important because it hydrolyzes the short-acting muscle relaxant succinylcholine as well as ester-type local anaesthetics (4). Although the physiological function of BuChE is not known, it has been suggested that it might be a precursor of AChE in the nervous system, and that it might contribute to the integrity of the myelin sheath of the central axons (5). According to recent investigations, BuChE activity progressively increases in patients with Alzheimer's disease and both BuChE and AChE seem to be involved in the aetiology and progression of this disease (6). Many data show that BuChE also plays a role in lipid and lipoprotein metabolism (1, 2, 7, 8).

For practical reasons it is important to determine whether a decrease in BuChE activity is caused by a qualitative change of the enzyme (genetic variant) or by its quantitative reduction. In the case of qualitative changes, the decrease in BuChE activity is inherited (a rare genetic variant of atypical or dibucaine-resistant enzyme) and constant. In such persons, the hydrolysis and inactivation of the muscle-relaxant drug suxamethonium is of long duration (9). The frequency of quantitative reduction is significantly higher and it could be a consequence of decreased enzyme synthesis due to cancer, malnutrition, liver or renal diseases (10, 11). It is also known that acute or chronic treatment with steroid hormones (glucocorticoids and estrogens) inhibits the activity of BuChE in plasma and liver (12, 13), but this effect does not occur *in vitro*. Therefore, it has been suggested that glucocorticoids reversibly depress the synthesis of BuChE in the liver (13). On the other hand, many drugs, such as neostigmine, pyridostigmine or propranolol, directly inhibit the active centre and peripheral anionic site of the enzyme (7, 14).

Our recent experiments with a single-non-lethal dose of cycloheximide (CHM), a strong inhibitor of protein synthesis in mammals, have shown that the catalytic activity of BuChE in the plasma of rats of both sexes remained unchanged for several days after CHM administration (15). At the same time, the catalytic activity of BuChE in the liver and white adipose tissue was significantly inhibited (15). The reason for the maintained BuChE catalytic activity in plasma could be a relatively long biological half-life of this enzyme in rat plasma (9–11 days). Significant differences in the dynamics of the inhibition of BuChE activity between the liver and white adipose tissue obtained in these experiments support the hypothesis that BuChE is also synthesized in adipose tissue.

The aim of this study was to determine the time-course of dexamethasone (DM)-related BuChE inhibition in the adipose tissue, liver, and plasma of rats of both sexes, because of the significant effect of sex hormones on BuChE catalytic activity. Based on the relationship between BuChE and plasma lipids, we wanted to find whether there was a positive correlation between BuChE and triglycerides and a negative correlation between BuChE and HDL during DM therapy. The effect of DM on plasma lipids concentration was measured and compared between rats of both sexes.

## EXPERIMENTAL

### *Chemicals*

Dexamethasone sodium phosphate (9 $\alpha$ -fluoro 16 $\alpha$ -methylprednisolone) was obtained from Krka (Slovenia).

### *Treatment of animals*

Male and female adult Wistar rats (240–280 g body mass) were fed a standard diet for laboratory rodents (Sljeme, Croatia). Animals had free access to water and were kept in macrolone cages under controlled conditions (room temperature 21 °C, light and dark cycles exchanging every 12 hours).

The animals (32 males and 32 females) were randomly divided in eight control ( $n = 3$ ) and eight test groups ( $n = 5$ ) receiving DM intraperitoneally at 48-hour intervals. Four test groups (2 male and 2 female) received 0.4 mg DM kg<sup>-1</sup> body mass (b.m.). Of these four groups, one male and one female group received two doses, while the others received four doses. The same scheme was used for the administration of higher DM doses (3.0 mg kg<sup>-1</sup> b.m.). The controls were given saline using the same experimental design. All treated animals were sacrificed with coal gas 48 hours after the last dose.

In order to achieve continuous pharmacodynamic effects of DM without serious side effects, and knowing that the biological half-life of DM is 56 hours, animals were treated every other day.

Blood samples were obtained directly from the heart, and adipose tissue was isolated from the epididymal (males) or parametrial (females) fat depot. The liver tissue was rinsed with saline. Plasma and tissue samples were stored and frozen immediately after sampling at -20 °C until further processing. Tissue samples were homogenized (200 mg tissue mL<sup>-1</sup> saline) and supernatant was obtained by centrifuging for 15 min at 2800  $\times$  g.

This study was performed with the approval of the Ethical Committee of the Institute for Medical Research and Occupational Health in Zagreb, Croatia.

### *BuChE assay*

The BuChE activity in plasma and tissues (liver and white adipose tissue) was determined by spectrophotometry using butyrylthiocholine (0.9 mmol L<sup>-1</sup>) (Sigma Chem Co., USA) as a substrate (16). Since the liver tissue contains BuChE and AChE, the BuChE assay was carried out with and without the specific BuChE inhibitor ethopropazine hydrochloride in the final concentration of 1.7 mmol L<sup>-1</sup> (Sigma Chem Co.). BuChE activity was calculated indirectly as the difference of the two measurements. The enzyme activity is expressed as  $\mu$ mol of substrate hydrolyzed per min per mL of plasma, *i.e.*,  $\mu$ mol of substrate hydrolyzed per min per g of fresh tissue. Since there was no statistical evidence difference in BuChE activity between control groups of the same sex either in plasma or in tissues, the mean BuChE activity in males and separately in females was taken as the control value. Relative changes in the enzyme activity in the treated animals are presented as the percentage of the control group activity.

### *Lipids and lipoproteins*

Total cholesterol in plasma was determined using a cholesterol enzymatic colorimetric test (»Herbos« Dijagnostika, Croatia) (17, 18) while triglycerides were determined using a triglyceride enzymatic colorimetric test – GPO-PAP method (»Olympus Diagnostica« GmbH, Germany) (19, 20). HDL cholesterol levels were determined using the method of Burstein *et al.* (21). Friedewald's formula was used to calculate LDL cholesterol levels from total cholesterol, triglycerides and HDL cholesterol (22). Concentrations of lipids and lipoproteins were measured in duplicate, and expressed as mmol L<sup>-1</sup> of plasma. Relative changes in lipid and lipoprotein concentrations in treated animals are shown as the percentage of all rats of the respective control group. Since there was no significant difference in triglycerides, total cholesterol, HDL cholesterol, and LDL cholesterol concentrations between the control groups, the mean concentrations of respective parameters of all rats were taken as control values.

### *Statistical analysis*

Data are shown as mean  $\pm$  standard deviation. The mean and medians were calculated using the software package Statistics<sup>®</sup> for Windows version 5.0 A. Statistical significance was determined by the parametric *t*-test and non-parametric Kolmogorov-Smirnov two-sample test, where appropriate. The differences discussed in this paper were considered significant at the  $p < 0.05$  level of significance.

## RESULTS AND DISCUSSION

In this study, the inhibitory effect of DM on BuChE catalytic activity in plasma, liver and white adipose tissue was demonstrated in most of our experimental groups when compared with the controls (results are summarized in Table I).

A significant decrease ( $p < 0.05$ ) in BuChE catalytic activity (approximately 20–80%) was found in the liver of rats of both sexes, which was dose- but not time-dependent. It is known that glucocorticoids interact with specific receptor proteins in the target tissue, thus regulating (reversible increase or decrease) the expression of corticosteroid-responsive genes that affect protein synthesis (23). Therefore, the decreased catalytic activity of BuChE in the liver may be attributed to DM inhibition of its synthesis. It is also known that the hepatic glucocorticoid receptor-binding capacity decreases significantly in rats after the scalding stress, mainly as a result of the increased concentration of serum corticosterone (24). Both doses of glucocorticoids applied in our experiments were pharmacologically high, and their plasma concentrations were high due to the long half-life of DM. Dose and dosing period increments did not further increase the inhibition of BuChE activity in rat liver, which suggests a reduced binding capacity of glucocorticoid receptors. Decrease in BuChE catalytic activity in rats receiving the higher dose was greater (65–80%) in the liver than in plasma (20–45%). The presence of BuChE that was synthesized and released into plasma before the DM administration and its relatively long-half-life in plasma (9–11 days) are probably the main reasons why the activity of BuChE was greater in plasma than in liver. A similar difference between the BuChE activity in the liver and plasma was reported by Verjee *et al.* (12).

Table I. Catalytic activity of BuChE and relative changes in plasma, liver and white adipose tissue<sup>a</sup>

Biological specimen	Unit	Control animals (n = 12)	Experimental animals (n = 5) <sup>b</sup>			
			Doses of DM			
			2	4	2	4
			0.4 mg kg <sup>-1</sup>		3.0 mg kg <sup>-1</sup>	
Plasma						
Males	μmol min <sup>-1</sup> mL <sup>-1</sup>	0.05 ± 0.01 (100)	0.04 ± 0.01 <sup>f</sup> (80)	0.02 ± 0.00 <sup>c</sup> (40)	0.04 ± 0.01 (80)	0.02 ± 0.00 <sup>e</sup> (40)
Females	(%)	0.15 ± 0.00 (100)	0.12 ± 0.01 (80)	0.07 ± 0.03 <sup>c</sup> (47)	0.09 ± 0.01 <sup>§</sup> (60)	0.08 ± 0.03 <sup>e</sup> (53)
Liver						
Males		0.36 ± 0.01 (100)	0.24 ± 0.01 <sup>§</sup> (67)	0.18 ± 0.04 <sup>§</sup> (50)	0.12 ± 0.03 <sup>e</sup> (33)	0.06 ± 0.02 <sup>h</sup> (17)
Females	μmol min <sup>-1</sup> g <sup>-1</sup> fresh tissue	0.50 ± 0.05 (100)	0.40 ± 0.01 <sup>§</sup> (80)	0.32 ± 0.10 <sup>c</sup> (64)	0.21 ± 0.06 <sup>e</sup> (42)	0.18 ± 0.08 <sup>e</sup> (36)
White adipose tissue						
Males		0.33 ± 0.17 (100)	0.29 ± 0.04 (88)	0.48 ± 0.01 <sup>§</sup> (145)	0.15 ± 0.04 <sup>c</sup> (45)	0.16 ± 0.04 <sup>h</sup> (48)
Females		0.45 ± 0.06 (100)	0.42 ± 0.04 (93)	0.62 ± 0.04 <sup>f</sup> (138)	0.23 ± 0.06 <sup>d</sup> (51)	0.24 ± 0.08 <sup>§</sup> (53)

<sup>a</sup> Mean ± SD.<sup>b</sup> Comparison with controls: <sup>c</sup> *t*-test  $p < 0.05$ , <sup>d</sup> *t*-test  $p < 0.01$ , <sup>e</sup> *t*-test  $p < 0.001$ , <sup>f</sup> Kolmogorov-Smirnov test  $p < 0.05$ , <sup>§</sup> Kolmogorov-Smirnov test  $p < 0.01$ , <sup>h</sup> Kolmogorov-Smirnov test  $p < 0.001$ .

The effect of DM on BuChE activity in the adipose tissue showed quite a different pattern. Two low doses of DM (0.4 mg kg<sup>-1</sup>) did not change BuChE activity in the adipose tissue of rats of either sex, but four administrations of the same dose caused an unexpected significant ( $p < 0.05$ ) increase in BuChE activity (about 35–45%) when compared to the controls. Both two and four administrations of high doses of DM (3.0 mg kg<sup>-1</sup>) produced a similar significant ( $p < 0.05$ ) decrease in BuChE activity (about 50%) in the white adipose tissue of rats of both sexes. This different pattern of BuChE activity in the adipose tissue and in the liver after a low DM dose administration could indicate that the binding capacity of glucocorticoid receptors and their sensitivity to DM in the adipose tissue differ from that in the liver. Our results indicate that the BuChE is also synthesized in the adipose tissue. The possibility that adipose tissue is a place of BuChE synthesis is supported by the results of Ballantyne (25) and Salvador and Kuntzman (26), who histochemically demonstrated the presence of BuChE in adipocytes.

According to our results, the administration of two different doses of DM to male and female rats significantly increases total cholesterol, HDL cholesterol and triglycerides in plasma (Table II). Plasma LDL cholesterol was lower than in the control groups treated with saline. These changes were not dose-dependent. Similar effects of DM on plasma lipids were reported by other authors (27, 28). It is not known why glucocor-

Table II. Lipids and lipoprotein concentrations and relative changes in plasma<sup>a</sup>

Lipids and lipoproteins	Unit	Control animals (n = 12)	Experimental animals (n = 5) <sup>b</sup>			
			Doses of DM			
			2	4	2	4
			0.4 mg kg <sup>-1</sup>		3.0 mg kg <sup>-1</sup>	
Triglycerides						
Males		1.22 ± 0.20 (100)	2.30 ± 0.20 <sup>e</sup> (188)	3.70 ± 0.60 <sup>e</sup> (303)	1.90 ± 0.10 <sup>c</sup> (155)	3.00 ± 0.20 <sup>h</sup> (246)
Females		1.10 ± 0.10 (100)	1.90 ± 0.10 <sup>e</sup> (173)	4.10 ± 0.90 <sup>e</sup> (372)	0.90 ± 0.10 (82)	3.80 ± 0.90 <sup>h</sup> (345)
Total cholesterol						
Males		1.40 ± 0.07 (100)	1.70 ± 0.07 <sup>c</sup> (121)	2.00 ± 0.02 <sup>e</sup> (143)	2.10 ± 0.10 <sup>e</sup> (150)	1.70 ± 0.30 <sup>d</sup> (121)
Females	mmol L <sup>-1</sup>	1.60 ± 0.10 (100)	1.54 ± 0.03 (96)	1.30 ± 0.04 <sup>g</sup> (81)	1.50 ± 0.30 (94)	1.60 ± 0.60 (100)
HDL cholesterol (%)						
Males		0.99 ± 0.15 (100)	1.20 ± 0.10 <sup>c</sup> (121)	1.30 ± 0.20 <sup>e</sup> (131)	1.70 ± 0.09 <sup>e</sup> (168)	1.30 ± 0.10 <sup>g</sup> (131)
Females		1.10 ± 0.10 (100)	1.20 ± 0.10 <sup>c</sup> (121)	0.80 ± 0.00 <sup>h</sup> (73)	1.20 ± 0.20 <sup>d</sup> (121)	1.10 ± 0.00 (100)
LDL cholesterol						
Males		0.17 ± 0.00 (100)	0.10 ± 0.00 <sup>d</sup> (59)	0.10 ± 0.00 <sup>d</sup> (59)	0.11 ± 0.01 <sup>g</sup> (65)	0.11 ± 0.02 <sup>g</sup> (65)
Females		0.14 ± 0.00 (100)	0.10 ± 0.00 <sup>f</sup> (71)	0.10 ± 0.00 <sup>f</sup> (71)	0.12 ± 0.04 (86)	0.10 ± 0.00 <sup>f</sup> (71)

<sup>a</sup> Mean ± SD.<sup>b</sup> Comparison with controls: <sup>c</sup> *t*-test *p* < 0.05, <sup>d</sup> *t*-test *p* < 0.01, <sup>e</sup> *t*-test *p* < 0.001, <sup>f</sup> Kolmogorov-Smirnov test *p* < 0.05, <sup>g</sup> Kolmogorov-Smirnov test *p* < 0.01, <sup>h</sup> Kolmogorov-Smirnov test *p* < 0.001.

ticoids have different effects on the plasma lipid profile. However, it is known that glucocorticoids may act through several mechanisms on different levels of the lipoprotein metabolism. Namely, corticosteroids may affect lipoprotein synthesis and increase the very-low-density lipoprotein (VLDL cholesterol) secretion in rats. On the other hand, they affect the lipoprotein catabolism. It has been shown that corticosteroids decrease lipoprotein lipase activity in the adipose tissue and therefore impair the plasma triglyceride metabolism. The mechanisms causing changes in HDL cholesterol are not well known either (27, 28). We have to stress that, according to our own results, changes in the lipid profile during DM treatment were not sex- and time-dependent.

The mean BuChE activity in plasma, liver and white adipose tissue was higher (1.5–3 times) in female than in male control rats. This sex-related difference is in agreement with the results published by other authors (29). They have noticed a negative modulatory effect of testosterone and a positive modulatory effect of estrogens on serum BuChE synthesis in the rat liver. The mode of action of both sex hormones on the enzyme synthesis in hepatocytes is not direct, but includes the hypothalamic-hypophyseal axis (30).

Our results indicate that the interaction between glucocorticoids and BuChE can be of clinical significance. Glucocorticoids are often used in the therapy of different diseases, and may cause a drop in BuChE activity. Therefore, this therapy could prolong hydrolysis of succinylcholine during anaesthesia.

## CONCLUSIONS

The decrease in the liver BuChE activity was similar in rats of both sexes after receiving either low or high pharmacological doses of DM. Furthermore, the dynamics of increase after a low dose and decrease after a high dose of DM was very similar in the adipose tissue of rats of either sex. It might be assumed that these changes in BuChE activity in the liver and adipose tissue are primarily a consequence of DM effects on the glucocorticoid receptors of target cells. We are also inclined to believe that DM had a synergistic effect with testosterone and an opposite effect with estrogens on BuChE synthesis in the liver of treated male and female rats. Dose-related differences in the effects of DM on BuChE activity in the white adipose tissue call for further investigation in this area.

There was neither a positive correlation between BuChE and triglycerides nor a negative correlation between BuChE and HDL. Changes in the lipid profile during DM treatment were not sex- and time-dependent.

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## S A Ž E T A K

### Učinek deksametazona na aktivnost butirilkolinesteraze i lipide plazme u štakora

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U radu su opisani učinci glukokortikoida deksametazona (DM) na katalitičku aktivnost butirilkolinesteraze (BuChE) u plazmi, jetri i bijelom masnom tkivu štakora oba spola. Ispitan je i učinak DM na koncentracije plazmatskih lipida i lipoproteina. Štakori su tretirani višekratno (2 i 4 puta) farmakološkim dozama (0,4 i 3,0 mg kg<sup>-1</sup> tjelesne mase) DM koji je primijenjen intraperitonealno. Životinje su žrtvovane 48 sati nakon što su primile zadnju dozu. Utvrđeno je da DM značajno snižava katalitičku aktivnost BuChE u plazmi i jetri štakora oba spola. Rezultati katalitičkih aktivnosti BuChE u bijelom masnom tkivu bili su različiti ovisno o veličini doze i broju aplikacija. Za razliku od jetre, gdje su obje doze izazvale značajnu inhibiciju BuChE, u masnom tkivu niža doza nije inhibirala aktivnost enzima, a inhibicija s višom dozom nije bila tako snažna kao u jetri. Rezultati govore u prilog hipotezi da se BuChE osim u jetri sintetizira i u masnom tkivu. Također je utvrđeno da DM značajno povećava koncentraciju triglicerida, ukupnog kolesterola i HDL-kolesterola, te smanjuje koncentraciju LDL-kolesterola u plazmi. Međutim, nije utvrđena pozitivna korelacija između BuChE i triglicerida, niti negativna korelacija između BuChE i HDL. Promjene koncentracija lipidnih frakcija tijekom primjene DM nisu ovisile o spolu eksperimentalnih životinja niti o trajanju pokusa.

*Ključne riječi:* deksametazon, butirilkolinesteraza, jetra, bijelo masno tkivo, sinteza proteina, lipidi, lipoproteini

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