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Changes in Butyrylcholinesterase Activity and Serum Lipids after Oxprenolol and Glibenclamide Treatments in Non-diabetic Rats

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Summary

The effects of chronic treatment with oxprenolol (CAS 6452-72-7) (OXP, 15 mg/ kg/day), or glibenclamide (CAS 10238-21-8) (GL, 2.5 mg/kg/day), or their combination administered for 6 and 12 weeks, on the butyrylcholinesterase (BuChE) activity in plasma and liver and on the plasma levels of triglycerides, total cholesterol and high density lipoprotein (HDL)-cholesterol were studied in normal, non-diabetic female rats. In all treated groups a significant increase of plasma BuChE activity was obtained after 6 weeks of either OXP (46%), or GL (36%) treatment, or of their concurrent application (24%). After 12 weeks of treatment, the increase in enzyme activity was significant only in the OXP group. The BuChE activity in the liver was increased (between 3-25%) in all treated groups except in one during 6 and 12 weeks of treatment. These effects of either OXP or GL, or their combination on BuChE activity in liver suggest their stimulating effects on enzyme synthesis. The changes of total plasma cholesterol in all groups were insignificant. On the other hand, HDL-cholesterol was significantly decreased in all treated groups. After 6 weeks of treatment, GL, OXP, or their combination caused a decrease in plasma HDL cholesterol by 19, 50 or 22% respectively, when compared with the control group. After 12 weeks of GL, OXP, or GL+OXP administration, HDL-cholesterol plasma levels in treated groups were 32, 25 and 22% lower than in the control group. Treatment with GL, OXP, or GL+OXP during 6 weeks had no significant effect on triglycerides level. However, after 12 weeks of GL, OXP, or GL+OXP administration, the triglycerides levels were significantly increased (9, 47 and 36%) when compared with the control group. These results have shown, that the increase in BuChE activity might be the first sign of altered triglyceride and lipoprotein metabolism.

Key words butyrylcholinesterase
CAS 6452-72-7
CAS 10238-21-8
Oxprenolol,
Glibenclamide
Plasma lipids

1. Introduction

Butyrylcholinesterase (EC3.1.1.8, acylcholine acylhydrolase, serum cholinesterase, butyrylcholinesterase, BuChE) is still an enzyme with unknown physiological function, although its structure, cloning and chromosome localization for enzyme in humans is known [1-3]. Beside the liver, where BuChE is synthesised and released into serum immediately following its synthesis, the enzyme is found to a lesser extent in the adipose tissue, small intestine, smooth muscle and other tissues [1,4]. In a mammalian organism, BuChE has no known biological substrate, but it hydrolyses a variety of choline esters including butyrylthiocholine [1]. The clinical importance of BuChE lies in its pharmacological property of hydrolysing the short-acting relaxant suxamethonium and ester type local anaesthetics (e.g. procaine and tetracaine hydrochloride) [5-7]. Therefore, a significant reduction in BuChE activity (e.g., due to liver disease, cancer, uraemia, treatment with glucocorticoids, reversible or irreversible cholinesterase inhibitors, etc.) may increase the intensity and duration of action of succinylcholine and the systemic toxicity of ester-type local anaesthetics [8-10]. In contrary, the increase of BuChE activity in anaesthesiology is of minor clinical significance.

The fact, that the BuChE activity is increased in certain metabolic disorders is known for a long time [11]. High BuChE activities are typical for patients with hypercholesterolemia, hypertension, obesity and Type I or Type II diabetes [12-17]. In such patients, BuChE activity correlates strongly and positively with serum levels of low density lipoprotein (LDL)-cholesterol and triglycerides (TG) and inversely with serum high density lipoprotein (HDL)-cholesterol. Similar changes were observed in animals [13]. Fat Zucker rats that exhibited a marked increase in VLDL-cholesterol have high serum BuChE activity [18]. Osada et al. have found that BuChE could be involved in the regulation of serum phospholipids level [19]. All these observations suggest a relationship between BuChE activity and lipoprotein metabolism, but the rationale for this connection is unclear.

Some antihypertensive agents also show similar changes of serum lipids. For example, a significant increase of serum TG levels and a decrease of HDL-cholesterol occurs in patients on chronic propranolol or oxprenolol treatment [20,21]. Unlike some investigators who claimed that beta-blocking drugs cause a reduction of BuChE activity *in vitro* and *in vivo* in rats [22,23], a significant increase of total cholesterol (TC) and BuChE after chronic oxprenolol (OXP) treatment during 6, 10 and 12 weeks

was shown in our experiments [24]. The increase of TG levels after 12 weeks of OXP treatment was not significant. We suppose that the increase of enzyme activity was initially due to the action of OXP on TC and TG metabolism, and not due to its direct effect on the enzyme.

Like OXP, prolonged administration of glibenclamide (GL) to normal rats causes an increase of serum lipids [25]. Therefore, it was interesting to assess whether these changes are also simultaneously accompanied by the changes in BuChE activity. Since concurrent treatment with GL and OXP in the same patients is sometimes used, we investigated the effects of GL in combination with OXP on BuChE activity and serum lipids as well as BuChE activity in the liver.

2. Materials and Methods

2.1. Test substances

The non-selective β-blocker oxprenolol (CAS 6452-72-7) and the antidiabetic drug glibenclamide (CAS 10238-21-8) obtained from Research Institute Pliva, Zagreb, Croatia, were used in our experiments.

2.2. Test animals

Female Wistar rats (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia) weighting 130-150 g were used in the studies. The animals were maintained under controlled laboratory conditions. Standard diet (food for laboratory rats and mice was manufactured by PLIVA, Kalinovica, Croatia) in pellet form was available *ad libitum* in control groups. OXP and GL were mixed in standard diet and offered to animals *ad libitum* in pellet form. Calculations for the concentration of OXP and GL in diet were performed according to the group mean body weight and group mean food consumption. The doses were expressed as mg of OXP/kg and as mg of GL/kg of body weight/day. Handling and treatment of the animals were conducted on basis of the international guidelines regarding use of laboratory animals. The experiments have been approved by local ethics committee.

2.3. Study design and dosage

The seventy animals were divided in two control groups (n=7 each) and six experimental groups. Two experimental groups (n=8 each) were on treated diet with OXP (15 mg/kg/day) for 6 and 12 weeks. The remainder four groups (each=10) were on treated diet with GL (2.5 mg/kg/day) or with a combination of OXP and GL in the same doses for 6 and 12 weeks. The animals were anaesthetised with ether. Blood samples were obtained by cardiac punction. Before collecting liver tissue, the liver had been washed out of blood *in situ*, with saline via the vena cava superior. Serum and liver samples were stored at 20° C until analysed. For the analysis, liver tissues were homogenised with normal saline in the ratio of 1: 5. The supernatants were obtained by centrifuging the homogenised samples at 16000 g for 15 min, at 4° C.

Glucose in whole blood was determined by a glucohaemo test 1-45, Pliva.

BuChE activity was measured using the spectrophotometric method of Ellman et al. with butyrylthiocholine (Sigma, ChemCo, St. Louis, USA) as a substrate [26]. BuChE measurements were carried out in the presence and absence of 10^{-4} M ethopropazine hydrochloride (Sigma, ChemCo, St. Louis, USA), a specific BuChE inhibitor, in order to exclude the effect of acetycholinesterase. Enzyme activities are expressed as μmol of substrate hydrolysed per min per ml of serum or g of tissue wet weight. Concentrations of total cholesterol and triglycerides in the serum were determined by cholesterol enzymatic colorimetric test (Pliva, Pharmaceutical, Chemical, Food and Cosmetic Industry, Zagreb, Croatia). HDL cholesterol was estimated after precipitation of VLDL and LDL cholesterol with PEG 20 000 (Quantolip HDL Immuno AG Vienna) and measured in supernatant by the cholesterol enzymatic colorimetric test (PLIVA, Pharmaceutical, Chemical, Food and Cosmetic Industry, Zagreb, Croatia). The concentrations were expressed as mmol/L.

2.4. Statistical analysis

Data are shown as mean ± standard error of the mean.

Analysis of variance (ANOVA) was performed to compare the results from weeks 6 and 12. Normality of the data was tested with Kolmogorov test. The assumption of equal group variances was tested with Levene's test.

The post-hoc test was Newman-Keuls test for group comparison. The results were considered as significant with $p \leq 0.05$.

3. Results

3.1. Clinical observation

The administration of GL or OXP, or their concurrent use did not induce any changes in the animal behaviour. There was no influence of both agents on body weight or food consumption when compared with the control groups.

3.2. Effect on serum glucose levels

After 12 weeks of treatment, GL, or OXP, or their combination induced an insignificant increase of serum glucose levels by 33.7%, 17.3% and 25.6% respectively, when compared with the control group and the treated animals after 6 weeks of treatment.

3.3. Effects on BuChE activity

Serum

Six weeks of treatment: The administration of GL or OXP induced a significant increase in BuChE activity (36 and 46%) in comparison with control. The increase of BuChE activity after their concurrent application was lower, but also significant (24%, vs. control).

*Twelve weeks of treatment***:** Serum BuChE activity was significantly elevated only after the OXP treatment (19%, $p < 0.05$ vs. control) while the increase of enzyme activity after GL or GL+OXP combination was small and insignificant.

Liver

Six and twelve weeks of treatment: GL or OXP or their concurrent administration induced an insignificant increase of BuChE activity (3-25%) in all groups except in the group on OXP treatment for 12 weeks. In this group, OXP treatment caused an insignificant decrease of BuChE activity by 5%.

3.4. Effects on serum lipids

Insignificant changes, i.e. a decrease of total cholesterol for 8-14%, were noted only after 12 weeks of treatment with GL or OXP or their concomitant administration. On the other hand, HDL-cholesterol significantly decreased in all treated groups. After 6 weeks of treatment, GL, OXP or their combination caused a decrease of HDL cholesterol (19, 50 or 22% respectively), when compared with the control. After 12 weeks of GL, OXP, or GL+OXP administration, the concentrations of HDL-cholesterol in treated groups were 31, 25 and 22% lower than in the control group. Treatment with GL, OXP, or GL+OXP during 6 weeks had no significant effect on triglycerides levels. However, after 12 weeks of GL, OXP, or GL+OXP administration, the triglycerides levels were significantly higher (9, 47 and 36%) when compared with the control group.

The decrease of HDL-cholesterol was not time dependent, but the increase of triglycerides was.

4. Discussion

We have shown a significant increase of serum BuChE activity (46%) after 6 weeks of OXP treatment. The increase after 12 weeks of treatment was insignificant (Table 1). These results are congruent with our earlier results obtained in male rats, which have also shown a significant increase in BuChE activity (27-51%) after 6, 10 and 12 weeks of OXP treatment [24]. Therefore, we have suggested that the sex-related differences concerning OXP effect on BuChE activity do not exist. The results of serum BuChE activity after GL treatment resemble those with OXP, i.e. the enzyme activity was significantly increased (36%) after 6 weeks of treatment and the same as in control after 12 weeks of treatment (Table 1). The BuChE activity in the liver increased or was the same as in control after 6 and 12 weeks of OXP or GL treatment or their combination (Table 1). Although the increase of BuChE activity in the liver after OXP or GL treatment was insignificant during both time intervals, these results prove a stimulating effect of OXP and GL on enzyme synthesis.

The stimulating effects of OXP on BuChE activity in serum and liver support the data showing that at least one beta-blocker does not inhibit the BuChE activity. This is different from the results of some other authors, who have found that propranolol, timolol and sotalol inhibit the BuChE activity in human serum as well as in heart and brain tissue *in vitro* and *in vivo* [22,23,27]. Alike, Hellenbrecht and Mueller have found that β-sympatholytics are non-specific inhibitors of serum BuChE

in vitro, and that the degree of BuChE inhibition directly depends on the hydrophobic properties of these drugs [28]. We have suggested that, due to the small partition coefficient and slight liposolubility, OXP has little affinity for BuChE, and that this is the main reason why this beta-blocker when compared with other drugs from the same group did not cause BuChE inhibition. We are also sure, that the increase of enzyme activity in liver and plasma is the consequence of direct interference of OXP with metabolism of TG, HDL, and/or TC, and that this is not due to OXP direct effect on the enzyme. Ryhanen et al have shown, that when cholesterol content in LDL particles is increased , the BuChE activity also increased. In HDL particles the situation is opposite, i.e. when cholesterol content in HDL increases, the enzyme activity is diminished [29]. According to our results (Table 1), a significant increase of TG by 47% ($p<0.05$) was found after 12 weeks of OXP treatment, and an significant decrease of HDL by 50% and 25% ($p<0.05$), occurred after 6 and 12 weeks of OXP treatment. During all this period, the BuChE activity was increased, or the same as in control.

These adverse effects of OXP on serum lipids in humans and animals are well known, but they are not consistent. In patients, a significant increase in serum TG, no change in TC and a decrease in HDL-cholesterol during OXP treatment was observed by Day et al [30]. However, no significant changes in TC, TG and HDL-cholesterol have been reported by Ferrara et al [31]. The full explanation of the mechanisms of the lipid modifying effects of these antihypertensive drugs remains unresolved, since different factors can be responsible. For example, a beta-blocker may decrease HDL and increase TG by decreasing lipoprotein lipase activity or lecithin:cholesterol acyltransferase (LCAT) activity [32].

The positive correlation of BuChE activity and serum TG we have proved, agrees with the results of other investigators, who have shown that the induction of diabetes in rats caused an increase in both BuChE activity and serum TG concentrations, while treatment with insulin resulted in normalization of these values [13]. Administration of a specific inhibitor of BuChE after induction of diabetes in these animals also reversed hypertriglyceridemia [13]. In a study on patients with diabetes type I or type II, BuChE activity correlated positively with TG concentration and inversely with insulin sensitivity [14].

Our results show that chronic treatment with GL caused a significant decrease of HDL-cholesterol by 19% and 32% after 6 and 12 weeks of treatments (Table 1). The 9% increase of TG ($p<0.05$) observed after 12 weeks of GL treatment, was very low in comparison with TG values after treatment with OXP or OXP+GL combination in the same period (Table 1). Since the increase of TG after OXP treatment was 1.3 times greater than the one after GL treatment, we suggest that the significant increase of TG by 36% after concurrent administration OXP and GL is the consequence of OXP action and not of GL. Concurrent use of GL and OXP had no additional effect on serum and liver BuChE activity, neither HDL-cholesterol. Also, the changes in BuChE activity and HDL-cholesterol were not time dependent. However, the TG concentration was significantly higher only after 12 weeks of OXP or OXP+GL treatment.

The data about the influence of GL and other sulphonylureas on lipid metabolism in non-diabetic or diabetic animals and diabetic patients are also inconsistent. According to George and Augusti, prolonged administration of GL (50 μg/kg daily, during 2 months) in normal rats, significantly decreased blood sugar, liver glycogen and protein, and significantly increased liver and serum lipids (e.g. triglyceride glycerol, total and free cholesterol) [33]. The triglyceride was more increased in the serum (35%) than in the liver (23%). GL administered at maximal clinical doses (0.4 mg/kg, daily intraperitoneal injection) to adult male Sprague-Dawley rats for 8 weeks, did not alter serum cholesterol, HDL-cholesterol or the TC:HDL-cholesterol ratio [34]. Gaafar et al have found that GL in daily dose of 2.5 mg/kg during 15, 30 and 60 days showed the hypercholesterolemic effect in non-diabetic rats [35]. Contrary to normal rats, GL has a significant hypocholesterolemic effect in aloxan diabetic rats [35]. While some studies on type 2 diabetes patients have shown an improvement in serum triglycerides during sulphonylurea therapy, other have failed. Most of the studies have failed to show a consistent effect on HDL cholesterol concentrations despite substantial improvements in glycaemia [25]. All these data in humans and animals suggest that the mode of action of sulphonylureas is still poorly understood.

Our findings on the relationship between the increase of BuChE activity and decreased level of HDL and/or increased TG level in experimental animals after treatment with OXP, or GL or both together, correspond well with the results of other authors who suggest that BuChE is connected with changes in lipid metabolism. The

data of Rustemeijer et al., who have found that BuChE activity in type II diabetes is directly related to TG synthesis, support this hypothesis [17]. The same authors also consider that the measurement of BuChE activity may therefore be a useful tool in the choice of drug for treatment of hypertriglyceridaemia in patients with diabetes.

Conclusion. Our results in non-diabetic rats show that chronic oxprenolol or glibenclamide treatment or their concurrent use during 6 and 12 weeks induce the increase of serum and liver BuChE activity. This, however, is not due to their direct effect on the enzyme, but to the consequence of altered lipid metabolism caused by oxprenolol and glibenclamide. Since BuChE activity was increased earlier than serum TG concentration, we suggest that the increase in BuChE activity might be the first sign of altered triglyceride metabolism. Our results have also shown that the synergistic action of GL and OXP combination on BuChE activity and plasma lipids does not exist.

Concerning these results about the relationship between BuChE and lipid metabolism lipids, further studies are clearly needed.

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Abbreviations

BuChE	butyrylcholinesterase
GL	glibenclamide
HDL-cholesterol	high density lipoprotein
LDL-cholesterol	low density lipoprotein
OXP	oxprenolol
TGs	triglycerides
TC	total cholesterol

Table 1. BuChE activities in plasma and liver, and serum lipids (Mean±SD) in female non-diabetic rats after the chronic oral administration of oxprenolol (15 mg/kg/day), or glibenclamide (2.5 mg/kg/day) or their concomitant administration. Relative changes are in brackets.

Time – weeks	Treatment	Glucose mmol/L	BuChE-plasma µmol/min/mL (%)	BuChE-liver µmol/min/g tissue (%)	Total Cholesterol concn. mmol/l (%)	HDL-Cholesterol concn. mmol/l (%)	Triglycerides Concn mmol/l (%)
6	Control	9.42±0.95 (100)	0.41±0.04 (100)	0.87±0.96 (100)	1.64±0.09 (100)	0.32±0.03 (100)	1.15±0.07 (100)
	OXP	9.0±0.6 (96)	0.60±0.03* (146)	1.1±0.1 (125)	1.7±0.1 (101)	0.16±0.02* (50)	1.1±0.1 (92)
	GL	9.5±0.9 (102)	0.56±0.05* (136)	0.90±0.1 (103)	1.7±0.1 (109)	0.26±0.04* (81)	1.2±0.2 (91)
	OXP+GL	8.4±0.3 (89)	0.51±0.04* (124)	1.02±0.1 (117)	1.6±0.1 (97)	0.25±0.03* (78)	1.2±0.2 (93)
12	Control	6.87±0.51 (100)	0.59±0.03 (100)	1.09±0.07 (100)	1.96±0.19 (100)	1.07±0.09 (100)	1.2±0.15 (100)
	OXP	9.1±0.9 (134)	0.70±0.05* (119)	1.0±0.1 (95)	1.8±0.1 (92)	0.80±0.07* (75)	1.87±0.35* (147)
	GL	8.1±0.4 (117)	0.6±0.0 (103)	1.3±0.1 (120)	1.7±0.1 (86)	0.74±0.07* (68)	1.39±0.21* (109)
	OXP+GL	8.6±0.4 (126)	0.6±0.0 (110)	1.2±0.1 (113)	1.7±0.1 (86)	0.83±0.04* (78)	1.73±0.09* (136)

* Indicates a statistically significant difference ($p<0.05$) when compared with the control group.
OXP – oxprenolol
GL - glibenclamide