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O. Zschörnig [a], D. Wiegel [a] & K. Arnold [a]

[a] Institute for Biophysics, School of Medicine, Karl Marx University, Leipzig, G.D.R.

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INTERACTION OF BETA-ADRENERGIC BLOCKING AGENTS WITH HUMAN LOW DENSITY LIPOPROTEINS DETECTED BY EPR

O. ZSCHÖRNIG, D. WIEGEL, K. ARNOLD
Institute for Biophysics, School of Medicine,
Karl Marx University, Leipzig, G.D.R.

INTRODUCTION

The influence of beta-adrenergic agents on the structure and physico-chemical properties of model and natural membranes has been investigated by several autors[1,2,3,4]. Knowledge of the mechanisms of the interaction between these pharmaca and membranes is necessary for a detailed description and further development of these pharmaca. One problem in understanding the pathways of pharmaca to the "target" membrane is the question of passing hydrophobic barriers (e.g., cell membranes). On the other hand, beta-adrenergic blocking agents have often been used in the treatment of coronary artery disease.
Their effects on the serum lipoprotein levels are different and difficult to interpret[10,11,12].
With a view to these questions we used electron paramagnetic resonance (EPR) spectroscopy to measure the incorporation of the ß-adrenergic blocking agents into low density lipoproteins (LDL) labelled with a fatty acid spin probe.

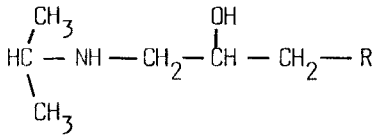
MATERIALS AND METHODS

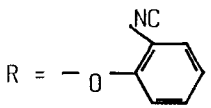
LDL was isolated from human plasma according to HAVEL et al[5]. After ultracentrifugation the samples were dialyzed against the appropriate buffer solution at 4°C overnight. Spin labelling was performed by adding the ethanolic solution of 10^{-2} mol/l 5-doxylstearic acid (Sigma, St. Louis, USA). In the sample the label/protein ratio was 1/50 (wt./wt.), i.e. label/LDL dry weight ratio was 1/250. The protein was determined according to LOWRY et al.[6]. The samples were incubated for 5 min. after the addition of the pharmaca and measured at room temperature with a ERS-231 spectrometer (ZWG; Berlin, GDR) using flat cells. Typical instrumental parameters were: microwave power, 20 mW; scan time, 6.6 min.; modulation amplitude, 10^{-4}T; time constant, 0.3 sec. For the estimation of the efficiency of the drugs in perturbating the LDL, the order parameter S was calculated from the EPR spectra. The inner and outer hyperfine splitting ($A_{\parallel}$ and $A_{\perp}$) were taken to calculate the lipid order parameter[7] which is a characteristic of the fluidity according to the formula

$$S = \frac{A_{\parallel} - A_{\perp}}{A_{zz} - (A_{xx}+A_{yy})/2} \qquad \frac{A_{xx} + A_{yy} + A_{zz}}{(A_{\parallel} + 2\,\overline{A}_{\perp})}, \text{ where} \tag{1}$$

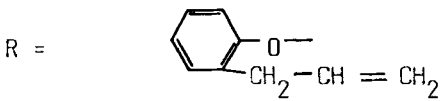
$$\overline{A}_{\perp} = A_{\perp} + 1.32 + 1.86 \log_{10} (1-S_o). \tag{2}$$

S_o is calculated by eq. (1) using $A_{\perp}$ instead of $\overline{A}_{\perp}$.
The A -tensors were taken from the paper of SEELIG[8].
The structures of the beta-adrenergic blocking agents used are

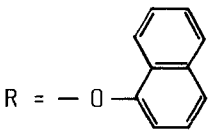




Bunitrolol



Alprenolol



Propanolol

RESULTS AND DISCUSSION

The influence of the drugs on the fluidity of the LDL particles is given in Figure 1. It is interesting to note that the optically isomeric types of propanolol show different effects on the fluidity of LDL. L-propanolol increased, d-propanolol decreased the fluidity of LDL in the region of the spin probe. Alprenolol increased the fluidity of LDL both at high and low ionic strengths, whereas bunitrolol decreased the fluidity. The measurement show that all pharmaca used penetrate into the LDL particles. Nosal et al.[3] investigated the interaction of alprenolol and propanolol with isolated platelet membranes using EPR. Their spin probe is comparable with that used in our experiments. Alprenolol and propanolol increased the fluidity of the platelet membranes.

The authors of [3] did not use the optical isomers of propanolol for their studies. SUREWICZ and LEYKO[9] described a membrane-stabilizing effect of propanolol on liquid-state bilayers. ROGERS et al.[2] described an ordering effect of propanolol on human erythrocytes. The interaction of propanolol and the other beta-adrenergic blocking agents was found to involve electrostatic interactions between cations and negatively charged binding sites on the cell surface, which may be protein, phospholipid or both in addition to a strong hydrophobic effect which perturbs the arrangement of molecules in the structure of the membrane.

According to the model of receptor-mediated endocytosis of BROWN and GOLDSTEIN[12] it seems possible that the incorporation of the beta-adrenergic blocking agents into LDL results in changed properties of the LDL surface (surface potential) and leads to different recognition conditions, which can explain the different levels of lipoproteins in human serum after treatment with beta-adrenergic blocking agents.

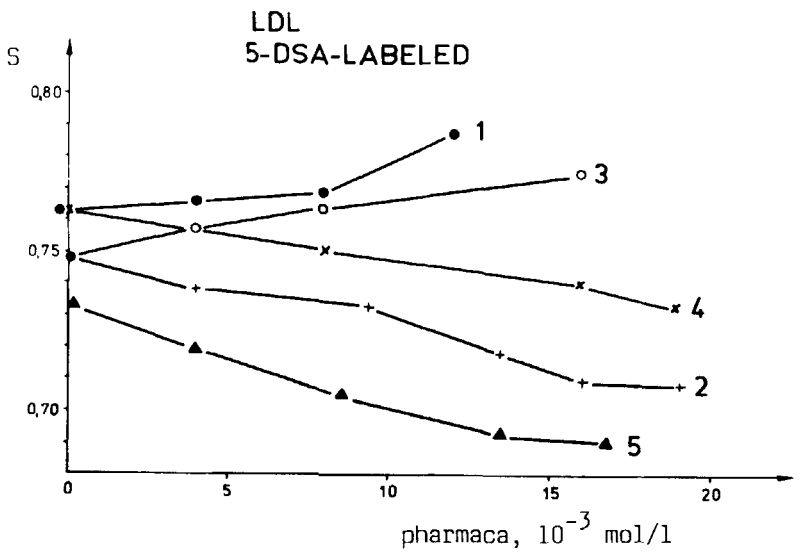


FIGURE 1. Influence of the pharmaca concentration on the calculated order parameter S of the spin probe.
1: Bunitrolol, LDL in 6.8 10^{-3} mol/l phosphate buffered solution (PBS), 1.4 10^{-1} mol/l NaCl, pH = 6.8
2: (-)-Propanolol, LDL in 10^{-2} mol/l tris, pH = 7.4
3: (+)-Propanolol, LDL in 6.8 10^{-3} mol/l PBS, 10^{-2} mol/l NaCl, 2.62 10^{-1} mol/l sucrose, pH = 6.8
4: Alprenolol, LDL in 6.8 10^{-3} mol/l PBS, 10^{-2} mol/l NaCl, 2.62 10^{-1} mol/l sucrose, pH = 6.8
5: Alprenolol, LDL in 6.8 10^{-3} mol/l PBS, 1.4 10^{-1} mol/l NaCl, pH = 6.8

REFERENCES

1. B. Shi an H.T. Tien, Biochim. Biophys. Acta, 859, 125 (1986).
2. J.A. Rogers, S. Cheng and G.V. Betagari, Biochem. Pharmacol., 35, 2259 (1986).
3. R. Nosal, V. Jancinova, K. Ondrias, J. Jakubovsky and P. Balgavy, Biochim. Biophys. Acta, 821, 217 (1985).
4. P. Schlieper, P.K. Medda and R. Kaufmann, Biochim. Biophys.Acta, 644, 273 (1981)
5. R.J. Havel, H.A. Eder and J.H. Brangdon, J.Clin.Invest. 34, 1345 (1955).
6. O.H. Lowry, N.J. Rosebrough, A.L.Farr and R.J. Randall, J.Biol. Chem., 193, 265 (1950)
7. O.H. Griffith and P.C. Jost, in Spin labeling. Theory and applications., edited by L.J Berliner (Academic Press, New York, 1976), pp. 453-489.
8. J. Seelig, ibid., pp. 454-523.
9. K.W. Surewicz and W. Leyko, Biochim.Biophys.Acta, 643, 387 (1981).
10. L. Wallenthin and B. Suudin, Atherosclerosis, 54, 241 (1985).
11. R.P. Ames, Drugs, 32, 335 (1986).
12. M.S. Brown and J.L. Goldstein, Science, 232, 34 (1986).