THEORETICAL STUDY ON CONFORMATION-RELATED ACTIVITY OF HYPOGLYCEMIC SULFONYLUREAS

R. Brasseur and M. Deleers

Laboratories of Macromolecules at Interfaces and Experimental Medicine, Faculty of Sciences and School of Medicine, C.P.206/2 Brussels Free University, 1050 Brussels, Belgium .

Received in final form 22 August 1983

SUMMARY Theoretical conformational analysis has been carried out for different hypoglycemic sulfonylurea –Ca complexes . The formed complex has an hydrophobic external surface and a low amphiphilic character. Our results suggest that Calcium may effectively be transported across membranes of Langerhans B cells and that the different biological potencies of the drugs may be due in part to the shape of the different complexes .

INTRODUCTION

The release of Insulin by hypoglycemic sulfonylureas (Malaisse 1974) is due to an accumulation of Ca^{++} in the islet B cell (Malaisse et al. 1972, Lebrun et al. 1982) presumably provoked by the Ca ionophoretic properties of these drugs (Couturier and Malaisse 1980_a) . This is quite conceivable because these sulfamides can transport Ca^{++} and Pr^{3+} into an organic phase (Couturier and Malaisse 1980_b, Deleers et al. 1981_a, 1982, 1983_a) or across lipid membranes (Deleers et al. 1980, 1983_b) and are quite lipophilic (Sehlin 1973, Hellman 1974, Taljedal 1974, Deleers and Malaisse 1983) . Moreover, the binding of these drugs to lipid membranes (Kaubish et al. 1982, Deleers and Malaisse 1983) and their relative ionophoretic capacity (Deleers et al. 1983_a) parallels their biological potency to stimulate insulin release. The aim of the present work is to propose that another factor may account for the different biological potencies of these widely used drugs . The present approach is based on the shape and steric hindrance of the most probable ionophoretic complexes which may cross the plasma membranes .

0031-6989/83/100901-07/$03.00/0

METHOD

We have computed the conformation of sulfonylureas of the second generation (Malaisse 1974) when they complex Ca^{++} in a 1 to 1 stoichiometry (Deleers and Malaisse 1983) in a medium of low dielectric constant (ε=3) representative of the hydrocarbon phase . The semi-empirical method for the systematic analysis of Ca-sulfonylureas complexes is based on a strategy described elsewhere (Brasseur et al. 1981, 1982, 1983, Deleers et al. 1982, 1983_c). The total internal energy (sum of Van der Waals interaction, torsional potential and electrostatic interaction) is calculated for each of the 6^7 conformation designated by the six positions due to increment of 60° on seven torsional angles . The seven torsional angles were defined in sequential order from the carbon of the urea group to the carbon of the amido group . The Ca^{++} ion was fixed at 2.65 Å from the ionized N atom located between the carbonyl and sulfonyl function . The N atom located at the amido group was also ionized . Out of the 279,936 conformations (for each sulfonylurea) derived from this study, the conformations with probability of existence of more than 8 % were then submitted to a minimization procedure (Nelder and Mead 1965) bearing on all torsional angles of the molecules, in order to further reduce their internal energy .

RESULTS AND DISCUSSION

Certain sulfonylurea such as Gliquidone and Glibenclamide bind Ca^{++} in a 1 to 1 molar ratio because these agents display two binding site for Ca^{++} (Deleers et al. 1983) . Glipizide and glisoxepide, two other sulfonylureas of the so-called "second generation" (Malaisse 1974) may bind Ca^{++} in a comparable manner . Our conformational analysis indicates that the molecules of sulfonylureas are capable of assuming a configuration for the insertion of a Ca ion into an hydrophilic cavity . Moreover, glibenclamide-Ca complex (P=64.5%) is quite

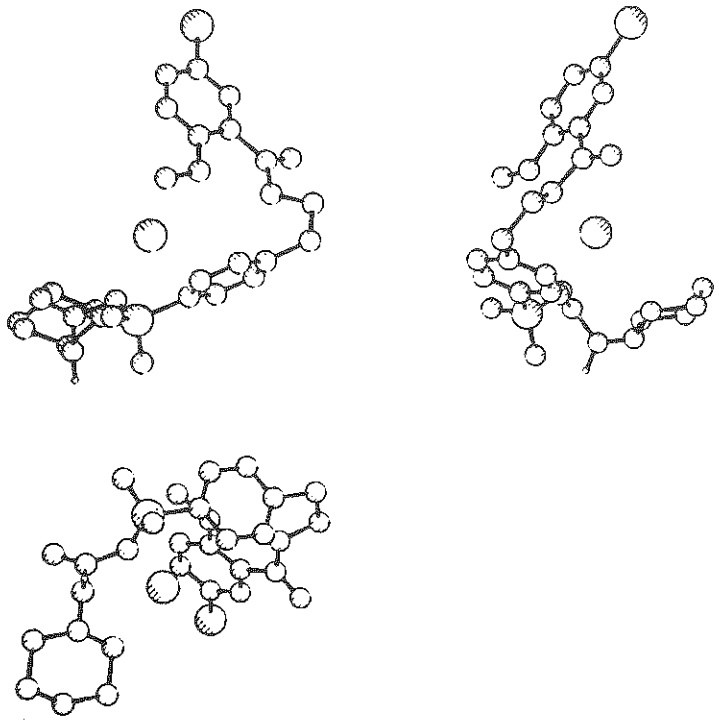

Fig. 1 : Views along 3 perpendicular axes of the most probable conformation for the Ca-glibenclamide complex (64.5%).

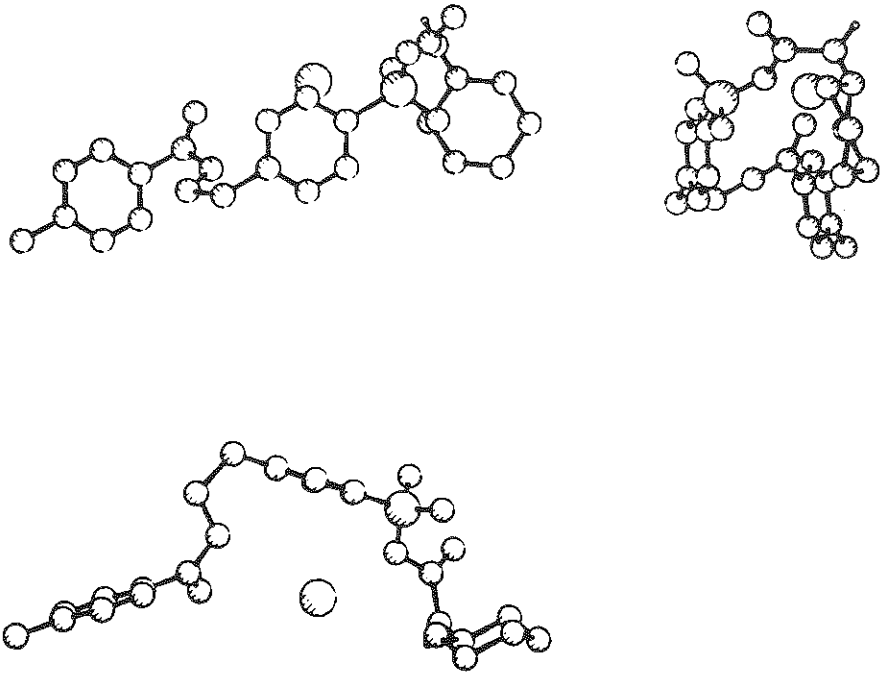

Fig. 2 : Views along 3 perpendicular axes of the most probable conformation for the Ca-glipizide complex (63%).

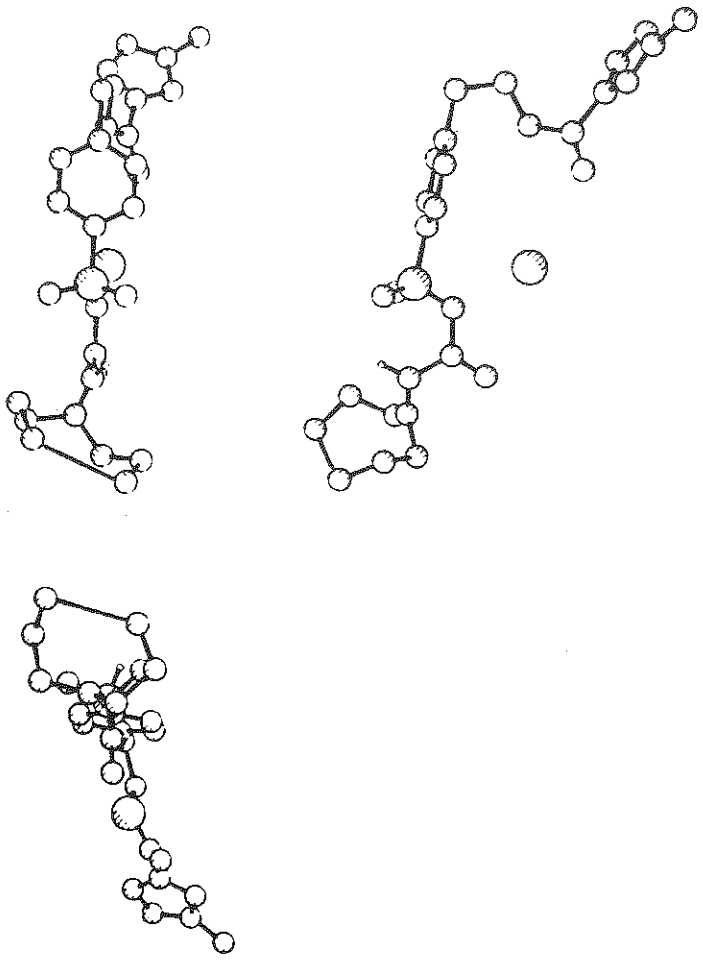

Fig. 3 : Views along 3 perpendicular axes of the most probable conformation for the Ca-glisoxepide complex (30%).

globular (Fig 1) with an external hydrophobic surface while glipizide-Ca and glisoxepide-Ca complexes (Figs 2,3) are more extended so that marked difference between an hydrophilic cavity and an hydrophobic external surface could not be entirely achieved . These latter configurations are then less favorable for the passage through membranes than the configuration of glibenclamide-Ca complex . In these conformations, the distance between Ca^{++} and the second site of ionization was not greater than 4.6 Å . Indeed, glibenclamide is two fold more potent than glisoxepide and three fold more potent

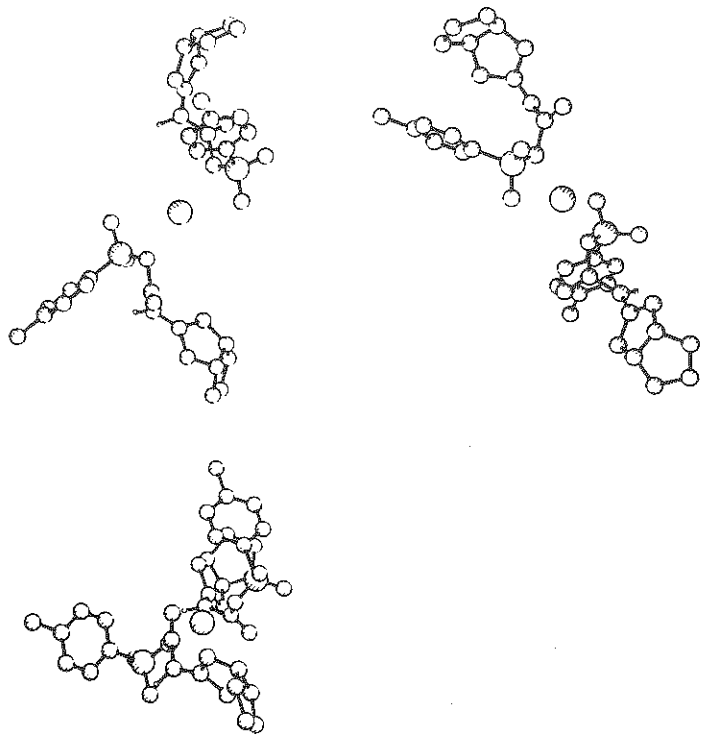

Fig. 4 : Views along 3 perpendicular axes of a conformation of the Ca-digliclazide complex .

than glipizide (Deleers and Malaisse 1983) . In order to compare, we show in Fig 4 the shape of a Ca(sulfonylurea)$_2$ complex (gliclazide$_2$Ca , Deleers et al 1982) which is larger than those described in this paper . The efficiency of the Ca transport and the pharmacological activity would be lowered, which is in fact the case (Deleers and Malaisse 1983). Moreover, we demonstrated that the transport of Ca-Ionophores complexes may be affected by their stoichiometries (Deleers and Malaisse 1982) . Another factor which may account for the Ca transport by hypoglycemic sulfonylureas is the formation of hybrid complexes with negative phospholipids which may serve as endogenous ionophores (Tyson et al. 1976,Weissmann et al. 1980, Serhan et al 1981,1982) . Indeed, the formation of hybrid complexes like those formed by A23187, X537A, Fod, and hypoglycemic sulfonylureas (Couturier et al 1980$_c$, Grandjean and Lazlo 1982, Deleers et al 1981$_b$,1982 ,1983$_d$) may have

important pharmacological implications in that exogenous drugs could better be able to display their ionophoretic capacity when acting synergistically with endogenous ionophores of pancreatic B cells .

The present findings on sulfonylureas show that the relatives insulinotropic potencies of these agents reveal a multifactorial phenomenon which always parallels the pharmacological potency if they are taken separately .

REFERENCES

Brasseur, R., Goormaghtigh, E. and Ruysschaert, J.M.: Biochem. Biophys. Res. Commun. 103, 301 (1981).
Brasseur, R., Deleers, M., Malaisse, W.J. and Ruysschaert, J.M.: Proc. Natl. Acad. Sci. USA 79, 2895 (1982).
Brasseur, R., Deleers, M. and Malaisse, W.J.: Biochem. Pharmacol. 32, 437 (1983).
Couturier, E. and Malaisse, W.J.: Diabetologia 19, 335 (1980a).
Couturier, E. and Malaisse, W.J.: Arch. Int. Pharmacodyn. Thérap. 245, 323 (1980b).
Couturier, E., Deleers, M. and Malaisse, W.J.: Pharm. Res. Commun. 12, 333 (1980c).
Deleers, M., Couturier, E., Mahy, M. and Malaisse, W.J.: Arch. Int. Pharmacodyn. Thérap. 246, 170 (1980).
Deleers, M., Couturier, E., Mahy, M., Gelbcke, M. and Malaisse, W.J.: Ann. Endocrinol. 42, 297 (1981a).
Deleers, M., Gelbcke, M. and Malaisse, W.J.: Proc. Natl. Acad. Sci. USA 78, 279 (1981b).
Deleers, M., Brasseur, R., Gelbcke, M. and Malaisse, W.J.: J. Inorg. Biochem. 16, 215 (1982).
Deleers, M. and Malaisse, W.J.: Chem. Phys. Lip. 31, 227 (1982).
Deleers, M., Brasseur, R. and Malaisse, W.J.: Biochem. Pharmacol. submitted (1983a).
Deleers, M., Gelbcke, M. and Malaisse, W.J.: FEBS Letters 151, 269 (1983b).
Deleers, M., Brasseur, R., Ruysschaert, J.M. and Malaisse, W.J.: Biophys. Chem. 17, 317 (1983c).
Deleers, M., Brasseur, R. and Malaisse, W.J.: Chem. Phys. Lip. in press (1983d).
Deleers, M. and Malaisse, W.J.: Diabetologia submitted (1983).
Grandjean, J. and Lazlo, P.: Biochem. Biophys. Res. Commun. 104, 1293 (1982).
Hellman, B.: Pharmacology 11, 257 (1974).
Kaubish, N., Hammer, R., Wollheim, C., Renold, A.E. and Offord, R.E.: Biochem. Pharmacol. 31, 1171 (1982).
Lebrun, P., Malaisse, W.J. and Herchuelz, A.: Diabetes 31, 1010 (1982).
Malaisse, W.J. in Cyclic AMP, New antidiabetic drugs, eds Glasser, B. and Benakis, A.
Nelder, J.A. and Mead, R.: Comput. J. 7, 303 (1965).
Sehlin, J.: Acta diabetol. lat. 5, 1052 (1973).

Serhan, C.N., Anderson, P., Goodman, I., Dunham, P.B., Weissmann, G.: J. Biol. Chem. 256, 2736 (1981).
Serhan, C.N., Fridrich, J., Goetzl, I.J., Dunham, P.B. and Weissmann, G.: J. Biol. Chem. 257, 4746 (1982).
Täljedal, I.-B.: Hormone Res. 5, 211 (1974).
Tyson, C.A., Vandezande, H. and Green, D.E.: J. Biol. Chem. 251, 1326 (1976).
Weissmann, G., Anderson, G., Serhan, C., Samuelsson, E. and Goodman, E.: Proc. Natl. Acad. Sci. USA 77, 1506 (1980).