Molecular Modelling Studies of Interaction of Antiarrhythmics with an Anionic Receptor Site

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The molecular mechanism of action of antiarrhythmics (AA) is still not thoroughly understood With respect to the structural heterogeneity of antiarrhythmics, these drugs were pharmacologically classified in several groups Lidocaine and mexiletine studied in this work are antiarrhythmic agents which belong to the class Ib category Their main antiarrhythmic effect is based on the interaction of these drugs with the sodium channel of the cardiac cell (Nattel 1991) However, the nature of these nonspecific interactions with myocardial membranes is not well defined

In our work theoretical ab initio SCF calculations were employed for the explicit modelling of the AA-receptor interaction The charged carboxylate and amine groups served as target for the binding of AAs to their supposed binding sites in the membrane On the basis of these calculations, a two-centre binding model for the antiarrhythmics to their receptor is proposed Within this model the lidocaine and mexiletine cations are in the first step recognised and bounded at the negatively charged part of the receptor In a subsequent step the interaction between the drug oxygen and cationic amine group of membrane protein may follow The influence of cations (Na^+, K^+, Mg^{2+}, and Ca^{2+}) on the strenght of the drug-anionic site interaction was investigated and the possible proton transfer from the drug towards the receptor was also studied

References

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Analgetically Active Substances Derived from Structures of Anpirtoline and Epibatidine

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