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ANA CAROLINE VASCONCELOS MARTINS

GluA2 - GLUTAMATERGIC RECEPTOR STUDY: A MOLECULAR APPROACH

FORTALEZA
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Thesis presented to the graduate program in Chemistry of the Universidade Federal do Ceará, as a requirement to obtain the Ph.D. degree in Chemistry, with expertise in Physical-Chemistry.

Supervisor: Profe. Dr. Pedro de Lima Neto
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To Jesus Christ all the honor, all the glory and all the praise.

I dedicate this work to my parents,

Felipe e Ana Martins.

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RESUMO

Os receptores de glutamato são os mediadores da maioria dos processos de neurotransmissão excitatória no sistema nervoso central, atuando como alvos proeminentes para o tratamento de vários distúrbios neurológicos, como Epilepsia, Esclerose Lateral Amiotrófica, Doença de Parkinson e Doença de Alzheimer. Assim, uma compreensão aprimorada de como o glutamato e outros ligantes interagem com o domínio de interação, desses receptores, pode trazer informações relevantes para o desenvolvimento de novos ligantes. Portanto, este trabalho teve por objetivo estudar a interação GluA2-ligante utilizando a estrutura de GluA2 co-cristalizada com os ligantes Glutamato, AMPA, Cainato e DNQX utilizando método baseado na Teoria do Funcional da Densidade combinado com o esquema de fracionamento molecular com capas conjugadas. Para abordar que a constante dielétrica do receptor GluA2 não é homogênea, foi proposta uma nova abordagem molecular, que foi aplicada para estudar a interação entre a GluA2 e os ligantes Glutamato, AMPA, Cainato e DNQX. Os resultados obtidos, considerando o modelo não-homogêneo, foram comparados com aqueles obtidos usando uma função dielétrica uniforme para o receptor GluA2 e com dados publicados na literatura, estabelecendo uma descrição mais detalhada dos resíduos de aminoácido mais relevantes para a interação proteína-ligante. Estudos de dinâmica molecular e cálculos DFT de sistemas proteicos normalmente consideram um valor fixo para a função dielétrica proteica. Nesse trabalho quando $\varepsilon = 1$ é considerado, muitos resíduos de aminoácido parecem relevantes, mas quando a blindagem da constante dielétrica foi considerada, eles perderam sua relevância. Os resultados apresentados para a energia de interação total GluA2-ligante e a energia de interação total D1-ligante e D2-ligante contribuiu com a diferenciação entre agonistas totais e agonistas parciais e entre agonistas e antagonistas. Além disso, os resultados permitem que seja feita hipótese sobre a correlação entre a energia de interação Glu705-ligante e a ação do ligante, abrindo caminho para o uso da função dielétrica não-homogênea para estudar receptores de glutamato e outros sistemas proteína-ligante. Por fim, os resultados também sugerem que para diferentes ligantes, diferentes constantes dielétricas homogêneas serão capazes de representar bem o sistema GluA2-ligante, tornando necessária a análise prévia com a abordagem da constante dielétrica não-homogênea.

Palavras-chave: GluA2. MFCC. DFT. constante dielétrica não-homogênea

ABSTRACT

Glutamate receptors are the mediators of most excitatory neurotransmission processes in the central nervous system, acting as prominent targets for the treatment of several neurological disorders such as Epilepsy, Amyotrophic Lateral Sclerosis, Parkinson's disease and Alzheimer's disease. Hence an improved understanding of how glutamate and other ligands interact with the binding domain, of these receptors, can bring relevant insights to the development of new ligands. Therefore, this work aims to study the GluA2–ligand interaction using the structure of GluA2 co-crystallized with the ligands glutamate, AMPA, kainate and DNQX applying a method based on the Density Functional Theory combined with the molecular fractionation with conjugate caps scheme. To address that the dielectric constant of the GluA2 receptor is not homogeneous, a novel molecular approach was proposed and it was applied to study the interaction between the GluA2 and the ligands glutamate, AMPA, kainate and DNQX. The results obtained, considering the inhomogeneous model, were compared with those obtained using an uniform dielectric function for the GluA2 receptor and with data published in the literature establishing a more detailed description of the relevant amino acid residues for the protein-ligand binding interaction. Molecular dynamics studies and protein DFT calculations usually consider a fixed value for the protein dielectric function. In this work when $\varepsilon = 1$ is considered, many amino acid residues seem important, but when the dielectric constant shield was considered, they lost their relevance. The results for the GluA2-ligand total interaction energy and the D1-ligand and D2-ligand total interaction energy also shed some light on the differentiation between full and partial agonists, and between agonists and antagonists. Additionally, the results allow a hypothesis on the correlation between the Glu705-ligand interaction energy and the ligand action, paving the way for the use of the inhomogeneous dielectric function to study glutamate receptors and other protein-ligand systems. Finally, the results also suggests that for different ligands, different homogeneous dielectric constant will be able to well represent the system GluA2-ligand, making it necessary the previous analyses with the inhomogeneous dielectric constant approach.

Key-words: GluA2. MFCC. DFT. inhomogeneous dielectric constant

FIGURES LIST

TABLES LIST

SUMMARY