Abstract

Cytochrome P450 1A2 is a human liver enzyme of a hemoprotein nature that belongs to the evolutionarily ancient group of cytochromes P450. Cytochrome P450 substrates include a wide range of drugs and most procarcinogens, making it a crucial enzyme for the study of carcinogenesis. The main reaction catalyzed by cytochrome P450 1A2 is monooxygenation, in which an oxygen atom is incorporated into a substrate molecule. This reaction takes place at an active site which, in the case of published structure of cytochrome P450 1A2, is buried in the core of the catalytic domain without an accessible tunnels. Molecular modeling techniques allow the study of dynamic phenomena in large systems and are therefore also suitable for simulations of the transport of substrate molecules to the active site. The tunnels are being made accessible due to structural fluctuations.

In this work, molecular modeling techniques were used to study the pathways that the naphthalene molecule uses to enter the active site of cytochrome P450 1A2. A system consisting of cytochrome P450 1A2 anchored in a phospholipid membrane, water, ion and naphthalene molecules was simulated. The simulations yielded trajectories with a total length of 8 μs and the analysis identified seven tunnels that can be used to transport substrates. Furthermore, immersion of naphthalene molecules by tunnels 2b and 2c directly to the active site of cytochrome P450 1A2 and partial immersion in tunnels 2f and 3 were observed. A correlation between the occurrence density of naphthalene in the vicinity of the tunnels, their opening and the entry of naphthalene was found.

Key words: cytochrome P450 1A2, naphthalene, protein tunnels, molecular dynamics