Multidrug ABC transporter Cdr1 of *Candida albicans* harbors specific and overlapping binding sites for human steroid hormones transport

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ABSTRACT

The present study examines the kinetics of steroids efflux mediated by the Candida drug resistance protein 1 (Cdr1p) and evaluates their interaction with the protein. We exploited our in-house mutant library for targeting the 252 residues forming the twelve transmembrane helices (TMHs) of Cdr1p. The screening revealed 65 and 58 residues critical for β-estradiol and corticosterone transport, respectively. Notably, up to 83% critical residues for corticosterone face the lipid interface compared to 54% for β-estradiol. Molecular docking identified a possible peripheral corticosterone-binding site made of 8/14 critical/non-critical residues between TMHs 3, 4 and 6. β-estradiol transport was severely hampered by alanine replacements of Cdr1p core residues involving TMHs 2, 5 and 8, in a binding site made of 10/14 critical residues mainly shared with rhodamine 6G with which it competes. By contrast, TMH11 was poorly impacted, although being part of the core domain. Finally, we observed the presence of several contiguous stretches of 3-5 critical residues in TMHs 2, 5 and 10 that points to a rotation motion of these helices during the substrate transport cycle. The selective structural arrangement of the steroid-binding pockets in the core region and at the lipid-TMD interface, which was never reported before, together with the possible rotation of some TMHs may be the structural basis of the drug-transport mechanism achieved by these type II ABC transporters.