Molecular modeling of salsolinol, a full Gi protein agonist of the ?-opioid receptor, within the receptor binding site

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(R/S)-Salsolinol is a full agonist of the ?-opioid receptor (?OR) Gi protein pathway via its (S)-enantiomer and is functionally selective as it does not promote ?-arrestin recruitment. Compared to (S)-salsolinol, the (R)-enantiomer is a less potent agonist of the Gi protein pathway. We have now studied the interactions of the salsolinol enantiomers docked in the binding pocket of the ?OR to determine the molecular interactions that promote enantiomeric specificity and functional selectivity of (R/S)-salsolinol. Molecular dynamics simulations showed that (S)-salsolinol interacted with 8 of the 11 residues of the ?OR binding site, enough to stabilize the molecule. (R)-Salsolinol showed higher mobility with fewer prevalent bonds. Hence, the methyl group bound to the (S)-stereogenic center promoted more favorable interactions in the ?OR binding site than in the (R)-orientation. Because (S)-salsolinol is a small molecule (179.2 Da), it did not interact with residues implicated in the binding of larger morphinan agonists that are located toward the extracellular portion of the binding pocket: W3187.35, I3227.39, and Y3267.43. Our results suggest that contact with residues which (S)-salsolinol interacts with are enough to elicit Gi protein activation, and possibly define a minimum set required by ?OR ligands to promote activation of the Gi protein pathway.