DISTINCT HETEROMERIC PARTNERS MODULATE (S)-METHADONE EFFICACY IN μ-OPIOID RECEPTORS

(R,S)-Methadone ((R,S)-MTD) is an opioid used as an analgesic and a maintenance therapy for opioid use disorder. (R,S)-MTD acts as a μ-opioid receptor (MOR) agonist but the therapeutic properties are believed to be mediated by the pharmacological actions of (R)-MTD, whereas (S)-MTD was historically considered the inactive enantiomer of (R,S)-MTD.
The μ-opioid receptor (MOR) is a class A G protein coupled receptor (GPCR) that couples to inhibitory Gi/o proteins, mediating analgesic and antistressor effects.
It has been described that MOR can form heteromers with several receptors, including galanin Gal_1 receptor (Gal_1R) and CRF_1 receptor (CRF_1R). MOR-Gal_1R heteromers play a significant role in the rewarding effects of opioids while MOR-CRF_1R modulates the antistressor effect of opioids and the hyperalgesia of opioid withdrawal.
Previous results indicated that when MOR forms heteromers with Gal_1R, (S)-MTD specifically loses its efficacy at activating MOR. Even if MOR-CRF_1R and MOR-Gal_1R share the same heteromeric disposition, *in vitro* experiments have revealed that (S)-MTD behaves in the MOR-CRF_1R heteromer as in the MOR that does not form heteromers with Gal_1R.
To understand the different behaviour of (S)-MTD at activating MOR in the presence of CRF_1R or Gal_1R at the molecular level, we have compared models of the MOR-CRF_1R and MOR-Gal_1R heteromer. MD simulations exposed a distinct rearrangement of MOR-MOR homomeric interfaces caused by Gal_1R or CRF_1R. This implied a different binding of (S)-MTD with the external MOR protomer, leading to a loss in efficacy in MOR-Gal_1R but no differences in MOR-CRF_1R compared with (R)-MTD.

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