

**Fig. S9:** *Interactions between the agonist NDP-α-MSH and the MC4R.* Potential hydrogen bonds and hydrophobic interactions were analyzed using HBPLUS <sup>1</sup> with a maximum donor acceptor distance of 3.5 Å as implemented in the program LigPlot+ v.2.1 <sup>2</sup>, which was used to draw this schematic view. Potential hydrogen bonds are indicated by black dashed lines and distance labels. Residues with closest distances of less than 3.9 Å are considered to be in van der Waals contact. These residues are shown as dashed, red segments of a circle. Water molecules (cyan color) and the calcium ion (green color) are depicted as spheres, respectively.