Endomorphin-2 is an arrestin-biased agonist because it induces greater MOPr phosphorylation than predicted from its efficacy for G protein coupling

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Our previous results (McPherson et al., 2010, Mol Pharm 78:756) suggested that the endomorphins show bias towards arrestin recruitment. Here we have investigated the signalling of endomorphin-2 in more detail. We firstly analysed our previous data according to the method described by Rajagopal et al (2011, Mol Pharm 80:367) in order to quantify ligand bias; this indicated that endomorphin-2 is significantly biased towards arrestin (bias factor -0.81±0.18; p<0.05), whilst morphine was not biased (bias factor -0.02±0.05). We next determined the efficacy of endomorphin-2 and other agonists for Ser\(^{375}\) phosphorylation of MOPr, by quantification of HEK293 cell imaging using an antiphosphoSer\(^{375}\) antibody in an INCell Analyser. This indicated that the efficacy of endomorphin-2-induced phosphorylation was as great as that of DAMGO, and much higher than that of morphine. Finally, the ability of endomorphin-2 to induce desensitization of inwardly rectifying K\(^+\) channels in neurones of the rat locus coeruleus (LC) was examined. The rate of desensitization induced by endomorphin-2 was faster than that of DAMGO and other agonists examined. These data indicate that endomorphin-2 is an arrestin biased ligand which has distinctive properties at MOPr in brain. The arrestin bias may be due to the ability of endomorphin-2 to induce greater MOPr phosphorylation than expected from its efficacy to induce coupling to G protein.