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Comparison of two downstream signaling pathways in the μ-opioid receptors activated by several opioids

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In Japan, morphine (MRP), fentanyl (FEN), oxycodone (OXY) and hydromorphone (HDM) have been approved as pain analgesics in palliative and supportive care. Although all of them are selective for μ-opioid receptors (μOR), their receptor-activated signaling properties are different. Moreover, the combined and switching effets among them are complicated. Recent molecular analyses of the properties of μOR revealed two downstream pathways either eliciting analgesic effects through a G protein-mediated pathway or through the β-arrestin-mediated pathway that causes adverse events (AEs). However, molecular charactrerization of interaction among opioids has not investigated sufficiently. We therefore investigated characterization of these opioids using cells stably expressing μOR by three cell-based CellKey™, GloSensor™ cAMP and internalization assays.

To Detect μOR-mediated G protein-mediated signaling, both CellKey™ assay and GloSensor™ cAMP assay were used; the former is an electric impedance-based measurement, the latter is the measurement of the real-time cAMP levels. Among four opioids, the rank order of EC_{50} of each opioid was FEN≤HDM<MRP≤OXY in the above two assays. On the other hand, internalization assay suggested that internalization of μOR by activation of β-arrstin-mediated pathway occurred only in the case of FEN.

Based on these data got by single opioid, we are now on the way to investigate charactrestics of these pathways by simultaneous administration of several combinations of opioids.