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UNIVERSITÉ PARIS DESCARTES

IPNP Seminar

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(Host Z Lenkei)

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Phosphorylation-deficient G-protein-biased μ-opioid receptors improve analgesia and diminish tolerance but worsen opioid side effects

Monday October 7th, 2019, 1pm

R04-45, 102-108 rue de la santé - 75014 Paris

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Pharmacologist Dr Andrea Kliewer studies the mechanisms for the development of tolerance to opioids such as fentanyl and morphine. She showed shown that desensitization of the μ-opioid receptor and interaction with β-arrestins is controlled by carboxyl-terminal phosphorylation. She demonstrated that the development of opioid tolerance is mediated by phosphorylation and desensitisation of the opioid receptor. She created knockin mice with a series of serine- and threonine-to-alanine mutations that render the receptor increasingly unable to recruit β-arrestins. Desensitization is inhibited in locus coeruleus neurons of mutant mice. Opioid-induced analgesia is strongly enhanced and analgesic tolerance is greatly diminished. Surprisingly, respiratory depression, constipation, and opioid withdrawal signs are unchanged or exacerbated, indicating that β-arrestin recruitment does not contribute to the severity of opioid side effects and, hence, predicting that G-protein-biased μ-agonists are still likely to elicit severe adverse effects.

Keywords: animal model, Autoradiographic binding assay, behavior study, electrophysiology, pharmacology