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Professor of Molecular Pharmacology

Area of research

Molecular mechanisms of desensitisation of G-protein coupled receptors

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Summary

There are more than 800 G protein-coupled receptors (GPCRs) in the genome and they represent a major target for clinically-prescribed drugs. Following prolonged or repeated exposure to agonist drugs that activate these receptors, the GPCRs invariably become less responsive to the agonist, a phenomenon called desensitisation. Desensitisation can limit the effectiveness of drug therapy. This group's research focuses on the molecular mechanisms of desensitisation of GPCRs.

A common mechanism of desensitisation involves phosphorylation of the GPCR by G protein-coupled receptor kinases (GRKs) or by second messenger-dependent protein kinases such as PKC and PKA. In many cases GPCR phosphorylation leads to the interaction of proteins called arrestins with the GPCR, which prevents further coupling of the receptor to G protein i.e. desensitisation. In our work we can measure the association of regulatory proteins such as GRKs and arrestins with GPCRs using a variety of imaging, immunological and molecular techniques.

We can also measure the trafficking of GPCRs around cells using confocal microscopy, and employ specific mutants to determine the molecular mechanisms of GPCR internalisation. Treatment of cells expressing mGluR1 α with glutamate induces internalisation that can be blocked by the co-expression of dominant-negative mutants of arrestin and dynamin, indicating that mGluR1 α internalises via clathrin-coated pits. Furthermore, the constitutive internalisation of the transferrin is not blocked by the arrestin mutant but is blocked by the dynamin mutant, indicating that transferrin internalisation is independent of arrestins.

Activities / Findings

- the molecular mechanisms that mediate desensitisation of the μ opioid receptor and its relationship to morphine tolerance
- the co-regulation of group I mGluRs by different protein kinases
- the internalisation, intracellular sorting, and recycling of P2Y receptor subtypes.

Methodologies

- Molecular biology
- viral vector construction
- Immunocytochemistry
- Confocal imaging
- FRET
- Cell Culture
- radioimmunoassay
- radioligand binding

Memberships

Organisations

[School of Physiology, Pharmacology & Neuroscience](#)

Research Areas

- [Receptor signalling and regulation](#)

Recent publications

- Henderson, G, Kelly, E & Gill, H, 2019, '[How the complex pharmacology of the fentanyl contributes to their lethality](#)'. *Addiction*.
- Hill, R, Disney, A, Conibear, A, Sutcliffe, K, Dewey, W, Husbands, S, Bailey, C, Kelly, E & Henderson, G, 2018, '[The novel \$\mu\$ -opioid receptor agonist PZM21 depresses respiration and induces tolerance to antinociception](#)'. *British Journal of Pharmacology*, vol 175., pp. 2653-2661
- Hill, R, Dewey, WL, Kelly, E & Henderson, G, 2018, '[Oxycodone-induced tolerance to respiratory depression: reversal by ethanol, pregabalin and protein kinase C inhibition](#)'. *British Journal of Pharmacology*, vol 175., pp. 2492-2503
- Kelly, E, Henderson, G & Bailey, CP, 2018, '[Emerging areas of opioid pharmacology](#)'. *British Journal of Pharmacology*, vol 175., pp. 2715-2716
- Alexander, SP, Striessnig, J, Kelly, E, Marrion, NV, Peters, JA, Faccenda, E, Harding, SD, Pawson, AJ, Sharman, JL, Southan, C, Davies, JA & , 2017, '[THE CONCISE GUIDE TO PHARMACOLOGY 2017/18: Voltage-gated ion channels](#)'. *British Journal of Pharmacology*, vol 174., pp. S160-S194
- Alexander, SP, Kelly, E, Marrion, NV, Peters, JA, Faccenda, E, Harding, SD, Pawson, AJ, Sharman, JL, Southan, C, Davies, JA & , 2017, '[THE CONCISE GUIDE TO PHARMACOLOGY 2017/18: Other ion channels](#)'. *British Journal of Pharmacology*, vol 174., pp. S195-S207
- Alexander, SP, Kelly, E, Marrion, NV, Peters, JA, Faccenda, E, Harding, SD, Pawson, AJ, Sharman, JL, Southan, C, Davies, JA & , 2017, '[THE CONCISE GUIDE TO PHARMACOLOGY 2017/18: Transporters](#)'. *British Journal of Pharmacology*, vol 174., pp. S360-S446
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- Alexander, SP, Fabbro, D, Kelly, E, Marrion, NV, Peters, JA, Faccenda, E, Harding, SD, Pawson, AJ, Sharman, JL, Southan, C, Davies, JA & , 2017, '[THE CONCISE GUIDE TO PHARMACOLOGY 2017/18: Catalytic receptors](#)'. *British Journal of Pharmacology*, vol 174., pp. S225-S271
- Alexander, SP, Fabbro, D, Kelly, E, Marrion, NV, Peters, JA, Faccenda, E, Harding, SD, Pawson, AJ, Sharman, JL, Southan, C, Davies, JA & , 2017, '[THE CONCISE GUIDE TO PHARMACOLOGY 2017/18: Enzymes](#)'. *British Journal of Pharmacology*, vol 174., pp. S272-S359

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Networks & contacts

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- Cornelius Krasel - Reading
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