JPS-ASCEPT Lecture 2022 (On-line)

12 月 3 日（土）9:30～10:30 第 6 会場（第 96 回日本薬理学会年会 4 日目）
座長：金井　好克（大阪大学／国際対応委員長）

Fine-tuning glutamate receptor activity with allosteric modulators for neurodegenerative and psychiatric disorders

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日本薬理学会とオーストラリア・ニュージーランド薬理学会（ASCEPT）の講師交換プログラムで Karen Gregory 先生が講演されます。Gregory 先生は、2009 年にオーストラリア Monash 大学で PhD を取得され、Vanderbilt University (US)でポスドクをされた後、2011 年に現所属に異動されています。Class C GPCR でのアロステリック調節と'biased agonism'、および構造生物学に関する最先端の研究を進めています。ASCEPT から交換プログラム講師としてご推薦いただき、薬理学会年会での講演をお願いすることになりました。
On-line でのご登壇ですが多数の会員のご視聴をお待ちしています

Glutamate neurotransmission is mediated via ionotropic and metabotropic glutamate receptors (mGlu). By acting at alternate non-conserved sites at the mGlu5 subtype, allosteric modulators offer promise to treat a range of neurodegenerative and psychiatric disorders. Allosteric modulators fine-tune receptor activity with spatio-temporal control, greater subtype selectivity and can bias mGlu5 activity to preference different cellular responses. Our central hypothesis is previously unappreciated biased activation and modulation of mGlu5 underpins translational failures of diverse allosteric modulators.

To build a more complete molecular fingerprint we assess multiple measures of mGlu5 activity using a combination of recombinant cells expressing human or rat mGlu5 as well as primary brain cell cultures. Rigorous analytical methods allow quantification of allosteric modulator cooperativity and affinity from kinetic binding assays, as well as second messenger and compartmentalised kinase biosensor assays. We found structurally diverse mGlu5 allosteric modulators have distinct kinetic profiles and differentially influence mGlu5 activity in a spatio/temporal fashion. Probe dependence was evident for modulating glutamate versus quisqualate. This has implications for translating profiles in primary brain cell cultures to in vivo effects.

By linking molecular pharmacological properties to known preclinical and clinical effects, we seek to provide an enriched understanding of the drivers of efficacy as well as failures. We imagine these molecular fingerprints of mGlu5 allosteric modulators can be employed to triage undesirable compounds and streamline future drug discovery efforts.

Selected recent original research articles：

Mol Pharmacol (2021), ***Biochem Pharmacol*** (2020), ***Nature*** (2016), ***Science*** (2014)