

Allosteric Modulation of Ionotropic Glutamate Receptors Special Issue

This special issue of *ACS Medicinal Chemistry Letters* is dedicated to highlighting recent medicinal chemistry as it relates to allosteric modulation of ionotropic (AMPA, NMDA, and Kainate) and metabotropic glutamate receptors (mGluRs). These receptors are widely expressed in the central nervous system (CNS), where they are activated by L-glutamic acid. Brogi et al. lead off the issue with an overview of the key concepts of allosteric modulation as it pertains to ionotropic glutamate receptors. The authors summarize the site and mechanism of action of key compounds that are frequently used as research tools. The ionotropic and metabotropic glutamate receptors are targets for existing therapeutic intervention, including the use of the negative allosteric modulator perampanel on AMPA receptors for the treatment of epilepsy. As described by Yuan et al., perampanel alters the single channel properties through effects on the process of gating, which could be of utility in a range of CNS disorders. Of note, interest in NMDA receptors has received considerable attention and is quite timely given the clinical data for ketamine in treatment-resistant major depression.¹ Chrovian et al. described the synthesis and structure–activity relationship for novel modulators of the GluN2B subtype of the NMDA receptor. Summer et al. provide structural insight into the allosteric regulators of GluN2C- and GluN2D-NMDA receptors, which is based on an earlier structure–activity relationship of GluN2A-selective NAMs that possesses a π – π stacking motif. Savall et al. describe a new way of modulating AMPA receptors via targeting accessory proteins (TARPs) and provide preclinical evidence for anticonvulsant activity. Laulumaa et al. provide new crystal structural data describing GluA2 bound to the novel modulators TDPAM01 and TDPAM02. Finally, Panarese et al. describe the characterization of a new PAM, VU2957 (or Valiglurax), which is selective for the metabotropic glutamate receptor mGluR4 and is relevant for Parkinson's disease.

Overall, these articles highlight recent and emerging science around these targets, where new structural insights and pharmacology offer new approaches to CNS disorders.

Nicholas I. Carruthers,[†] Guest Editor

Timothy W. Lovenberg,[†] Guest Editor

Stephen F. Traynelis,^{*,‡} Guest Editor 

[†]Janssen Research & Development, LLC, La Jolla, California 92121, United States

[‡]Department of Pharmacology, Emory University School of Medicine, Atlanta, Georgia 30322, United States

AUTHOR INFORMATION

ORCID

Stephen F. Traynelis: [0000-0002-3750-9615](https://orcid.org/0000-0002-3750-9615)

Notes

Views expressed in this editorial are those of the authors and not necessarily the views of the ACS.

REFERENCES

- (1) Murrrough, J. W.; Iosifescu, D. V.; Chang, L. C.; Al Jurdi, R. K.; Green, C. E.; Perez, A. M.; Iqbal, S.; Pillemer, S.; Foulkes, A.; Shah, A.; Charney, D. S.; Mathew, S. J. *Am. J. Psychiatry* **2013**, *170* (10), 1134–42.

Special Issue: Allosteric Modulation of Ionotropic Glutamate Receptors

Published: March 14, 2019

