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Editorial

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The Endocannabinoid System: From Basic Research to Translational Opportunity

This special issue of *ACS Chemical Neuroscience*, which was guest-edited by Rao Rapaka, Joni Rutter, and David Shurtleff and relates to a NIDA-ICRS co-sponsored workshop in July of 2011 entitled "Endocannabinoid Metabolic Enzymes and Drug Development", focuses on the molecular composition, pharmacologic targeting, and physiological significance of the endocannabinoid system, a lipid signaling network that is the target of the psychoactive component of marijuana, Δ^9-tetrahydrocannabinol (THC). In the early 1990s, the cannabinoid receptors CB1 and CB2 were identified as the molecular targets of THC and soon thereafter the endogenous cannabinoid ligands ("endocannabinoids") *N*-arachidonoylethanolamine (anandamide) and 2-arachidonoylglycerol (2-AG) were discovered.[1,2] Endocannabinoid signaling has been implicated in numerous physiological processes, including pain, inflammation, appetite, reproduction, and neurodegeneration.

Preparations of the *Cannabis* plant have been used for medicinal purposes for thousands of years; however, the characteristic "high" elicited by direct cannabinoid agonists such as THC and their concomitant detrimental effects on cognition and motor control limit their widespread clinical use. Alternative strategies to harness the therapeutic potential of the endocannabinoid system include amplifying the actions of the body's own endocannabinoids by disrupting their metabolism and utilizing bioactive, nonpsychoactive phytocannabinoids.

Several of the articles featured in this issue describe the characterization of endocannabinoid metabolic enzymes, which are considered to be promising drug targets for the treatment of conditions such as chronic pain and neuropsychiatric disorders. Piscitelli and Di Marzo present a review highlighting how the complexity of endocannabinoid inactivation may impact endocannabinoid hydrolase-based analgesics.[3] Exemplifying this complexity, anandamide and related *N*-acylethanolamines can be hydrolyzed by multiple enzymes including fatty acid amide hydrolase (FAAH) and *N*-acylethanolamine-hydrolyzing acid amidase (NAAA).[4] Kaczocha and colleagues describe FAAH-mediated anandamide hydrolysis in lipid vesicles,[5] while Tai and colleagues report on endogenous molecules that stimulate NAAA activity.[6] 2-AG degradation in the brain and many peripheral tissues is catalyzed primarily by monoacylglycerol lipase (MAGL).[4] To investigate the mechanisms of pharmacological inactivation of MAGL, Karageorgos and colleagues describe the generation and characterization of engineered human MAGL mutants.[7] In addition to hydrolysis, polyunsaturated endocannabinoids are prone to enzymatic oxidation, which Dainese and colleagues demonstrate affects membrane properties.[8]

Selective pharmacological agents that disrupt endocannabinoid metabolism have proven to be powerful tools to investigate the effects of enhanced endocannabinoid signaling in vivo. In this issue, two articles describe the development of advanced small-molecule inhibitors of endocannabinoid hydrolases. Otrubova and Boger have contributed a review summarizing the history of α-ketoheterocycle-based FAAH inhibitors.[9] Niphakis and colleagues describe a class of *O*-hydroxyacetamide carbamates, which potently and selectively block endocannabinoid hydrolases.[10]

This issue also contains two basic science research articles describing the metabolomic and behavioral consequences of blocking endocannabinoid metabolism in mammals. Wiskerke and colleagues employed in vivo microdialysis techniques to directly monitor interstitial endocannabinoid levels in the brains of rats and mice following inhibition of endocannabinoid clearance.[11] Wise and colleagues describe the effects of simultaneously inhibiting FAAH and MAGL on short-term memory in mice.[12]

Two additional papers focus on physiological processes affected by endo- and exocannabinoids. In a review contributed by Sun and Dey, the role of endocannabinoid signaling in female fertility is discussed.[13] Valdeolivas and colleagues present new research describing the neuroprotective effects of a combination of phytocannabinoids in an inflammatory model of Huntington's disease.[14]

Together, the papers presented in this special issue of *ACS Chemical Neuroscience* nicely capture the many exciting advances that have been made in our understanding of the endocannabinoid system. This knowledge, combined with the emergence of selective and in vivo active chemical probes to perturb specific protein components of the endocannabinobid system, promises to enable a full exploration of its physiological functions and translational potential for treating a range of human diseases.

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REFERENCES

(1) Lambert, D. M., and Fowler, C. J. (2005) The Endocannabinoid System: Drug Targets, Lead Compounds, and Potential Therapeutic Applications. *J. Med. Chem. 48*, 5059−5087.
(2) Di Marzo, V., Bisogno, T., and De Petrocellis, L. (2007) Endocannabinoids and Related Compounds: Walking Back and Forth between Plant Natural Products and Animal Physiology. *Chem. Biol. 14*, 741−756.
(3) Piscitelli, F., and Di Marzo, V. (2012) "Redundancy" of endocannabinoid inactivation: new challenges and opportunities for pain control. *ACS Chem. Neurosci.*, DOI: 10.1021/cn300015x.
(4) Ahn, K., McKinney, M. K., and Cravatt, B. F. (2008) Enzymatic Pathways That Regulate Endocannabinoid Signaling in the Nervous System. *Chem. Rev. 108*, 1687−1707.
(5) Kaczocha, M., Lin, Q., Nelson, L. D., McKinney, M. K., Cravatt, B. F., London, E., and Deutsch, D. G. (2012) Anandamide Externally-

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added to Lipid Vesicles Containing Trapped Fatty Acid Amide Hydrolase (FAAH) is Readily Hydrolyzed in a Sterol-modulated Fashion. *ACS Chem. Neurosci.*, DOI: 10.1021/cn300001w.
(6) Tai, T., Tsuboi, K., Uyama, T., Masuda, K. R., Cravatt, B. F., Houchi, H., and Ueda, N. (2012) Endogenous Molecules Stimulating *N*-Acylethanolamine-Hydrolyzing Acid Amidase (NAAA). *ACS Chem. Neurosci.*, DOI: 10.1021/cn300007s.
(7) Karageorgos, I., Zvonok, N., Janero, D. R., Vemuri, V. K., Wales, T. E., Engen, J. R., and Makriyannis, A. (2012) Endocannabinoid Enzyme Engineering: Soluble Human Thio-monoacylglycerol Lipase (sol-S-hMGL). *ACS Chem. Neurosci.*, DOI: 10.1021/cn3000263.
(8) Dainese, E., Sabatucci, A., Angelucci, C. B., Barsacchi, D., Chiarini, M., and Maccarrone, M. (2012) Impact of Embedded Endocannabinoids and Their Oxygenation by Lipoxygenase on Membrane Properties. *ACS Chem. Neurosci.*, DOI: 10.1021/cn300016c.
(9) Otrubova, K., and Boger, D. L. (2012) α-Ketoheterocycle-Based Inhibitors of Fatty Acid Amide Hydrolase (FAAH). *ACS Chem. Neurosci.*, DOI: 10.1021/cn2001206.
(10) Niphakis, M. J., Johnson, D. S., Ballard, T. E., Stiff, C., and Cravatt, B. F. (2012) *O*-Hydroxyacetamide Carbamates as a Highly Potent and Selective Class of Endocannabinoid Hydrolase Inhibitors. *ACS Chem. Neurosci.*, DOI: 10.1021/cn200089j.
(11) Wiskerke, J., Irmina, C., Cravatt, B. F., De Vries, T. J., Schoffelmeer, A. N. M., Pattij, T., and Parsons, L. H. (2012) Characterization of the effects of re-uptake and hydrolysis inhibition on interstitial endocannabinoid levels in the brain: an in vivo microdialysis study. *ACS Chem. Neurosci.*, DOI: 10.1021/cn300036b.
(12) Wise, L. E., Long, K. A., Abdullah, R. A., Long, J. Z., Cravatt, B. F., and Lichtman, A. H. (2012) Dual Fatty Acid Amide Hydrolase and Monoacylglycerol Lipase Blockade Produces THC-Like Morris Water Maze Deficits in Mice. *ACS Chem. Neurosci.*, DOI: 10.1021/cn200130s.
(13) Sun, X., and Dey, S. K. (2012) Endocannabinoid Signaling in Female Reproduction. *ACS Chem. Neurosci.*, DOI: 10.1021/cn300014e.
(14) Valdeolivas, S., Satta, V., Pertwee, R. G., Fernandez-Ruiz, J., and Sagredo, O. (2012) Sativex-like Combination of Phytocannabinoids is Neuroprotective in Malonate-Lesioned Rats, an Inflammatory Model of Huntington's Disease: Role of Cb1 and Cb2 Receptors. *ACS Chem. Neurosci.*, DOI: 10.1021/cn200114w.