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In This Issue

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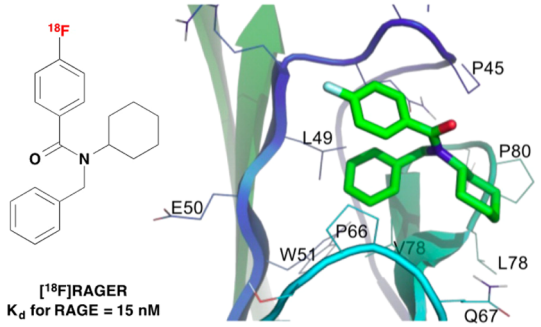
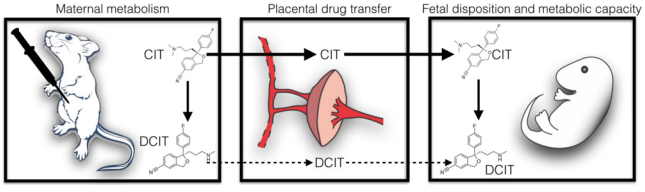
A NOVEL RADIOTRACER FOR IMAGING RAGE



The Receptor for Advanced Glycation Endproducts (RAGE) is a transmembrane receptor that belongs to the immunoglobulin superfamily of cell surface molecules. It is thought to play a role in Alzheimer's disease (AD) by mediating the influx of circulating amyloid-β (Aβ) into the brain as well as amplifying Aβ-induced pathogenic responses. While a ^{99m}Tc monoclonal antibody and ^{18}F labeled S100 protein targeting RAGE have been reported, neither crosses the BBB. Currently, there is no known brain permeable radiotracer for RAGE. To address this gap, Cary et al. (DOI: 10.1021/acschemneuro.5b00319) synthesized [^{18}F]RAGER as the first small molecule radiotracer, based upon a known RAGE inhibitor.

The authors report the synthesis of [^{18}F]RAGER and docking studies to propose a likely binding interaction with RAGE and initial preclinical evaluation using autoradiography with AD brain samples and in vivo imaging in rodent and nonhuman primate. [^{18}F]RAGER autoradiography showed colocalization with RAGE identified by immunohistochemistry in AD brain samples, and [^{18}F]RAGER microPET confirmed CNS penetration and increased uptake in areas of the brain known to express RAGE. This first generation radiotracer represents initial proof-of-concept and a promising first step toward quantifying CNS RAGE activity using PET.

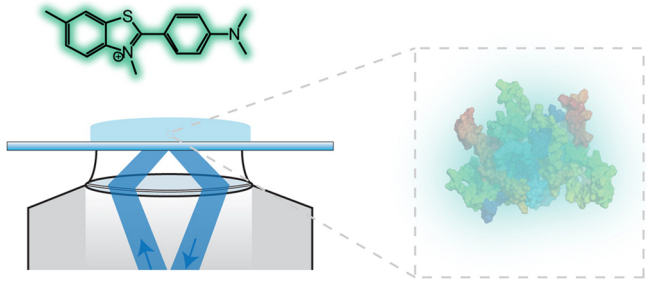
EFFECTS OF SSRI ANTIDEPRESSANT USE DURING PREGNANCY



Selective serotonin reuptake inhibitor (SSRI) antidepressants are commonly prescribed in the treatment of depression, which during pregnancy leads to fetal drug exposures. These exposures could affect fetal development and long-term offspring health; therefore, a better understanding of how pregnancy-induced physiological changes in mothers, fetuses, and the placenta influence fetal SSRI exposures during gestation is critically needed. Now, Velasquez et al. (DOI: 10.1021/acschemneuro.5b00287) present an in-depth study of maternal and fetal pharmacokinetics of the selective serotonin reuptake inhibitor (SSRI) citalopram in mice. The results directly address this important knowledge gap in the field of developmental neuropharmacology.

The authors show that pregnancy affects the maternal pharmacokinetics of citalopram and that the drug and its primary metabolite readily cross the placenta into the fetal compartment, leading to fetal exposures during both mid- and late-gestation. The results also reveal that fetal drug metabolic capacity develops in late gestation, resulting in elevated circulating and fetal brain concentrations of citalopram metabolites. Thus, fetal exposure to the SSRI citalopram in murine pregnancy is influenced by both maternal gestational stage and embryonic development.

SINGLE-MOLECULAR METHOD TO TRACK AGGREGATION IN CEREBROSPINAL FLUID



In the current issue, Horrocks et al. (DOI: 10.1021/acschemneuro.5b00324) report the development a new technique capable of directly visualizing the disease-causing species in many neurodegenerative diseases, namely, soluble extended β-sheet oligomers. Through a combination of ultrasensitive optical single-molecule fluorescence and an understanding of the physical principles of dye photophysics, the authors were able to visualize a variety of unlabeled proteins that are implicated in protein aggregation diseases such as Alzheimer's and Parkinson's disease.

Building on previous work, the authors demonstrate the value of this new tool by characterizing the oligomerization process of α-synuclein. Previously, this required the use of protein coupled to an organic fluorophore, which can affect the behavior of the system under study and limits the experiments to purified proteins. However, the new method reported here does not require prior labeling of the protein, and can therefore be used on many other aggregating proteins to directly compare their oligomerization processes as well as in complicated mixtures. The authors also demonstrate this by imaging oligomers of the proteins associated with Alzheimer's disease, that is, amyloid-β and tau. Furthermore, the authors demonstrate that these can extend our technique from purified in vitro assays into human samples, and for the first time visualize individual oligomers in human cerebrospinal fluid (CSF). Most excitingly, by measuring the properties of oligomers one-by-one, the authors discovered a significant difference between the CSF from Parkinson's disease patients when compared to healthy controls. This work therefore has

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major implications as a diagnostic test, and could potentially be used to monitor oligomer levels in patients undergoing targeted therapeutics, as well as providing a test for the efficacy of possible treatments.

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