ACS Chemical Neuroscience

In This Issue

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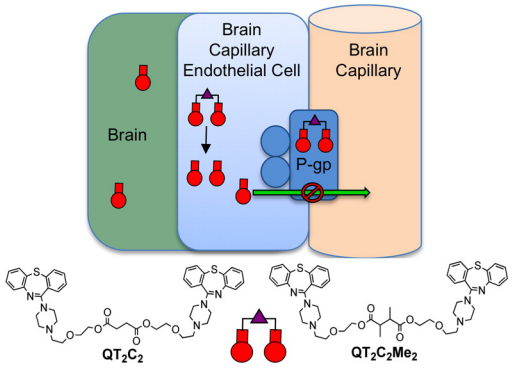
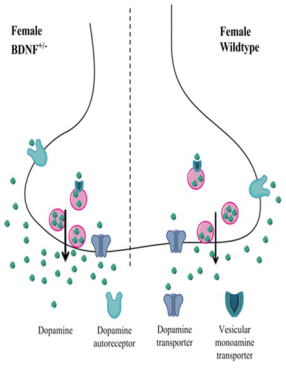
NEW STRATEGY TO AUGMENT DELIVERY INTO THE BRAIN



The effective treatment of schizophrenia necessitates the penetration of antipsychotic agents across the blood-brain barrier (BBB), a process that is limited due to drug efflux proteins such as P-glycoprotein (P-gp) at the endothelial cells membrane of the BBB. In this issue, Emmert et al. (DOI: 10.1021/cn4002329) present an innovative strategy toward therapeutic brain penetration with the P-gp substrate and the antipsychotic agent, quetiapine.

The authors describe dimeric prodrugs of quetiapine that were designed to have two functions: to inhibit P-gp efflux at the BBB, and to act as prodrugs and revert to the functional, monomeric therapeutic by cellular esterases. To these ends, they demonstrated that the optimized dimeric compound was a potent inhibitor of P-gp in human brain endothelial cells and was sensitive to cellular esterases, while showing stability in human plasma. The authors also directly demonstrated that these dimeric agents bind to both H- and R-sites of P-gp with higher affinity than the monomeric substrate drug. Importantly, they have also shown these dimers to be effective P-gp inhibitors in isolated rat brain capillaries in vitro and at the BBB in a rat perfusion animal model.

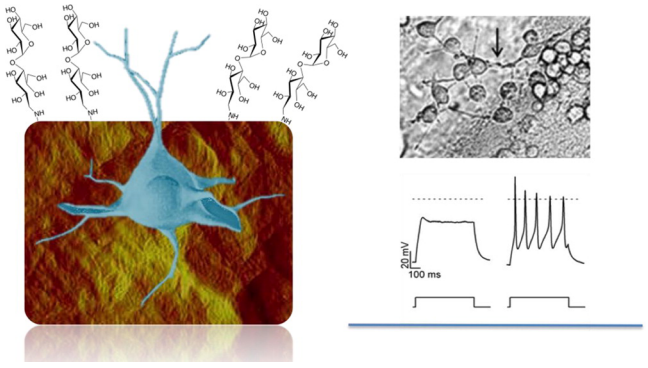
DIFFERENCE IN DOPAMINE RELEASE BETWEEN SEXES



Susceptibility to developing neurological diseases and disorders differs significantly between men and women. In order to better understand these sex differences, Birbeck et al. (DOI: 10.1021/cn400157b) used a mouse model that had a 50% reduction in the protein brain-derived neurotrophic factor (BDNF), which has been linked to various neurological diseases such as attention-deficit hyperactivity disorder, depression, and Parkinson's disease.

The objective of this study was to evaluate the neurotransmitter, dopamine, in female BDNF-deficient mice in the striatum region of the brain. The striatum was chosen for this study because it is a dopamine-rich brain region that has been linked to the aforementioned neurological diseases. The authors show that alterations in BDNF protein cause significant differences between male and female mice. The most striking feature is that female BDNF-deficient mice release greater amounts of dopamine. Understanding neurochemical sex-differences is critical toward discovering more appropriate therapeutic treatments.

NEURONAL DIFFERENTIATION BY GLUCOSYLATED COLLAGEN SUBSTRATES



Although carbohydrates are known to elicit specific biological responses, glycans have rarely been exploited in the study of neuronal physiology. In the current issue, Russo et al. (DOI: 10.1021/cn400222s) report the effects of neoglucosylated collagen matrices on neuroblastoma F11 cell line behavior.

Morphological and functional analysis showed that neoglucosylated collagen matrices were able to drive cells to differentiate. These data show for the first time that F11 cells can be driven from proliferation to differentiation without the use of chemical differentiating agents.

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