ACS Chemical Neuroscience

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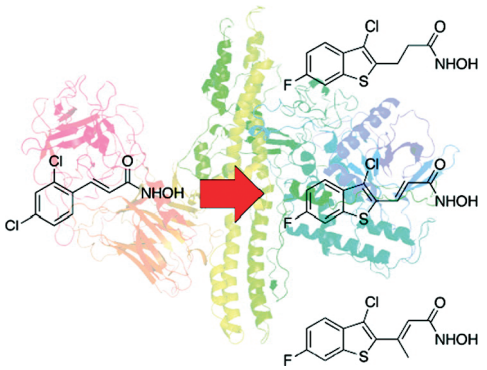
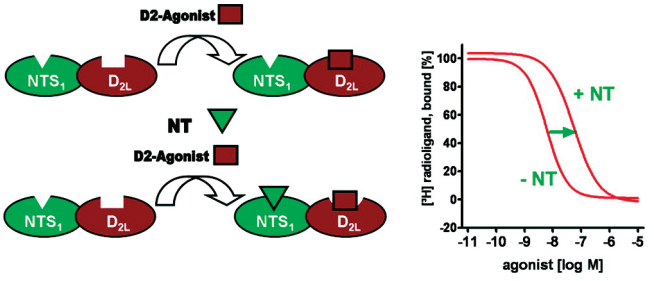
Targeting Botulism



Botulism is a potentially life-threating neuroparalytic disease caused by a neurotoxin produced by the soil bacteria *Botulinum clostridium*. The development of drugs against botulinum neurotoxin (BoNT) is important, given the characterization of this toxin as a potential bioterrorism weapon. To date, chemical inhibitors to BoNT suffer from poor pharmacokinetic properties. In this issue, Capek et al. (DOI: 10.1021/cn200021q) report the development of a class of compounds that provides a significant advance in the fight against the most deadly toxin known to man.

The compound 2,4-dichlorocinnamate hydroxamic acid is the best known small molecule inhibitor of BoNT. However, this compound suffers from several pharmacokinetic deficiencies that could preclude its efficacy as a drug against BoNT. To improve the efficacy of this "lead" compound, the authors synthesized variants which led to the discovery of a class of benzothiophene vinyl hydroxamates with enhanced stability and significantly improved absorption, distribution, metabolism, and excretion characteristics. Thus, using rational design, a new class of BoNT inhibitors has been established that serves as a superior starting point for future drug development.

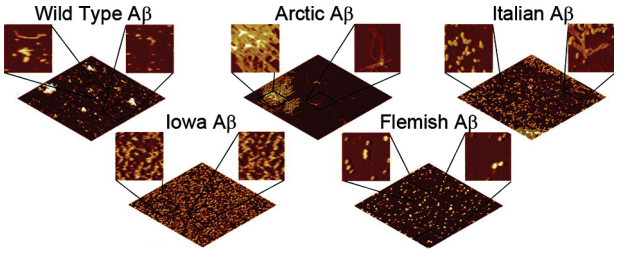
Cross-Receptor Binding of Clinical Importance



Neurotensin (NT) is a short peptide known to interact with the dopaminergic system and is linked to brain diseases such as schizophrenia and Parkinson's. This modulatory neuropeptide binds transmembrane G-protein coupled NT receptors. NT has also been shown to hinder binding of a dopamine receptor agonist. However, the interaction between dopamine and NT receptors and subsequent complex formation is not well understood. Koschatzky et al. (DOI: 10.1021/cn200020y) characterize this interaction with a study of significant importance to anti-Parkinson's drug development.

The authors demonstrated binding between dopamine D2L receptor and NT receptor NTS1 when coexpressed in human embryonic kidney cells. The interaction was characterized using a combination of radioligand binding experiments and coimmunoprecipitation studies. NT was demonstrated to affect binding of dopaminergic ligands to D2L in a transmodulatory manner via NTS1. The observation of increased NT levels in the brain of patients suffering from Parkinson's disease indicates the interaction between these receptors holds promise as a novel therapeutic target.

Surfaces Influence β-Amyloid Aggregation



Formation of amyloid plaques composed of β-amyloid peptide (Aβ) aggregates is a well-established pathological feature in the progression of Alzheimer's disease. Variations in the morphology of these aggregates are linked to deleterious effects associated with Aβ. Recent studies have implicated the role of environmental surfaces in modulating aggregate shape. In this issue, Yates et al. (DOI: 10.1021/cn200001k) seek to address the influence of surfaces on Aβ aggregate formation and provide a better understanding for the mechanism underlying its toxicity.

The central hydrophobic core of Aβ is the site for several well-characterized point mutations. The authors sought to study these mutant variations for differences in morphological features in free solution versus surfaces of different physical characteristics. Using atomic force microscopy, the authors observed that each mutant formed its own unique aggregate morphology when confronted with anionic surfaces. Interestingly, these disparate morphologies were not observed in free solution, implicating physical surface characteristics as an important factor in Aβ aggregation morphology and its corresponding toxicity.

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