ACS Chemical Neuroscience

In This Issue

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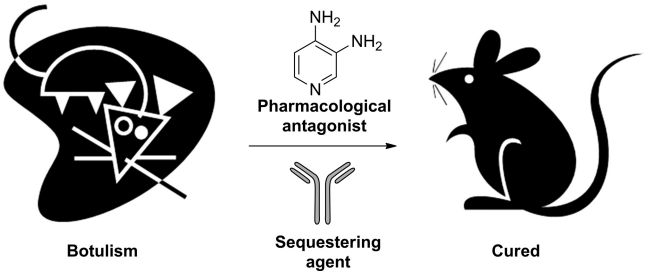
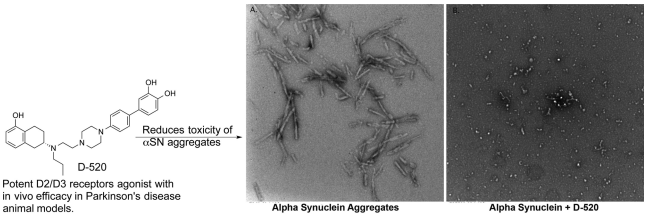
NOVEL STRATEGY TO ALLEVIATE BOTULINUM INTOXICATION



Botulinum neurotoxins (BoNT) are responsible for botulism, a disease of humans that is characterized by peripheral neuromuscular blockade and flaccid paralysis. Due to the extreme potency of serotype A (BoNT/A), the Centers for Disease Control has classified it as a high-risk threat agent for bioterrorism. Currently there are no approved medical countermeasures in a postexposure scenario. In this issue, Harris et al. (DOI: 10.1021/cn500135h) report a platform that can be used to ablate botulinum neurotoxicity in a mouse lethality assay and provides the first proof-of-principle of a successful combination treatment for BoNT/A intoxication in a postexposure occurrence.

Therapeutic antibodies can be used to diminish BoNT concentration in circulation, but they are unable to enter nerve cells. Thus, there is a small therapeutic window for treatment, otherwise paralysis will lead to respiratory failure and result in death. Pharmacological antagonists can enter the nerve cell, but these compounds have an inherently short half-life relative to that of BoNT. As such, sustained administration would be required over the duration of BoNT intoxication, as the compound is unable to remove toxin circulation in the periphery. The authors successfully introduce a combination strategy where a sequestering agent (therapeutic antibody) is administered in tandem with a pharmacological antagonist (3,4-diaminopyridine) to leverage the therapeutic value of each countermeasure, while simultaneously limiting the liabilities associated with each independent treatment option. Ultimately, this platform allows for the exchange of any sequestering agent and/or pharmacological antagonist for therapeutic optimization. To this end, the authors applied a prodrug approach to 3,4-diaminopyridine and characterized the kinetic decomposition pathway.

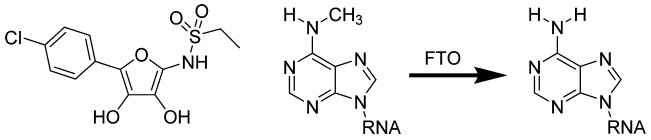
A STEP TOWARD FINDING A CURE FOR PARKINSON'S DISEASE



Parkinson's disease is a progressive neurological disorder that affects movement. It is caused by insufficient quantities of dopamine due to degeneration of dopaminergic neurons in the substantia nigra of the brain. Now, Modi et al. (DOI: 10.1021/cn500084x) report the development of unique multifunctional drugs for symptomatic and neuroprotective treatment of Parkinson's disease.

Specifically, the authors show the development of a brain penetrant lead molecule agonist (D-520) for dopamine receptors, D2/D3, which could modulate aggregation and toxicity of pathogenic α-synuclein protein. Furthermore, the lead drug showed neuroprotection properties in an in vitro Parkinson's disease model with dopaminergic MN9D cells. This work signifies the importance of targeting multiple factors to treat Parkinson's disease rather than a single target.

NOVEL ANTISEIZURE LEAD COMPOUNDS



Epilepsy is a chronic condition of recurring seizures due to abnormal activity of the brain and for which current drugs are not effective for a significant number of patients. In the current issue, Zheng et al. (DOI: 10.1021/cn500042t) describe the rationale for and the synthesis of a new class of compounds that inhibit a particular enzyme, FTO, which has been linked to various brain disorders.

The compounds described in this study are designed to mimic a substrate of FTO and to inhibit its RNA demethylase activity, which the authors demonstrate. The lead compound also shows anticonvulsant activity in mice at nontoxic doses. Finally, the lead compound is shown to modulate microRNA, a class of small noncoding RNA recently shown to be involved in the pathological mechanism leading to epilepsy. Thus, this study reports a series of novel compounds that show antiseizure activity and modulate an enzyme and a RNA that are linked to the pathology of various brain conditions.

Published: August 20, 2014

dx.doi.org/10.1021/cn500170s | *ACS Chem. Neurosci.* 2014, 5, 617–617