ACS Chemical Neuroscience

In This Issue

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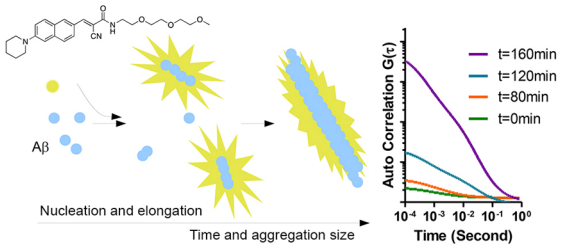
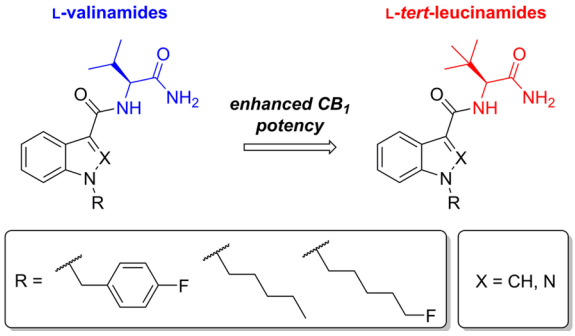
OBSERVING AMYLOID AGGREGATION IN REAL-TIME



Amyloid-targeting molecules have generated significant interest as potential in vivo and ex vivo labeling agents for the diagnosis and monitoring of amyloid-associated neurodegenerative disorders such as Alzheimer's or prion diseases. In the current issue, Guan et al. (DOI: 10.1021/acschemneuro.5b00176) demonstrate, for the first time, that a novel fluorescent probe, ARyl Cyano AMide (ARCAM) 1, can be combined with a time-resolved spectroscopic detection methodology based on fluorescence correlation spectroscopy.

Due to the large increase in fluorescence when ARCAM 1 binds to an Aβ aggregate, the authors termed the new detection method Probe Enhancement FCS (PE-FCS). Using this new probe and methodology, detection of early assembly intermediates of Aβ aggregation at concentrations much lower than traditional bulk fluorescence methods was achieved. Moreover, PE-FCS also provides an estimate of the size for these intermediate assemblies that are consistent with previous studies. This new sensitive methodology, due to a combination of a new chemical reagent and new FCS analysis method, paves the way for diagnostic applications using patient samples.

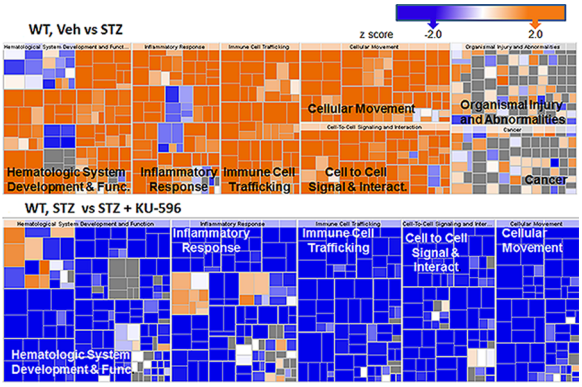
INVESTIGATION INTO THE EFFECTS OF RECREATIONAL DRUGS



Synthetic cannabinoids (SCs) are the most rapidly growing class of recreational "designer drugs", and their use is associated with serious adverse effects including death. Now, Banister et al. (DOI: 10.1021/acschemneuro.5b00112) provide details of the synthesis and pharmacological evaluation of novel, small molecule SC ligands, and several analogues.

Despite human use of these substances, little is known regarding the biological activity of SC ligands. The authors provide convenient synthetic routes and describe preliminary structure–activity relationships (SARs) within these classes. Using a fluorometric imaging plate reader membrane potential assay, all ligands were found to possess potent agonist activity at CB_1 and CB_2 receptors. Additionally, the authors performed biotelemetry studies in rats to describe some of their in vivo effects. These results represent one of a few efforts in understanding the structural features essential to the CNS activity of emerging cannabimimetic drugs of abuse.

CORRECTING NERVE DYSFUNCTION IN DIABETIC PERIPHERAL NEUROPATHY



It has been previously shown that modulating molecular chaperones with KU-32, a novobiocin derivative, ameliorates physiologic and bioenergetic deficits of diabetic peripheral neuropathy (DPN). Replacing the coumarin core of KU-32 with a meta-fluorinated biphenyl ring system created KU-596, a novobiocin analogue (novologue) that showed neuroprotective activity in a cell-based assay. The current study by Ma et al. (DOI: 10.1021/acschemneuro.5b00165) sought to determine whether KU-596 offers similar therapeutic potential for treating DPN and to identify putative mechanisms of action.

While the drug shows substantial efficacy as the next generation novologue for improving clinical indices of DPN in wild type mice, it was ineffective in reversing DPN in Hsp70 knockout mice. To gain further insight into the mechanisms by which the drug improves DPN via Hsp70, the authors employed RNA Seq analysis. Bioinformatic analysis of the differentially expressed genes indicated that diabetes strongly increased inflammatory pathways and that KU-596 therapy effectively reversed these increases independent of Hsp70. In contrast, the effects of KU-596 on decreasing the expression of genes regulating the production of reactive oxygen species were more Hsp70-dependent. These data indicate that modulation of molecular chaperones by novologue therapy offers an effective approach toward correcting nerve dysfunction in DPN, but that normalization of inflammatory pathways alone by novologue therapy seems to be insufficient to reverse sensory deficits associated with insensate DPN. The current study represents the first report characterizing the efficacy and potential mechanism of action of KU-596, which is now progressing toward clinical trials for use in insensate DPN.

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