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In This Issue

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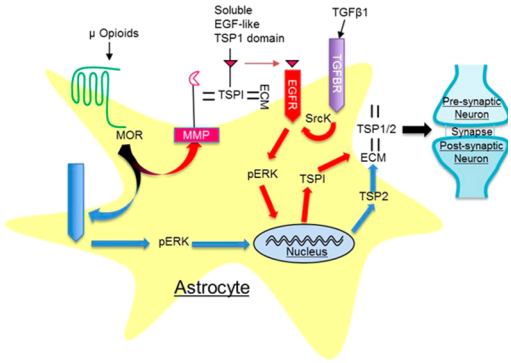
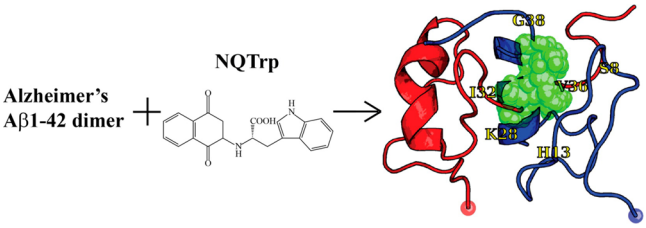
MECHANISM BY WHICH OPIOIDS ALTER SYNAPTIC ACTIVITY



Opioids target opioid receptors, which regulate astrocyte activation and are present in astroglia. Opioids induce a major neuronal adaptation known as synaptic plasticity, which entails changes in the number and strength of synapses that serve as points of contact between neurons to enable them to communicate with each other. Astrocyte activation in synaptogenesis may play a critical role in opioid tolerance, withdrawal, and dependence, the main features of addiction. In the current issue, Phamduong et al. (DOI: 10.1021/cn400172n) characterize a novel/opioid receptor-mediated signaling pathway that regulates the gliotransmitter, thrombospondins 2, in astrocytes.

Thrombospondins 1 and 2 (TSP1/2) are astrocyte-secreted proteins that promote synapse formation. Previously, the authors discovered that chronic μ opioids inhibit TSP1 expression in astrocytes by a signaling pathway involving crosstalk between three different classes of receptors, μ opioid receptor, epidermal growth factor receptor (EGFR), and transforming growth factor receptor-β (TGFβR). Moreover, EGFR acts as a signaling hub for opioid and TGFβ1 actions. In the current study, the authors compared the mechanisms of chronic opioid inhibition of expression of TSP isoforms 1 and 2 in vivo and in immortalized rat cortical astrocytes. The authors show that μ opioids may deter synaptogenesis via both TSP1/2 isoforms, but by distinct mitogen activated protein kinase-mediated mechanisms.

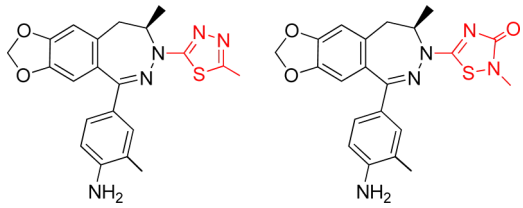
CHARACTERIZING AN INHIBITOR OF Aβ AGGREGATION



Aggregation of the amyloid β-protein (Aβ) peptide with 40/42 residues is one key feature in Alzheimer's disease (AD). The 1,4-naphthoquinon-2-yl-L-tryptophan (NQTrp) molecule was previously reported to alter Aβ self-assembly and reduce toxicity. Studies characterizing NQTrp interaction with Aβ peptides spanning the regions 12−28 and 17−42 have been performed; however, none of these studies were conducted on the full-length Aβ1−42 peptide. To this end, Zhang et al. (DOI: 10.1021/cn400197x) provide an atomic picture of the modes of action of NDTrp on Aβ1−42 dimer to better understand its inhibitory mechanism on Aβ oligomerization and toxicity.

The interactions between NQTrp and Aβ1−42, which change the Aβ interface by reducing most of the intermolecular contacts, were found to be very dynamic, leading to many transient binding sites. The authors identified 10 key residues at the Aβ/NQTrp interface which may serve as "hot spots" underlying Aβ toxicity. The simulations used in this study provide novel hints to design a more effective inhibitor of Aβ1−42 aggregation. Moreover, the computational strategy adopted here suggests a general first-order approach to screen amyloid/inhibitor interactions.

NEW AMPA RECEPTOR INHIBITORS



2,3-Benzodiazepine derivatives are a class of inhibitors of AMPA-subtype glutamate ion channels and are thought to be the most promising drug candidates for potential treatment of neurological diseases such as epilepsy, stroke, and ALS. To date, there are several hundred 2,3-benzodiazepine synthesized compounds; however, a lack of mechanistic characterization of these compounds has hampered the development of potent 2,3-benzodiazepine compounds which act as selective AMPA receptor inhibitors. In the current issue, Wang et al. (DOI: 10.1021/cn400193u) investigate the design and mechanistic characterization of a new structural template that combines a thiadiazole with a 2,3-benzodiazepine scaffold.

The authors specifically characterized two thiadiazolyl compounds, one containing a 1,3,4-thiadiazole moiety and the other with a 1,2,4-thiadiazole-3-one moiety, and found that linking a thiadiazole scaffold to a 2,3-benzodiazepine yields an inhibitor with significantly better potency and selectivity on AMPA receptors than the 2,3-benzodiazepine scaffold alone. The potencies of these compounds were the strongest ever documented in the AMPA receptor inhibitor field. Significantly, no other noncompetitive inhibitors are currently known to effectively inhibit the GluA3 and GluA4 AMPA receptor subunits. As a synthetically extendable scaffold, a 5-membered heterocyclic thiadiazole ring structure can be readily chemically modified to produce even better noncompetitive inhibitors of AMPA receptors. This work points to a new structural template for designing and producing potent AMPA receptor-selective inhibitors as potential drug candidates.

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