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In This Issue

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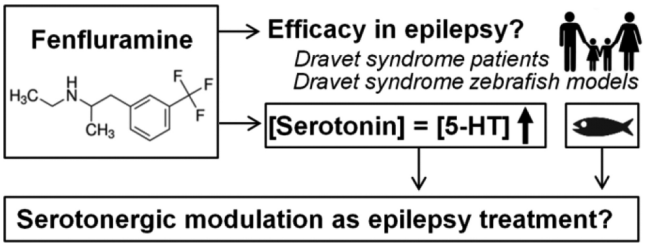
SEROTONERGIC MODULATION FOR DRAVET SYNDROME TREATMENT

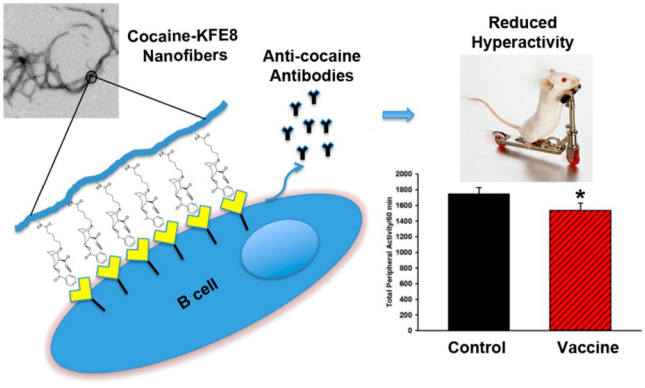


Dravet syndrome (DS) is one of the most drug-resistant and debilitating forms of infantile epilepsy syndromes. Hence, novel antiepileptic drugs with an innovative mechanism-of-action would improve current treatment options. In a small clinical trial, fenfluramine, a potent serotonin releaser, led to seizure-freedom in 70% of children with pharmacoresistant Dravet syndrome (DS).

In the current issue, Sourbron et al. (DOI: 10.1021/acschemneuro.5b00342) demonstrate the high conservation of the serotonin (5-HT) subtype receptors in zebrafish, as compared to humans. Furthermore, pharmacological stimulation with selective agonists of the 5-HT_{1D}, 5-HT_{2C}, and especially the 5-HT_{2A}-receptor showed an interesting anti-epileptiform activity in a zebrafish model of DS. As opposed to fenfluramine, there is no stimulation of the 5-HT_{2B} receptor that contributes to fenfluramine-induced cardiac valvulopathy.

Interestingly, the authors also found a significant decrease of serotonin in the heads of this zebrafish model of DS, which suggest that neurochemical defects might play a crucial role in the pathophysiology of DS. Taken together, these results provide new avenues in the field of antiepileptic drug discovery for efficient and safe DS treatment.

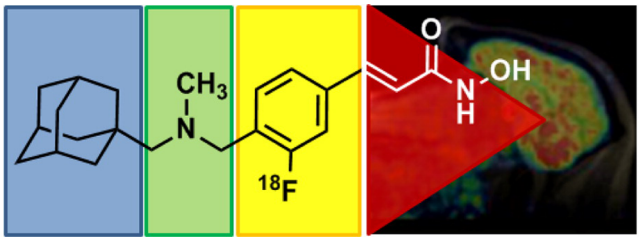
NANOFIBER VACCINE AGAINST COCAINE



Cocaine use disorder remains a significant health challenge with over 900 000 Americans meeting the criteria for diagnosis in 2014 for which there is no FDA approved medication. The development of anticocaine vaccines that counteract the rewarding effects of the drug are currently being investigated as adjunct therapies. However, major limiting factors in the success of cocaine vaccines is the degree and specificity of immunity evoked by the addictive drug analogue and the lack of powerful yet safe adjuvants approved for use in humans. To overcome these barriers, Rudra et al. (DOI: 10.1021/acschemneuro.5b00345) have generated novel cocaine analogues modified at the P3 (nitrogen) site and conjugated it to a self-assembling peptide domain to generate multivalent cocaine nanofibers.

In mice, the cocaine-bearing peptide nanofibers raised anticocaine antibodies without the need for exogenous adjuvants. Using behavior assays, the authors demonstrate that cocaine-nanofiber vaccinated mice are protected against hyperactive effects of the drug. This work is the first report involving novel cocaine analogues and completely synthetic and adjuvant-free vaccine delivery systems showing efficacy in animal models.

QUANTIFYING HDAC IN VIVO



The development of a radiotracer for histone deacetylases (HDAC), an enzyme class critically involved in the epigenetic regulation of our genome, is of high importance. Abnormal expression and activity levels of HDAC have been associated with many different diseases, but the current understanding of HDAC in the living human brain remains limited due to our inability to quantify the protein in vivo. Now, Strebl et al. (DOI: 10.1021/acschemneuro.5b00297) provide a robust HDAC tracer molecule to fill this gap.

A radiolabeled molecule, [^{11}C]Martinostat, is able to enter the brain efficiently and help imaging scientists obtain these urgently needed measurements. However, its isotope half-life is only 20 min, which is a major limitation for its broad application. In this paper, the authors identified and validated a much longer lived analogue, [^{18}F]MGS3, which has a half-life of almost 2 h, by radiolabeling and imaging in rats and baboons. Beyond overcoming the logistical challenges, by investigating several structural analogues, the authors were able to identify which structural motifs enabled both tracers to enter the brain efficiently.

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