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Diminished nicotine withdrawal in adolescent rats: implications for vulnerability to addiction

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abnormalities detected in schizophrenia. Some of the pathways identified suggest possible avenues for augmentation pharmacotherapy of schizophrenia with other existing agents. Other pathways are new potential targets for drug development. Lastly, a comparison with our earlier work on bipolar disorder illuminates the significant molecular overlap between schizophrenia and bipolar disorder.
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615. Odor-Specific Threshold Sensitivity Deficits Implicate Intracellular Cyclic AMP Signal Transduction Abnormalities in Schizophrenia

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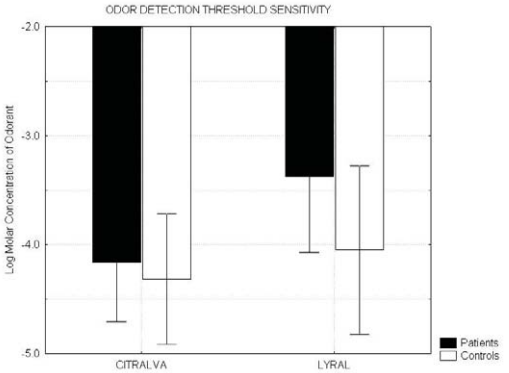
Background: Recent evidence suggests that disrupted cAMP signalling may contribute to schizophrenia pathology.1 It is well known that 1)olfactory receptor neurons respond to odor molecules via cAMP intracellular signal transduction mechanisms, and 2)schizophrenia patients have marked olfactory deficits. We investigated whether patients' olfactory deficits could denote cAMP abnormalities by assessing odor detection thresholds for odorants that induced high vs. low intracellular cAMP responses.
Methods: Olfactory threshold detection sensitivity was assessed in 31 patients and 25 healthy controls, using the odorants citralva and lyral. These odorants have qualitatively similar floral scents, but citralva induces high levels of adenylate cyclase activity, while lyral has little effect on adenylate cyclase.2 Importantly, the level of induced adenylate cyclase in vitro correlates with perceived odor intensity.3
Results: Controls had comparable thresholds levels for the two odorants (p=.43), but patients were less able to detect the presence of lyral than citralva (p=.01). This resulted in a selective patient deficit for lyral (p=.03, 1-tailed), but no deficit for citralva (p=.60).
Conclusions: Olfactory threshold deficits in schizophrenia are not universal, but rather are odor-specific. A differential impairment, based on whether an odorant induces high or low adenylate cyclase activity, suggests that perturbations in this intracellular signalling mechanism may be the cause of olfactory sensitivity deficits in patients. It further supports the hypothesis that cAMP signalling is implicated in the pathophysiology of schizophrenia.



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616. Association of Single Nucleotide Polymorphisms (SNPs) in Glutamate Receptor Gene with Theta Power of Event-Related Oscillations and Alcohol Dependence

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Background: Endophenotypes reflect more proximal effects of genes than diagnostic categories, and hence they provide a more powerful strategy in searching for genes involved in complex psychiatric disorders. There is solid evidence for the P3 amplitude of the event-related potential as an endophenotype for the risk of alcoholism and other disinhibitory disorders. The P3 component is not unitary, but consists of superimposed event-related oscillations (EROs) of different frequency bands, primarily frontal theta (4-5 Hz) and posterior delta (1-3 Hz).
Methods: A subset sample of the Collaborative Study on the Genetics of Alcoholism (COGA) comprising 1,049 Caucasian subjects (from 209 families with 462 individuals diagnosed as alcohol dependent by DSM-IV) was included in genetic association analyses using the Family-based association test (FBAT). Neural activities were recorded from scalp electrodes during a visual oddball task in which rare targets elicited P3s.
Results: Significant associations ($p<0.05$) were found between the event-related frontal theta power (4-5 Hz) to target visual stimuli and alcohol dependence with multiple SNPs in GRM8 gene located at chromosome 7q31.3-q32.1 within the region of 171 cM where we previously identified a significant linkage (LOD=3.5) using a genome-wide linkage scan of the same phenotype (theta band for the target stimuli).
Conclusions: Our results suggest that glutamate receptor genes may be involved in modulating event-related theta oscillations in frontal regions during information processing and in vulnerability to alcoholism and related disorders. These findings underscore the utility of using electrophysiology and the endophenotype approach in the molecular genetic study of psychiatric disorders.
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SYMPOSIUM

Tobacco, Cannabis, and the Developing Adolescent Brain: New Research Findings

Saturday, May 19, 2007 2:30 PM - 5:00 PM
Location: California Ballroom A - 2nd Floor
Chair: Leslie K. Jacobsen*
Co-Chair: Georg Winterer

*Supported by RO1DA14655, RO1DA017333

617. Diminished Nicotine Withdrawal in Adolescent Rats: Implications for Vulnerability to Addiction

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Background: Vulnerability to nicotine addiction is increased in individuals who begin smoking during adolescence, but the physiological basis for this phenomenon is unknown. The enhanced reinforcing effects of nicotine during

adolescence appear to contribute to the rapid development of dependence in this age group. However, the contribution of nicotine withdrawal to dependence in this age group is unclear.
Methods: Somatic signs of nicotine withdrawal were assessed after administration of the nicotinic receptor antagonist mecamylamine in adult and adolescent rats receiving nicotine for via osmotic pumps. Subsequent studies compared somatic signs of withdrawal using various doses of nicotine to produce dependence and one dose of mecamylamine to precipitate withdrawal, and various doses of mecamylamine to precipitate withdrawal and one dose of nicotine that produced equivalent nicotine levels in these age groups. Affective signs of nicotine withdrawal were compared using the intracranial self-stimulation procedure following administration of mecamylamine in adolescent and adult rats that received nicotine via pumps.
Results: Adolescents displayed fewer somatic signs of nicotine withdrawal relative to adults regardless of the nicotine or mecamylamine dose. Adolescent rats did not display the decreases in brain reward function observed in adults experiencing nicotine withdrawal.
Conclusions: The negative effects of nicotine withdrawal are lower during adolescence relative to later periods of development. Therefore, both the enhanced rewarding effects and the diminished nicotine withdrawal likely contribute to the rapid development of nicotine dependence during adolescence.
Supported by California Tobacco-Related Disease Research Program (11FT-0112 to AWB, 12RT-0099 to GFK, and 12RT-0231 to AM), and the National Institute on Drug Abuse (DA11946 to AM)

618. Heavy Marijuana Use in Adolescence and Cognitive Functioning

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Background: Marijuana is the most widely used illicit drug in the United States and many other nations, with 6% of high school seniors reporting daily use. This presentation will describe neurobehavior and brain function in adolescents who use marijuana heavily.
Methods: Neuropsychological and neuroimaging results of marijuana users and demographically similar controls ages 16-18 are presented. All participants were free from psychiatric, medical, and neurological disorders. Assessments were collected after 28 days of monitored abstinence.
Results: After controlling for alcohol use, adolescent marijuana users demonstrate significantly poorer scores on tests of planning, sequencing, and attention compared to controls (N=65). Structural magnetic resonance imaging studies (N=63) indicated larger hippocampal volumes as a function of more cannabis abuse/dependence criteria met. Using diffusion tensor imaging (N=33), adolescent marijuana users showed less white matter coherence in the splenium of the corpus callosum. Functional magnetic resonance imaging results (N=33) indicate that, although marijuana users performed adequately on tasks, they showed different activation levels than non-users in right dorsolateral prefrontal, occipital, and parietal regions during inhibition and spatial working memory tasks, suggesting altered neural systems to meet task demands.
Conclusions: The pattern of results suggests that even after a month of abstinence, adolescent marijuana users show subtle deficits in attention as well as abnormalities in brain structure and function. It is possible that marijuana use during adolescence may influence neuromaturation and cognitive development. Longitudinal studies are needed to better understand the degree to which adolescent marijuana use produces such differences.
Supported by R01DA021182

619. Impact of Smoking Abstinence on Brain Function and Functional Connectivity in Adolescent Daily Tobacco Smokers

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Background: Efficient function of neurocircuitry that supports working memory occurs within a narrow range of dopamine neurotransmission. Recent work in rodents has provided evidence that exposure to nicotine during adolescent development leads to sustained nicotine withdrawal emergent alterations dopamine neurotransmission. We tested for evidence of smoking cessation induced reductions in the efficiency of working memory neurocircuitry in adolescent tobacco smokers.
Methods: Fifty-five adolescent daily tobacco smokers were compared with 38 nonsmokers who were similar in age, gender and education, using functional magnetic resonance imaging (fMRI) while subjects performed a verbal working memory task. Smokers were studied during smoking and after 24 hours of abstinence from tobacco use.
Results: Performance of a task with high working memory load in the context of smoking abstinence was associated with greater activation of components of the verbal working memory neurocircuit, including left ventrolateral prefrontal cortex and left inferior parietal lobe, among smokers relative to nonsmokers. During smoking abstinence, smokers did not exhibit the increases in functional connectivity between components of the working memory neurocircuit with increasing working memory load observed in nonsmoking adolescents and in prior studies of adults.
Conclusions: Smoking abstinence associated reductions in the efficiency of working memory neurocircuitry and alterations in the functional coordination between components of the working memory neurocircuit may reflect withdrawal emergent changes in dopamine neurotransmission stemming from effects of nicotine exposure on catecholaminergic systems during adolescent development.
Supported by DA14655, DA017333

620. Smoking Impacts on Prefrontal Attentional Network Function in Young Adult Brains

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Background: There is abundant evidence from clinical and preclinical studies that acute administration of nicotine has beneficial effects on attentional network function in brain. In contrast, little is known about potentially neurotoxic effects on the attentional network during neurodevelopmentally critical periods such as during adolescence and early adulthood.
Methods: Using event-related fMRI, we investigated prefrontal attentional network function in young adults (N = 15 regular smokers and N = 12 never-smokers; age: 22.6±1.5 years). Duration of smoking was 6.9±2.3 years (range: 2-10). Smokers were allowed to smoke ad libidum before the fMRI scanning was conducted.
Results: As expected from literature, prefrontal attentional network activity was significantly reduced in smokers compared to non-smokers ($Z = 2.1$; $P = 0.036$). In smokers, we found that history of smoking duration (years) is directly related to the extent of diminished attentional network activity ($R = -0.67$; $P = 0.012$).
Conclusions: To our best knowledge, the relationship between the duration of smoking history and prefrontal attentional network function has not yet been