



The mission of the University of Pennsylvania Transdisciplinary Tobacco Use Research Center (TTURC) is to translate discoveries in basic neuroscience, pharmacology, genetics, and behavioral science to improve treatment for nicotine dependence.



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## Nicotine Triggers the Same Brain Reward Circuitry as Opiates

A research team led by TTURC investigator Julie Blendy, Ph.D. reported in the June issue of *Neuron* that nicotine administration in mice produces increased levels of phosphorylated CREB which is known to control genes involved in drug reward. However, pretreatment with the mu opioid receptor antagonist naloxone blocked CREB activation and the behavioral expression of nicotine preference in this mouse model. Also, mu opioid receptor knockout mice did not show an increase in CREB activity when they received nicotine, suggesting that this receptor plays an important role in nicotine reward. This study also pro-

vided the first evidence that an environment associated with nicotine can activate CREB in a manner similar to nicotine itself, an effect blocked by naloxone. These data support the important role of nicotine cues and suggest that opioid antagonist medications may be useful for nicotine dependence treatment. This hypothesis is now being tested in a human laboratory investigation at the TTURC. *Written by Angela Pinto*

Walters, C. L., Cleck, J. N., Kuo, Y. C., & Blendy, J. A. (2005). Mu-opioid receptor and CREB activation are required for nicotine reward. *Neuron*, 46(6), 933-943.

## Nicotine Enhances Event-Related Potentials

Researchers from the UPenn TTURC have been studying the ability of nicotine to enhance early information processing. Steven Siegel M.D., Ph.D. and colleagues examined the effects of chronic and acute nicotine on mouse auditory event-related potentials (ERPs). ERPs are stimulus-induced tracings of electrical activity in the brain composed of positive and negative components, and are a potential index of sensory information processing. Acute nicotine enhanced the amplitude and gating of the P20 ERP component and decreased amplitude and gating of the N40 component. It is believed that the mouse P20 and N40 components are analogous to the human P50 and N100 ERP components and may provide insight into early sensory information processing. The findings, to be published in an upcoming issue of *Biological Psychiatry*, further support a potential role for acute nicotine administration as a therapeutic strategy for conditions with impaired sensory processing, such as schizophrenia. Follow-up studies examining antagonism of nicotine's ERP enhancement and the effects of nicotine on other measures of electrical activity in the brain are underway.

Siegel and colleagues have also reported an enhancement of P20 by acute nicotine in the journal *Neuroscience*. Additionally, bupropion,

approved by the FDA as a smoking cessation aid, caused disruptions in the amplitude and gating of the N40 ERP component similar to those observed in individuals with schizophrenia. A combination treatment of nicotine and the antipsychotic haloperidol successfully attenuated the bupropion-induced disruptions. The findings suggest that bupropion's actions are a combined result of its nicotinic receptor antagonism and dopamine reuptake inhibition. Bupropion's nicotinic and dopaminergic based disruption of ERPs may represent a new, multi-mechanism model for sensory information processing deficits. Drs. Siegel, Strasser and Lerman are planning human ERP studies to translate these findings.

*Written by Jennifer Phillips, Ph.D.*

Metzger, K.L., Maxwell, C.R., Liang, Y., & Siegel, S.J. (in press). Effects of nicotine vary across two auditory evoked potentials in the mouse. *Biological Psychiatry*.

Siegel, S. J., Maxwell, C. R., Majumdar, S., Trief, D. F., Lerman, C., Gur, R. E., Kanes, S. J., & Liang, Y. (2005). Monoamine reuptake inhibition and nicotine receptor antagonism reduce amplitude and gating of auditory evoked potentials. *Neuroscience*, 133(3), 729-738.



## Atomoxetine – a Potential Therapeutic Agent for Nicotine Withdrawal

Recent work, led by UPenn TTURC researcher Tom Gould, Ph.D. at Temple University, suggests that atomoxetine, a norepinephrine reuptake inhibitor approved for attention deficit hyperactivity disorder (ADHD) treatment, may be a potential therapeutic agent for the cognitive disruptions caused by withdrawal from nicotine. In mice, atomoxetine increased prepulse inhibition of the acoustic startle response (PPI). PPI is believed to be a measure of sensory information processing and gating, processes that may be compromised in nicotine withdrawal. The PPI-enhancing effects of atomoxetine were not blocked by the nicotinic antagonist mecamylamine, suggesting that its actions are not based in the nicotinic acetylcholinergic system. Atomoxetine may provide relief from cognitive symptoms of nicotine withdrawal without relying on nicotinic acetylcholinergic receptor systems that may be altered during chronic nicotine use. These data were published in the March 2005 issue of *Neuroscience Letters*.

Additional work by Gould and other UPenn TTURC researchers described impairments in contextual fear



conditioning in mice caused by withdrawal from chronic nicotine. While acute nicotine administration enhanced contextual fear conditioning, chronic nicotine had no effect, and mice withdrawn from nicotine showed conditioning deficits. An acute nicotine challenge reversed these withdrawal-induced deficits and produced levels of conditioning similar to those seen in control animals treated with acute nicotine. In parallel to this animal work, TTURC investigators are studying the effects of atomoxetine on nicotine withdrawal associated deficits in cognitive function in humans.

Written by Jennifer Phillips, Ph.D.

Gould, T. J., Rukstalis, M., & Lewis, M. C. (2005). Atomoxetine and nicotine enhance prepulse inhibition of acoustic startle in C57BL/6 mice. *Neuroscience Letters*, 377(2), 85-90.

Davis, J. A., James, J. R., Siegel, S. J., & Gould, T. J. (2005). Withdrawal from chronic nicotine administration impairs contextual fear conditioning in C57BL/6 mice. *Journal of Neuroscience*, 25(38), 8708-8713.

## Studies in Mice and Humans Show that Nicotine May be Less Rewarding in Obese Subjects

In cross-species investigations of nicotine reward, researchers at the UPenn TTURC found that nicotine may be less rewarding in obese versus non-obese subjects.

The human study, led by Dr. Caryn Lerman, required male and female smokers to complete a cigarette choice procedure in which smokers could puff from nicotine containing or denicotinized cigarettes. The number of puffs taken from the nicotine vs. the denicotinized cigarette provides a measure of the relative reinforcing value of nicotine.

Under the direction of Dr. Julie Blendy, nicotine reward in mice was assessed using a conditioned place paradigm. Mice fed either a high fat diet or a normal diet received nicotine vs. saline on training days, always paired with a particular side of the conditioning box. On test day, mice were allowed to roam free; time spent on the nicotine paired versus the unpaired side reflects the behavioral expression of nicotine reward.



Results showed that, in humans, obese smokers self-administered nicotine via cigarettes significantly less often than non-obese smokers and showed reduced hedonic effects of nicotine-containing cigarettes compared to denicotinized cigarettes. Similarly, mice exposed to a high fat diet did not exhibit a behavioral preference for nicotine, while mice exposed to the normal diet did show a preference. mRNA levels for mu-opioid and leptin receptors were also down-regulated in the ventral tegmental area of mice fed a high fat diet, suggesting that reduced nicotine reward in obese smokers may be mediated by dietary influences on the endogenous opioid system.

Written by Freddie Patterson

Blendy, J. A., Strasser, A., Walters, C. L., Perkins, K. A., Patterson, F., Berkowitz, R., & Lerman, C. (2005). Reduced nicotine reward in obesity: Cross-comparison in human and mouse. *Psychopharmacology*, 180(2), 306-315.



## Functional Variant in Dopamine D2 Receptor Gene (*DRD2*) Predicts Response to Smoking Cessation Medications

Recent data from the UPenn TTURC suggest that a common polymorphism in the *DRD2* gene that affects transcriptional efficiency, *DRD2* -141 *Ins/DelC*, predicts response to smoking cessation pharmacotherapy. In the January 2006 issue of *Neuropsychopharmacology*, TTURC investigators reported results from two pharmacogenetic trials for nicotine dependence treatment: a placebo-controlled trial of bupropion and an open label trial comparing transdermal nicotine to nicotine nasal spray. Data show that smokers who are homozygous (carry 2 copies) for the *DRD2*-141 *Ins C* allele achieve significantly greater benefit from bupropion than smokers carrying the *Del C* allele. By contrast, smokers carrying the *Del C* allele had significantly higher quit rates if they used nicotine replacement therapy (NRT) compared to those with the *Ins C* allele. These observations were extended in an article to be published in *The Pharmacogenomics Journal*. Dahl and colleagues reported that variation in the gene encoding the Neuronal Calcium Sensor-1 protein (*FREQ*), which regulates dopamine D2 receptor desensitization, moderated the effect of the *DRD2*-141C variant on smoking cessation following NRT. Sixty-two percent of the smokers with one copy

of the *DRD2* -141 *Del C* allele and two copies of the *FREQ* rs1054879 A allele were abstinent from smoking, compared to 29%-38% abstinence rates for other smokers in the NRT trial. Following validation of these findings in an independent trial, genetic variation in the dopamine D2 receptor and its interacting proteins could potentially be used to tailor choice of pharmacotherapy for individuals with nicotine dependence.

Written by Freddie Patterson

Lerman, C., Jepson, C., Wileyto, E. P., Epstein, L. H., Rukstalis, M., Patterson, F., Kaufmann, V., Restine, S., Hawk, L., Niaura, R., & Berrettini, W. (2006). Role of functional genetic variation in the dopamine D2 receptor (*DRD2*) in response to bupropion and nicotine replacement therapy for tobacco dependence: Results of two randomized clinical trials. *Neuropsychopharmacology*, 31(1), 231-242.

Dahl, J. P., Jepson, C., Levenson, R., Wileyto, E. P., Patterson F., Berrettini, W. H., & Lerman, C. (2006). Interaction between variation in the D2 dopamine receptor (*DRD2*) and the neuronal calcium sensor-1 (*FREQ*) genes in predicting response to nicotine replacement therapy for tobacco dependence. *Journal of Pharmacogenomics*.

### UPenn TTURC Presentations at the Society for Research in Nicotine and Tobacco's, Annual Conference 2006



- Associations of two *CHRNA-4* SNPs with smoking behavior and abstinence in a nicotine replacement therapy trial. Christopher Jepson, et al.
- Clinical Theme Lecture: Pharmacogenetic Approach to Nicotine Dependence Treatment. Caryn Lerman, et al.
- Mecamylamine blocks nicotine induced enhancement of the P20 component of the auditory event related potential and evoked Gamma oscillations. Jennifer M. Phillips, et al.
- Association of genetic variation in mu opioid receptor interacting proteins with response to nicotine replacement therapy. Riju Ray, et al.
- Effects of reduced nicotine cigarette products on smoking topography and harm exposure. Andrew A. Strasser, et al.
- The effect of smoking cessation PSAs on cognitive and physiological responses. Andrew A. Strasser, et al.
- Effects of nicotine vary across two auditory evoked potentials in the mouse. Steven J. Siegel, et al.

**Nicotine Short Course.** Under the direction of Dr. Janet Audrain-McGovern, the UPenn TTURC Training Core conducted a 10-week short course entitled "Nicotine Addiction, from Cells to Society." Presentation topics included: Uptake and Progression of a Smoking Habit, Pharmacogenetic Investigation of Nicotine Dependence, The Genetic Basis of Nicotine Dependence, and Clinical Implications of Genetic Information for Nicotine Dependence.

## Translating Genetic Information to Clinical Practice

Led by Dr. Alexandra Shields, investigators in the TTURC *Research to Practice Core* reported results of a survey of primary care physicians to assess their attitudes toward future genetic-based approaches for the treatment of nicotine dependence. As part of the survey, physicians were randomly assigned one of two scenarios describing a new test that would allow the physician to tailor smoking cessation treatment. Both scenarios were identical, with the exception of the test description. In one scenario, the test was described as a “genetic test” while in the other the test was described as a “serum protein” test. Physician respondents expressed a high likelihood of adopting genetic testing to tailor treatment overall; however, levels of anticipated adoption were higher for the serum protein test as compared to the genetic test. As reported in the February 2005 issue of the *Journal of General Internal Medicine*, barriers to adoption may include the limited genetics training of primary care physicians and limited time to provide appropriate informed consent and counseling based on test results.



In related work published in *American Psychologist*, TTURC investigators argued that although self-identified race can be useful for tracking health disparities, it may be less appropriate as a proxy for human genetic heterogeneity in genetic studies of smoking and other behavioral traits. The authors warn that self-identified race variables have significant social risks. The authors suggest that a biologically relevant measure of geographical ancestry may be a more appropriate and accurate assessment.

Written by Molly McGinn-Shapiro and Freddie Patterson

Shields, A. E., Blumenthal, D., Weiss, K. B., Comstock, C. B., Currivan, D., & Lerman, C. (2005). Barriers to translating emerging genetic research on smoking into clinical practice: Perspectives of primary care physicians. *Journal of General Internal Medicine*, 20(2), 131-138.

Shields, A. E., Fortun, M., Hammonds, E. M., King, P. A., Lerman, C., Rapp, R., & Sullivan, P. F. (2005). The use of race variables in genetic studies of complex traits and the goal of reducing health disparities: A transdisciplinary perspective. *American Psychologist*, 60(1), 77-103.

## UPenn TTURC Collaborates with the Center of Excellence in Cancer Communication Research

The UPenn TTURC and the Center of Excellence in Cancer Communication Research (CECCR), based in the Annenberg School for Communication at UPenn, are working together to investigate effects of media messages related to nicotine dependence and smoking cessation. The CECCR is directed by Robert C. Hornik, Ph.D., Wilbur R. Schramm Professor of Communication, and funded by the National Cancer Institute.

Led by Joseph Cappella, Ph.D., investigators are studying how information about genetic risk of nicotine addiction can be framed to make it more effective, increasing perceived personal efficacy and a sense of control. This research is two pronged: a comprehensive content analysis of the frames used in broadcast and print news reports of research on genetics, smoking, and disease is underway. The effects on audiences perceived efficacy, control, and knowledge of different frames will

be investigated experimentally.

As published in *Communication Research*, smokers with a strong family history of smoking who were exposed to a credible news story about the genetic basis for nicotine addiction were significantly more likely to infer a greater personal genetic susceptibility to smoking addiction. Results from studies about genetic frames will contribute to an understanding of the impact of news stories about genetics and smoking on public perceptions and personal efficacy, and will help to identify effective messages for the communication of genetic information in public arenas.

Written by Megan Kasimatis

Cappella, J. N., Lerman, C., Romantan, A., & Baruh, L. (2005). News about genetics and smoking: Priming, family smoking history, and news story believability on inferences of genetic susceptibility to tobacco addiction. *Communication Research*, 32, 478-502.

## UPenn TTURC Welcomes New Faculty Members

We are pleased to announce the appointment of **Drs. Daniel Rodriguez, Robert Schnoll and Andrew Strasser** to the positions of Assistant Professor in the Department of Psychiatry at the University of Pennsylvania. Both Drs. Rodriguez and Strasser conducted their post-doctoral and research associate work with the UPenn TTURC.

Dr. Rodriguez's research focuses on the role of physical activity, team sport participation and depression in the onset and progression of adolescent tobacco use.

Dr. Strasser's research interests include behavioral variations and individual differences in cigarette smoking and the effect of media and advertising on beliefs about harm reduction and “safe” cigarettes.

Dr. Schnoll was recruited from the Fox Chase Cancer Center, where he directed their tobacco control program. He is the Principal Investigator of an NIH R01 grant to test the efficacy of bupropion for smoking cessation among cancer patients, work that he will continue to develop at the UPenn TTURC.