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Advancing Transdisciplinary Science and Policy Studies

The Networker

Showcasing Interesting TTURC Science

This issue of the Networker features stories of the interesting science coming out of the TTURCs. The research topics included in this issue range from exciting new genetics investigations, animal models of nicotine dependence, cross-cultural research, the effects of harm reduction, and the development of a new measurement of dependence. We are also looking forward to showcasing additional cutting-edge TTURC science and exciting research findings at the 2004 SRNT preconference TTURC meeting. Mark your calendars for this event!

Examining Genetic Variants' Impact on Smoking Cessation

By Megan Kasmatis



Through ongoing clinical trials, researchers at the PENN/Georgetown TTURC are evaluating the role of genetic factors in smokers' responses to different smoking cessation therapies. The data generated from these studies have important implications for the development of more effective smoking cessation therapies and the tailoring of different approaches based on smokers' genetic profiles. Recent findings from a randomized clinical trial evaluating the effectiveness of bupropion indicate that smokers with a decreased activity variant of the CYP2B6 gene may be more vulnerable to cigarette cravings and

relapse when trying to quit smoking. This study, titled "Pharmacogenetic Investigation of Smoking Cessation Treatment," appeared in a recent edition of *Pharmacogenetics* (2003, v.12, no.8, p. 627-634).

"This study provides an important first step toward utilizing genotype to identify smokers who are more vulnerable to relapse and who may benefit most from more intensive smoking cessation treatment." - Caryn Lerman

Principal Investigator Caryn Lerman, Ph.D., and her colleagues examined genetic data from 426 smokers enrolled in a randomized clinical trial of bupropion for smoking cessation. Participants all provided blood samples and received bupropion or placebo plus seven sessions of behavioral group counseling. Smoking status, abstinence symptoms, and side effects were recorded weekly, and smoking status was verified at the end of treatment and again at a six-month follow-up appointment. The researchers found that partici

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Investigating Genetic Vulnerability to Nicotine Dependence

By Suzanne Moriarty

“Estimation of genetic and environmental effects through twin and family designs provide guideposts for molecular genetic and intervention studies, offering the basis for genetic mapping to identify specific genes that influence smoking and perhaps the co-occurrence of smoking and depression” - Ray Niaura

Molecular genetics and twin studies within behavioral medicine are the major research interests of Jeanne McCaffery, Ph.D., Co-Investigator on the TTURC: NEFS Genetics Core. Before joining the Centers for Behavioral and Preventive Medicine in 2000 as a psychology intern, McCaffery’s research centered on genetic and environmental contributions to cardiovascular behavioral medicine and specific variants in DNA that predict physiological responses to psychological stress.

As a clinical psychology intern working with Raymond Niaura, Ph.D., McCaffery expanded her research interests into the tobacco field, analyzing the genetic and environmental associations between depression and smoking behavior. She describes her findings in, “A study of depressive symptoms and smoking behavior in adult male twins from the NHLBI twin study”, published in the current issue of *Nicotine and Tobacco Research* (2003, v.5, p. 77-83).

“These results point out that the nature of the association between depression and smoking may differ according to the severity of the depressive symptoms”, explains McCaffery. “Using a twin design, results suggest that

environmental factors accounted for the association between less severe forms of depressive symptoms and smoking. Previous research has suggested that biologic or genetic factors account for co-occurrence of smoking and severe depressive symptomology.”

The association between subclinical depression and smoking behavior is an area that will be further explored through TTURC NEFS. “We’ll use family designs to study aspects of smoking behavior (initial uptake, progression to nicotine dependence, difficulty quitting) and how the associations of smoking and depression are influenced by genetic or environmental effects,” explains McCaffery. Looking at these parameters within three generations of the NEFS cohort will provide critical data to explore these issues.



Jeanne McCaffery, Ph.D.

“Estimation of genetic and environmental effects through twin and family designs provide guideposts for molecular genetic and intervention studies,” adds Niaura, “offering the basis for genetic mapping to identify specific genes that influence smoking and perhaps the co-occurrence of smoking and depression.” Working within a transdisciplinary context, the combined knowledge of genetic and environmental influences on vulnerability to nicotine dependence should lead to improved, targeted strategies for prevention as well as tailored behavioral and pharmacologic interventions to treat nicotine dependence.

Exploring Nicotine’s Effect on Neuron’s

By Pem McNerney



Darlene Brunzell, Ph.D.

Researchers have long suspected that nicotine addiction happens, in part, because nicotine changes the brain with repeated use. Those changes might suggest why some smokers find it hard to quit as the brain adapts to nicotine use in a way that produces pleasurable feelings. Also, nicotine-induced changes might prompt addicted smokers to crave a cigarette when they are exposed to certain cues, such as driving to work or being in a bar.

Prolonged nicotine use causes neural plasticity, changes in

the way neurons communicate with one another. Why, exactly, this happens is still something of a mystery. But researchers have new insight that might help eventually solve that puzzle, thanks to Darlene H. Brunzell, Ph.D., a postdoctoral associate with Dr. Marina Piccotto’s lab in the Yale School of Medicine’s Department of Psychiatry. Brunzell’s area of specialty is the molecular and behavioral psychopharmacology of drugs of abuse.

“One particularly significant, interesting finding was a profound decrease in the active form of the transcription factor CREB (cyclic AMP regulated binding protein) in the nucleus accumbens ... This decrease in CREB activation has also been seen with chronic exposure to cocaine and alcohol, and could contribute to ongoing smoking behavior”. - Darlene Brunzell

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Measuring Dependence: UW TTURC's WISDM-68 Scale

By Gloria Meyer

"We developed the measure with the notion that smokers may have many different motives for smoking and each motive may contribute to compulsive drug use, withdrawal and relapse—three key criteria of dependence. By assessing dependence as a multidimensional construct, we are able to examine differences among smokers, something current measures do not allow us to do." - Megan Piper

TTURC scientists at the University of Wisconsin have developed a new measure to gauge tobacco dependence. The measure, called the Wisconsin Inventory of Smoking Dependence Motives, or WISDM-68, is intended to redress the shortcomings of previous tobacco dependence measures. It is a multi-dimensional measure of

dependence based on theoretically-grounded motives for drug use and may help reveal the nature of dependence, allowing theoreticians, researchers and clinicians to better prevent its development in beginning smokers and weaken its grip on those already addicted.

"We developed the measure with the notion that smokers

may have many different motives for smoking and each motive may contribute to compulsive drug use, withdrawal and relapse—three key criteria of dependence," says Megan E. Piper, M.A., a graduate student working with the principal investigator, Timothy Baker, Ph.D., on the WISDM-68. Piper is the lead author of a paper under review on the new measure's validation. She adds, "By assessing dependence as a multidimensional construct, we are able to examine differences among smokers, something current measures do not allow us to do."



Megan Piper, M.A.

To create WISDM-68, Baker and fellow researchers identified 13 separate motives for drug use based on current research and theories of drug use and abuse motivation. These motives include affiliative attachment, cognitive enhancement and negative and positive reinforcement. They then

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Exploring Nicotine's Effect on Neurons Continued...

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Brunzell studies the effects of nicotine exposure on molecular and neurochemical changes within neurons.

Brunzell, working with others in Piccotto's lab and the Yale TTURC's laboratory core, recently examined the extracellular regulated protein kinase (ERK) pathway to find out if it might play a role in the way the brain adapts to nicotine use. She decided to study the ERK pathway because it has been shown in-vitro in cell lines to be stimulated by nicotine, and in animals to be involved in brain changes that underlie learning.

To simulate human nicotine intake, Brunzell administered nicotine in sweetened water to C57Bl/6J mice, a strain that is known to like drugs of abuse. Sweetened nicotine water was used, because the drinking of nicotine by mice simulates human nicotine intake more closely than other methods, such as injection. Brunzell examined mice that received acute and chronic doses of nicotine, and mice that were withdrawn for 24 hours following chronic exposure to nicotine.

She found several changes in the molecules in the MAP

kinase ERK signaling pathway that were specific to chronic exposure. These changes could be adaptations to nicotine exposure that contribute to nicotine addiction. "One particularly significant, interesting finding was a profound decrease in the active form of the transcription factor CREB (cyclic AMP regulated binding protein) in the nucleus accumbens," said Brunzell. "The nucleus accumbens is an area of the brain that contributes to motivation and reward and is generally implicated in drug addiction. This decrease in CREB activation has also been seen with chronic exposure to cocaine and alcohol, and could contribute to ongoing smoking behavior."

Brunzell's work is of particular interest because one of the Yale TTURC's goals is to link intracellular changes to behaviors associated with addiction in an effort to find new targets for pharmacological interventions in smokers. Her recent article, "In vivo nicotine treatment regulates mesocorticolimbic CREB and extracellular regulated kinase signaling in C57Bl/6J mice," has been published in the *Journal of Neurochemistry* (2003, v.84, p.1431-1441).

Reasons to Smoke: Chinese and American Teenagers

By Jeff Baskin

“What we term depression in the U.S. may be expressed in different ways in other cultures. In China and elsewhere, it may be more appropriate to express feelings of sadness through physical ailments than to say ‘you’re sad’ or ‘you feel like a failure.’” - Elahe Nezami

USC TTURC researchers have found that personality traits and emotional states associated with smoking differ between American and Chinese youth and within ethnic groups in the U.S. These findings could help identify genetic phenotypes and/or explain cultural variation in mood regulation of smoking behavior.

Cross-sectional and longitudinal survey data for the study were collected from paper and pencil surveys administered to 1,041 seventh-grade students in the U.S. and 588 seventh- and ninth-grade students in Wuhan China.

In the U.S., Hispanic/Latino, multiethnic and White students demonstrated the highest levels of depressive symptoms. Depressed students were more likely to state their intention to smoke in the next year and to have started experimenting with cigarette smoking. When acculturation, socioeconomic status, gender and ethnicity were controlled for, depressive symptoms remained a significant predictor of intention to smoke. In addition, depressive symptoms showed the strongest association with actual smoking behavior for Hispanic/Latino youth.

A different pattern emerged when examining the data from Chinese students. Initial analyses indicate that for Chinese youth, anxiety and sensation seeking were strong predictors of both intention to smoke and smoking experimenta-

tion while depression was only a moderate predictor. In the U.S. sample, anxiety was a significant predictor of smoking in Chinese American students as well. However, Chinese American youth demonstrated lower levels of depression and smoking experimentation than the Wuhan cohort and the U.S. population at large.

These findings suggest that students of Chinese ancestry living in the U.S. have different psychological profiles than students living in urban China and that these profiles may be useful in predicting smoking behavior.



Elahe Nezami, Ph.D.

Elahe Nezami, Ph.D., principal investigator of the study, said, “Further studies need to refine the definition of depression across cultures. What we term depression in the U.S. may be expressed in different ways in other cultures. In China and elsewhere, it may be more appropriate to express feelings of sadness through physical ailments than to say ‘you’re sad’ or ‘you feel like a failure.’”

Additional activities utilizing these data include analyses on the relationships between anxiety and smoking in the two Chinese groups: those in Wuhan and those in California; analysis of China and California survey data to assess the potential moderating effects of westernization in the Chinese cohort and acculturation in the California cohort; and analyses of peer influences as a mediator between depression and smoking.

Measuring Dependence: UW TTURC’s WISDM-68 Scale Continued...

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designed 285 items that broadly tapped each motive and administered the measure to 778 participants. All subjects had to be at least 18 years old and to have smoked a cigarette within the last four weeks. Participants completed the WISDM-68, the Fagerström Test of Nicotine Dependence, the Tobacco Dependence Screener (a measure of DSM-IV dependence), a smoking history questionnaire, a demographics questionnaire and provided a breath sample for carbon monoxide analysis.

Preliminary data indicates that all 13 subscales of the WISDM-68 have acceptable internal consistency, are differentially present across levels of smoking heaviness, and

have a multidimensional structure. Validity analyses indicate that WISDM-68 subscales are significantly related to dependence criteria such as smoking heaviness, DSM-IV symptoms of dependence, and relapse.

“We are continuing to examine the ability of the WISDM-68 to predict other indicators of dependence, such as severity of withdrawal and potential for relapse,” says Piper. “Thus far, our data supports the use of the WISDM-68 subscales for research purposes, especially for examining heterogeneous processes among smokers.”

Animal Studies Show Strong Reinforcing Effects of Tobacco

By Louri Groves

It has been shown that most adult smokers start smoking as adolescents, and that relatively few people start smoking for the first time as adults. While there are undoubtedly multiple determinants of teenage smoking, Frances Leslie, Ph.D. and James Belluzzi, Ph.D., have designed experiments to examine one potential cause: heightened sensitivity to the reinforcing effects of tobacco constituents during adolescence.

“To date, treatments for adolescent smoking cessation have met with little success. Improved understanding of the biological mechanisms underlying youth tobacco use and addiction, derived from animal studies such as ours, offers promise for improvements in future treatment strategies.” - Frances Leslie

In order to examine the period of the greatest reinforcing effects of nicotine, Leslie and Belluzzi tested adolescent and adult rats for conditioned place preference, a test where drug injections are paired with distinctive environmental cues. Whereas animals initially show no preference for either of the two distinct compartments, they will later choose to spend more time in an environment in which they received the drug if that drug is reinforcing. While using the same nicotine doses, Leslie and Belluzzi found that conditioning occurred in adolescent rats, but not in adult rats. In fact, they discovered that nicotine reinforcement occurred only during the earliest adolescent stage, but not during later adolescence.

In a second study, Leslie and Belluzzi used self-administration to test nicotine reinforcement. In this test, drugs were administered via a catheter implanted in the jugular vein. Animals self-administer the drug by poking their nose into a hole equipped with electronic sensors. In this very stringent test of reinforcement, the animals did not self-administer nicotine alone. However, adolescent animals self-administered large amounts of nicotine when combined with acetaldehyde, another major constituent of tobacco smoke.

These studies add to a growing body of findings that suggest that adolescence may be a developmental period during which the rewarding pathways in the brain are highly responsive to nicotine. What is more, nicotine may not be the only reinforcing constituent of tobacco. Acetaldehyde, which is a product of burning sugar, appears to potentiate nicotine’s reinforcing actions during early adolescence.

A promising area of future research will be examination the effects of multiple components of tobacco smoke in adolescence. Such research should provide insight into the complex behavioral and biochemical changes that underlie the high rate of smoking initiation in adolescents.

“To date, treatments for adolescent smoking cessation have met with little success” says Leslie. “Improved understanding of the biological mechanisms underlying youth tobacco use and addiction, derived from animal studies such as ours, offers promise for improvements in future treatment strategies.”

Examining the Effects of Harm Reduction

By Sheran McNiff



The primary objective of the studies conducted by the University of Minnesota TTURC researchers is to examine approaches for the reduction of tobacco toxin exposure. This topic of research is important because many smokers are unable or unwilling to quit. Therefore, new interventions for treating resistant smokers are needed, and, according to the Institute of Medicine, reducing tobacco toxin exposure may be a feasible complement to the prevention and cessa-

tion of tobacco use and requires further study. Reduction in smoking using pharmacological approaches has recently received a great deal of attention in smokers not interested in quitting.

Dorothy Hatsukami, Ph.D., is the principal investigator for a study that examines the extent to which tobacco toxin exposure is reduced as a result of reduced cigarette smoking using nicotine replacement products. Smokers who were unwilling to quit smoking were asked to reduce their cigarette smoking by at least 25% over a two-week period, 50% during

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Genetic Variants' Continued...

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pants with a decreased activity variant of the CYP2B6 gene reported greater increases in cravings for cigarettes following the quit date and were about one and a half times more likely to relapse during the treatment phase.

“This study provides an important first step toward utilizing genotype to identify smokers who are more vulnerable to relapse and who may benefit most from more intensive smoking cessation treatment,” said Caryn Lerman, Ph.D.

In previous research, the CYP2B6 enzyme (the product of this gene) has been found to affect both nicotine metabolism and bupropion metabolism. Lerman and her colleagues speculate that the effect of the genetic variant on cessation may be due to inherited differences in nicotine metabolism. “Brain concentrations of human CYP2B6 may alter local metabolism of nicotine. Such effects could contribute to neuroadaptations that alter the subjective effects of abstinence from smoking, thereby promoting relapse,” said Lerman. The present data do not suggest that the CYP2B6 genetic effect on smoking cessation is attributable to individual differences in bupropion metabolism; however, Lerman believes further research in this area is needed.

The study also provides preliminary evidence that bupropion may help smokers, especially females, overcome the effects of this genetic predisposition on early relapse. Among women with the CYP2B6 polymorphism, 54 percent of those who were treated with bupropion were abstinent at the end of treatment, compared with 19 percent of those who received placebo. The researchers believe that this difference might be due to bupropion’s effect on abstinence-induced negative moods that are more common among women.

This research helps to illustrate how individual genetic differences might impact responsiveness to bupropion. Through future findings, TTURC researchers hope to identify which individuals respond best to alternate smoking cessation therapies and apply this knowledge to the development of more effective treatment strategies.

Harm Reduction Continued...

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the second two weeks, and 75% during the subsequent two weeks. They were asked to sustain that level of reduction thereafter.

In order to measure reduced toxin exposure, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) was used. All subjects were given nicotine replacements for up to 12 weeks. Total NNAL is a composite of NNAL and NNAL-glucuronide, which are urinary metabolites of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK). NNK is a potent lung carcinogen.

There was a significant reduction in number of cigarettes smoked, achieving about a 75% reduction at weeks 6, 8, and 12. In addition, there was a significant reduction in total NNAL over this time period. However, the reduction in total NNAL was not as dramatic as the reported reduction in number of cigarettes. The reduction in total NNAL did not exceed 30% even with the 75% reduction of cigarettes. Similar results were observed with biochemical verification of self-reported cigarette reduction by measuring anatabine, a biomarker for a tobacco alkaloid. This result would suggest that even with significant reductions in cigarette smoking, only modest reductions are observed in exposure to carcinogens. Similar findings were observed in a study that the UMN TTURC conducted using bupropion SR. Therefore, reduction of cigarettes using the currently available interventions may not lead to significant health benefits.

TTURC News and Happenings

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