Neuropsychopharmacology (2010) 35, 2322–2323

www.neuropsychopharmacology.org

Commentary

Preclinical Data Elucidate Molecular and Neural Mechanisms of Perinatal Nicotine Effects on Neurodevelopment and Behavior: Translational Opportunities and Implications

Caryn Lerman*[,1]

[1]*Department of Psychiatry and Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA, USA*

Neuropsychopharmacology (2010) **35,** 2322–2323; doi:10.1038/npp.2010.147

Developmental exposure to nicotine, the addictive constituent in tobacco, alters early brain development, leading to defects in sensory and cognitive processing. In this issue of *Neuropsychopharmacology*, Heath *et al* (2010) utilize a novel mouse model of developmental nicotine exposure to clarify the molecular and neural mechanisms underlying the effects of perinatal nicotine on the developing brain and behavior. The authors show that mice exposed to nicotine during a critical period for corticothalamic development exhibit increased sensitivity to passive avoidance behavior, characterized by a longer latency to enter a chamber in which mild footshock was administered. Further, they provide compelling evidence that this neurobehavioral effect of developmental nicotine is mediated by $\alpha4\beta2\alpha5$ nicotinic acetylcholine receptors (nAChRs) expressed in the corticothalamic pathway. These preclinical findings are novel and important, informing human neuropsychopharmacology investigations that may lead to improved prevention and treatment of nicotine addiction and its consequences.

On the basis of their experiments and prior data, the authors suggest that the passive avoidance phenotype reflects altered sensory processing, which heightens the aversive effects of the mild footshock administered. As they point out, humans exposed to tobacco smoke *in utero* exhibit a range of processing deficits in both sensory and cognitive domains (Jacobsen *et al*, 2007). In contrast, however, nicotine exposure in adult animals and humans can enhance sensory processing and cognitive function (Evans and Drobes, 2009). Taken together, these data may support a translational hypothesis that the increased incidence of smoking among persons exposed to tobacco smoke *in utero* (Buka *et al*, 2003) reflects 'self-medication' with nicotine to reverse sensory and cognitive deficits. Preclinical investigations can define, under controlled experimental conditions, the specific cognitive and sensory domains altered by perinatal tobacco exposure, thereby informing clinical investigations to better characterize nicotine dependence phenotypes in this subgroup of smokers.

The mouse model of developmental nicotine exposure could also be used to screen nicotine dependence medications. On the basis of the paucity of data on the efficacy and safety of existing pharmacotherapies for pregnant smokers, nonpharmacological (behavioral) cessation interventions are recommended as first-line treatment despite their relatively lower efficacy in the general population of smokers (Oncken and Kranzler, 2009). Thus, by elucidating the molecular and neurobehavioral effects of perinatal exposure to cessation medications, preclinical studies can inform the clinical treatment of pregnant smokers.

Data presented by Heath *et al* (2010) also suggest novel molecular mechanisms important in the neurodevelopmental effects of nicotine exposure. They find that the $\alpha5$ nAChR subunit expressed with $\alpha4\beta2$ nAChRs on corticothalamic neurons has an important modulatory role in developmental cholinergic function and sensory processing. Interestingly, a common polymorphism in the $\alpha5$ nAChR subunit (*CHRNA5*) gene has been associated with persistence of smoking during pregnancy (Freathy *et al*, 2009) and with the subjective effects of the initial smoking experience (Sherva *et al*, 2008). The current preclinical findings (Heath *et al*, 2010) suggest the hypothesis that altered sensory processing is an intermediate mechanism linking *CHRNA5* with nicotine dependence.

Lastly, data pointing to the corticothalamic circuit as important in nicotine's developmental effects helps to advance human neuroimaging research aimed at elucidating the functional neurocircuitry underlying nicotine dependence phenotypes. In humans, genetic variation at *CHRNA5* and the severity of nicotine dependence have both been associated with reduced resting functional connectivity in a dorsal cingulate cortical circuit (Hong *et al*, 2010). Thus, parallel preclinical and human studies lend support to the premise that assessment of functional cortical connectivity

*Correspondence: Dr C Lerman, Department of Psychiatry and Abramson Cancer Center, University of Pennsylvania, 3535 Market Street, Suite 4100, Philadelphia, PA 19104, USA, Tel: +2 15 746 7141, Fax: +2 15 746 7140, E-mail: clerman@upenn.edu
Received 3 August 2010; accepted 3 August 2010

may be a useful translational biomarker of nicotine's effects. The preclinical data by Heath *et al* (2010) suggest the value of examining corticothalamic connectivity in future clinical investigations of developmental nicotine effects.

Thus, the paper by Heath *et al* (2010) provides an excellent example of the value of preclinical research for informing clinical research and practice. Not only does it suggest directions for human neuropsychopharmacology studies of the adverse effects of developmental nicotine, but it also highlights important translational opportunities to elucidate the functional neurobiology of nicotine addiction and develop better treatments for nicotine-addicted smokers.

ACKNOWLEDGEMENTS

This work was supported by NIH grants P50CA143187, U01DA020830 and R01DA026849.

DISCLOSURE

Dr Lerman has served as a consultant and/or has received research funding from GlaxoSmithKline, AstraZeneca, Pfizer and Targacept. In the past 3 years, she has also received compensation for professional services from the National Institutes of Health, University of North Carolina, American Association of Cancer Research, the Cancer Prevention Research Institute of Texas, Moffitt Cancer Center, University of New Mexico, Memorial Sloan Kettering Cancer Center, University of Virginia, University of Illinois, Washington University in St Louis, Northwestern University and Rutgers University.

REFERENCES

Buka SL, Shenassa ED, Niaura R (2003). Elevated risk of tobacco dependence among offspring of mothers who smoked during pregnancy: a 30-year prospective study. *Am J Psychiatry* **160**: 1978–1984.

Evans DE, Drobes DJ (2009). Nicotine self-medication of cognitive-attentional processing. *Addict Biol* **14**: 32–42.

Freathy RM, Ring SM, Shields B, Galobardes B, Knight B, Weedon MN *et al* (2009). A common genetic variant in the 15q24 nicotinic acetylcholine receptor gene cluster (CHRNA5-CHRNA3-CHRNB4) is associated with a reduced ability of women to quit smoking in pregnancy. *Hum Mol Genet* **18**: 2922–2927.

Heath CJ, King SL, Gotti C, Marks MJ, Picciotto MR (2010). Corticothalamic connectivity is vulnerable to nicotine exposure during early postnatal development through α4/β2/α5 nicotinic acetylcholine receptors. *Neuropsychopharmacology* **35**: 2324–2338.

Hong LE, Hodgkinson CA, Yang Y, Sampath H, Ross TJ, Buchholz B *et al* (2010). A genetically modulated, intrinsic cingulate circuit supports human nicotine addiction. *Proc Natl Acad Sci USA* **107**: 13509–13514.

Jacobsen LK, Slotkin TA, Mencl WE, Frost SJ, Pugh KR (2007). Gender-specific effects of prenatal and adolescent exposure to tobacco smoke on auditory and visual attention. *Neuropsychopharmacology* **32**: 2453–2464.

Oncken CA, Kranzler HR (2009). What do we know about the role of pharmacotherapy for smoking cessation before or during pregnancy? *Nicotine Tob Res* **11**: 1265–1273.

Sherva R, Wilhelmsen K, Pomerleau CS, Chasse SA, Rice JP, Snedecor SM *et al* (2008). Association of a single nucleotide polymorphism in neuronal acetylcholine receptor subunit alpha 5 (CHRNA5) with smoking status and with 'pleasurable buzz' during early experimentation with smoking. *Addiction* **103**: 1544–1552.