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Editorial
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Editorial

Biomarkers for Tobacco Exposures, Toxicology, Regulation, and Cessation

This month's issue of Nicotine & Tobacco Research provides the reader with a dozen original research papers evaluating the effects of acute and chronic tobacco exposures on a wide variety of behavioral, developmental and metabolic responses, and two linked editor's choice articles on smoking cessation that review "omic" studies and encourage collaborative efforts in future genomic studies of smoking cessation. The original research articles include animal model, human laboratory, and population-based studies ranging widely over the acute or chronic effects of nicotine or tobacco product exposures.

One animal model study demonstrated reduction of the inflammatory response pathway, activation of the dopaminergic neurotropic pathway and reduced postoperative cognitive dysfunction following nicotine administration immediately after anesthesia induction.[1] Two model studies focused on the effects of waterpipe smoke on embryonic development,[2] and adult learning and memory.[3] The first study adds avian model evidence at the organismal, tissue and genic levels to the tobacco smoke developmental toxicology literature and novel evidence for the effects of waterpipe smoke, while the second provides evidence of the effects of prenatal exposure on learning and memory at the behavioral and molecular level. The contrast in effects observed on hippocampal brain derived neurotrophic factor, where the postoperative cognition study observed acute reduction attenuation,[1] and the waterpipe exposure study where chronic reduction was observed,[3] adds to our understanding of the toxicity of tobacco smoke.

One human laboratory study focused on nicotine pharmacokinetics and subjective effects in a comparison of a novel nicotine delivery device combining nicotine and lactic acid, and a nicotine replacement therapy inhalator[4]; the novel device, which generates a nicotine aerosol, provided a more rapid maximum plasma nicotine level than the inhalator. The other human laboratory studies evaluated the acute effects of nicotine delivery via an electronic nicotine delivery system or a cigarette in terms of β^{2}*-nAChR occupancy using a novel neuroimaging radiotracer,[5] or chronic effects of cigarette smoking on anatomic and functional brain imaging measures.[6,7] The former identified dose–response effects by e-liquid nicotine concentration, whereas the cigarette resulted in greater maximal nicotine concentration, but similar nicotine exposure, to the highest nicotine concentration e-liquid; in general, subjective effects did not differ. The latter two studies compared different brain volume and functional measures in smokers and nonsmokers, where chronic smoking is associated with reduced cerebellum grey matter and functional connectivity with several systems,[6] and reduced thalamus volume,[7] with both findings inversely associated with a common measure of nicotine dependence, revealing a dose–response effect.

The population-based studies with hundreds to thousands of participants evaluated chronic environmental exposures to tobacco,[8–12] and in one case, genomic variation,[13] in diverse settings by age, ancestry, country, and occupation. The adolescent studies[8,10] examined two large cohorts through questionnaire and urinary cotinine to investigate environmental tobacco smoke (ETS) exposures and associated effects. The US cohort found 18% of adolescents with the highest category of ETS (ie, suggesting active smoking), with significantly increased glycated hemoglobin observed in males with evidence of active smoking[10]; the Mexican cohort identified increased dependence (time to first cigarette) with increased ETS, independent of adolescent smoking intensity.[8] Both studies point to ETS as a target for tobacco control and cessation programs in this critical developmental period.

Two studies evaluated tobacco exposures in waterpipe smokers and nonsmokers in social[9] and occupational[11] settings. Social exposure to waterpipe smoking in lounges or in residential settings resulted in significant increases in a biomarker for the toxin acrolein for both smokers and nonsmokers, with implications for health communication and waterpipe tobacco additive regulation.[9] Exhaustive sampling and analysis of biospecimens, indoor air and occupational roles in a study of waterpipe lounge employees in three countries revealed multiple risk factors (smoking status, customer-centric role, hours at work, and increased indoor air nicotine) for increased exposures of nicotine metabolites, a tobacco-specific nitrosamine, and polyaromatic hydrocarbons,[11] with implications for waterpipe lounge regulation to reduce employee exposures.

Two studies evaluated questionnaire-assessed smoking behaviors in cohorts defined by ancestral origin: two Native American populations that included biospecimen analysis of cotinine,[12] and four Hispanic populations that included genomic variation analysis.[13] Both represent tobacco exposure risk investigations into ancestries infrequently studied using these approaches. A majority of smokers and substantial fractions of nonsmokers exhibited cotinine levels suggestive of active smoking across the two populations with significant effects of self-reported second-hand smoke exposure observed[12]; enhancement of tobacco control policies would reduce risk. Genomic analysis of Hispanic American populations demonstrated that this ancestry shares the single largest genomic predictor of smoking heaviness (the chromosome 15q25.1 *CHRNA5* cholinergic locus) at genome-wide significance with European and African American ancestries; evidence at other cholinergic loci was concordant with prior results.[13]

The two reviews focused on smoking cessation omic analyses resulted from the efforts of the Genetics and Treatment Networks of the Society for Research on Nicotine and Tobacco: review of past omic biomarker findings, including associations with smoking cessation,[14] and outline of the collaborative consortial efforts necessary to obtain adequate sample sizes for identifying and translating genomic

predictors of response to therapy.[15] The omic review focuses on a genomic biomarker of smoking heaviness, biomarkers of nicotine metabolism, and emerging epigenomic markers of exposure and cessation; the cessation consortial review focuses on trial design, biospecimens, ethics, outcomes, and analysis approaches to foster biomarker discovery and translation.

This issue provide abundant evidence that biomarker-based tobacco research extends from exposure assessment to tobacco attributable disease studies, uses animal and human models at multiple levels to evaluate effects of tobacco toxicants, and informs cessation therapy. In other areas of research and translation (eg, drug development), increasingly formal approaches to defining context of use and utility of biomarkers for further development have arisen through a multiple stakeholder framework,[16] with strong support from the FDA.[17] Tobacco biomarker development is a priority for tobacco control[18] and for cessation therapy.[19,20] A continued focus on tobacco biomarkers taking advantage of efforts to formalize biomarker development should help translation to tobacco control, tobacco product regulation and cessation therapy.

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Declaration of Interests

None declared.

References

1. Wei P, Zheng Q, Liu H, et al. Nicotine-induced neuroprotection against cognitive dysfunction after partial hepatectomy involves activation of BDNF/TrkB signaling pathway and inhibition of NF-κB signaling pathway in aged rats [published online ahead of print July 27, 2017]. *Nicotine Tob Res*. 2018;20(4):515–522.
2. Ashour AA, Haik MY, Sadek KW, et al. Substantial toxic effect of water-pipe smoking on the early stage of embryonic development[published online ahead of print June 12, 2017]. *Nicotine Tob Res*. 2018;20(4):502–507.
3. Al-Sawalha N, Alzoubi K, Khabour O, Alyacoub W, Almahmmod Y, Eissenberg T. Effect of prenatal exposure to waterpipe tobacco smoke on learning and memory of adult offspring rats [published online ahead of print June 20, 2017]. Nicotine Tob Res. 2018;20(4):508–514.
4. Teichert A, Brossard P, Felber Medlin L, et al. Evaluation of nicotine pharmacokinetics and subjective effects following use of a novel nicotine delivery system. [published online ahead of print May 06, 2017]. *Nicotine Tob Res*. 2018;20(4):458–465.
5. Baldassarri SR, Hillmer AT, Anderson JM, et al. Use of electronic cigarettes leads to significant beta2-nicotinic acetylcholine receptor occupancy: evidence from a PET imaging study [published online ahead of print April 29, 2017]. *Nicotine Tob Res*. 2018;20(4):425–433.
6. Shen Z, Huang P, Wang C, Qian W, Yang Y, Zhang M. Cerebellar gray matter reductions associate with decreased functional connectivity in nicotine-dependent individuals [published online ahead of print July 27, 2017]. *Nicotine Tob Res*. 2018;20(4):440–447.
7. Yu D, Yuan K, Cheng J, et al. Reduced thalamus volume may reflect nicotine severity in young male smokers [published online ahead of print June 23, 2017]. *Nicotine Tob Res*. 2018;20(4):434–439.
8. Bronstein AB, Gascón JL, Eugenio González CI, Barrientos-Gutierrez T. Environmental tobacco exposure and urinary cotinine levels in smoking and non-smoking adolescents [published online ahead of print June 03, 2017]. *Nicotine Tob Res*. 2018;20(4):523–526.
9. Kassem NOF, Kassem NO, Liles S, et al. Acrolein exposure in hookah smokers and non-smokers exposed to hookah tobacco Secondhand Smoke: Implications for regulating hookah tobacco products [published online ahead of print July 17, 2017]. *Nicotine Tob Res*. 2018;20(4):492–501.
10. Merianos AL, Hossain MM, Khoury JC, Matt GE, Melinda Mahabee-Gittens E. Serum cotinine and hemoglobin A1c among a national sample of adolescents without known diabetes [published online ahead of print June 01, 2017]. *Nicotine Tob Res*. 2018;20(4):474–481.
11. Moon KA, Rule AM, Magid HS, et al. Biomarkers of secondhand smoke exposure in waterpipe tobacco venue employees in Istanbul, Moscow, and Cairo [published online ahead of print June 03, 2017]. *Nicotine Tob Res*. 2018;20(4):482–491.
12. Tanner JA, Henderson JA, Buchwald D, Howard BV, Nez Henderson P, Tyndale RF. Relationships between smoking behaviors and cotinine levels among two American Indian populations with distinct smoking patterns [published online ahead of print May 26, 2017]. Nicotine Tob Res. 2018;20(4):466–473.
13. Saccone NL, Emery LS, Sofer T, et al. Genome-wide association study of heavy smoking and daily/nondaily smoking in the Hispanic Community Health Study / Study of Latinos (HCHS/SOL) [published online ahead of print May 17, 2017]. *Nicotine Tob Res*. 2018;20(4):448–457.
14. Saccone NL, Baurley JW, Bergen AW, et al. The value of biosamples in smoking cessation trials: a review of genetic, metabolomic, and epigenetic findings [published online ahead of print May 03, 2017]. *Nicotine Tob Res*. 2018;20(4):403–413.
15. Chen L-S, Zawertailo L, Piasecki TM, et al. Leveraging genomic data in smoking cessation trials in the era of precision medicine: why and how [published online ahead of print May 12, 2017]. *Nicotine Tob Res*. 2018;20(4):414–424.
16. Leptak C, et al. What evidence do we need for biomarker qualification? *Sci Transl Med*. 2017;9(417). doi:10.1126/scitranslmed.aal4599
17. Amur S, LaVange L, Zineh I, Buckman-Garner S, Woodcock J. Biomarker qualification: toward a multiple stakeholder framework for biomarker development, regulatory acceptance, and utilization. *Clin Pharmacol Ther*. 2015;98(1):34–46.
18. Leischow SJ, Zeller M, Backinger CL. Research priorities and infrastructure needs of the Family Smoking Prevention and Tobacco Control Act: science to inform FDA policy. *Nicotine Tob Res*. 2012;14(1):1–6.
19. Bough KJ. et al. Biomarkers for smoking cessation. *Clin. Pharmacol. Ther*. 2013;93(6):526–538.
20. Mamoun M, Bergen AW, Shieh J, Wiggins A, Brody AL. Biomarkers of response to smoking cessation pharmacotherapies: progress to date. *CNS Drugs*. 2015;29(5):359–369.