

BÖLÜM 5

NİKOTİN YOKSUNLUĞUNUN ÖĞRENME VE HAFIZA ÜZERİNE ETKİLERİ

Sena DEVECİ¹

İlay BURAN KAVURAN²

GİRİŞ

Öğrenme, bireyin çevresiyle etkileşimi sonucu bilgi ve davranışlarında meydana gelen kalıcı değişiklikleri ifade ederken; hafıza, bu bilgilerin kodlanması, depolanması ve gerektiğinde hatırlanmasını sağlayan bilişsel bir süreçtir. Her iki işlev de sinaptik plastisite ve nöral ağlardaki değişimlerle gerçekleşmektedir. Özellikle hipokampus, prefrontal korteks gibi beyin yapıları bu süreçlerde merkezi rol oynar. Glutamat, asetilkolin ve dopamin gibi nörotransmitterler ise öğrenme ve hafızanın nörokimyasal temelini oluşturmaktadır. Öğrenme ve hafıza, bireyin çevresine uyum sağlaması, karar alma ve davranışlarını düzenlemesi açısından kritik öneme sahiptir (1). Nikotin; tarihsel, farmakolojik, biyolojik ve davranışsal boyutları olan karmaşık ve çok yönlü bir maddedir. Tütün bitkisinden elde edilen ve tarihsel olarak 16. yüzyılda Avrupa'ya tanıtılan nikotin, adını Fransız elçisi Jean Nicot'tan almış ve günümüzde dünyada en yaygın kullanılan psikoaktif maddelerden biri haline gelmiştir. Nikotin, merkezi sinir sistemine (MSS) etki eden güçlü bir alkaloiddir ve tütün ürünlerinin bağımlılık yapıcı temel bileşenidir. Beyindeki nikotinik asetilkolin reseptörlerine (nAChR) bağlanarak çeşitli nörotransmitter sistemlerini etkilemektedir. Bu etkileşim, öğrenme ve hafıza gibi yüksek düzey bilişsel işlevler üzerinde hem olumlu hem de olumsuz etkiler doğurabilir (2).

Nikotinin etkisi, ilgili dokuları oluşturan farklı hücre tiplerinde bulunan nikotinik asetilkolin reseptörlerinin (nAChR) ekspresyonuna bağlıdır. Uzun süreli

¹ Fırat Üniversitesi, Tıp Fakültesi, Tıbbi Biyoloji AD, YL öğrencisi, dvc.sena23@gmail.com, ORCID iD: 0009-0001-0601-8928.

² Dr. Öğr. Üyesi, Fırat Üniversitesi, Tıp Fakültesi, Tıbbi Biyoloji AD., iburan@firat.edu.tr, ORCID iD: 0000-0002-2890-3952.

hipokampus temelli bellek süreçlerinde kayıplara yol açtığını net biçimde ortaya koymaktadır (47–49). Bu bulgular, yalnızca nikotin bağımlılığının nörobiyolojik temellerini değil, aynı zamanda yoksunluğa bağlı bilişsel defisitlerin mekanizmalarını da aydınlatmaktadır.

Sonuç olarak nikotin bağımlılığı, dopaminerjik ödül devreleriyle sınırlı kalmayıp, öğrenme ve hafıza ile ilişkili geniş bir nörotransmitter ağı, gen ekspresyonu ve sinaptik plastisite mekanizmalarını da kapsamlı biçimde etkilemektedir. Bu nedenle hem hayvan hem de klinik düzeyde yürütülecek davranışsal, nörokimyasal ve moleküler çalışmalar, nikotin yoksunluğuna bağlı bilişsel bozuklukların önlenmesi ve tedavisinde yeni farmakolojik yaklaşımların geliştirilmesi gerektiğini vurgulamaktadır.

KAYNAKLAR

1. Sansone L, Milani F, Fabrizi R, Belli M, Cristina M, Zagà V, vd. Nicotine: From Discovery to Biological Effects. *IJMS*. 26 Eylül 2023;24(19):14570.
2. Dani JA, Balfour DJK. Historical and current perspective on tobacco use and nicotine addiction. *Trends Neurosci*. Temmuz 2011;34(7):383-92.
3. Davis JA, Gould TJ. Hippocampal nAChRs mediate nicotine withdrawal-related learning deficits. *Eur Neuropsychopharmacol*. Ağustos 2009;19(8):551-61.
4. Mansvelder HD, McGehee DS. Cellular and synaptic mechanisms of nicotine addiction. *J Neurobiol*. 2002;53(4):606–17.
5. Gould TJ. Nicotine and hippocampus-dependent learning: Implications for addiction. *Mol Neurobiol*. 2006;34(2):93–107.
6. McKay BE, Placzek AN, Dani JA. Regulation of synaptic transmission and plasticity by neuronal nicotinic acetylcholine receptors. *Biochemical Pharmacology*. Ekim 2007;74(8):1120-33.
7. Wittenberg RE, Wolfman SL, De Biasi M, Dani JA. Nicotinic acetylcholine receptors and nicotine addiction: A brief introduction. *Neuropharmacology*. Ekim 2020;177:108256.
8. Ca2+ permeability of nicotinic acetylcholine receptors in rat hippocampal CA1 interneurons [Internet]. Blackwell Science Inc; [a.yer 13 Eylül 2025]. Erişim adresi: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1464780>
9. Borkar NA, Thompson MA, Bartman CM, Khalfaooui L, Sine S, Sathish V, vd. Nicotinic receptors in airway disease. *American Journal of Physiology-Lung Cellular and Molecular Physiology*. 01 Şubat 2024;326(2):L149-63.
10. Gotti C, Zoli M, Clementi F. Brain nicotinic acetylcholine receptors: native subtypes and their relevance. *Trends in pharmacological sciences*. 27:482.
11. Shen J xin, Yakel JL. Nicotinic acetylcholine receptor-mediated calcium signaling in the nervous system. *Acta Pharmacol Sin*. Haziran 2009;30(6):673-80.
12. Gipson CD, Fowler CD. Nicotinic Receptors Underlying Nicotine Dependence: Evidence from Transgenic Mouse Models. İçinde: Shoaib M, Wallace TL, editörler. *Behavioral Pharmacology of the Cholinergic System* [Internet]. Cham: Springer International Publishing; 2020 [a.yer 13 Eylül 2025]. s. 101-21. (Current Topics in Behavioral Neurosciences; c. 45). Erişim adresi: http://link.springer.com/10.1007/7854_2020_134
13. Garai N, Petrovic K, Peric S, Djordjevic I, Pesovic J, Brkusanin M, vd. Causal Variants in CHRNA1 and CHRNB1 Genes for Anti-acetylcholine Receptor Antibody Positive Myasthenia Gravis: Evidence from Bayesian Fine-Mapping and Genetic Association Study. *Mol Neurobiol*.

- Eylül 2025;62(9):11286-96.
14. Demontis D, Rajagopal VM, Thorgeirsson TE, Als TD, Grove J, Leppälä K, vd. Genome-wide association study implicates CHRNA2 in cannabis use disorder. *Nat Neurosci*. Temmuz 2019;22(7):1066-74.
 15. Barrie ES, Hartmann K, Lee SH, Frater JT, Seweryn M, Wang D, vd. The CHRNA5/CHRNA3/CHRNA4 Nicotinic Receptor Regulome: Genomic Architecture, Regulatory Variants, and Clinical Associations: HUMAN MUTATION. *Human Mutation*. Ocak 2017;38(1):112-9.
 16. Levin ED, McClernon FJ, Rezvani AH. Nicotinic effects on cognitive function: behavioral characterization, pharmacological specification, and anatomic localization. *Psychopharmacology*. 184:523.
 17. Bierut LJ, Stitzel JA, Wang JC, Hinrichs AL, Grucza RA, Xuei X, vd. Variants in Nicotinic Receptors and Risk for Nicotine Dependence. *AJP*. Eylül 2008;165(9):1163-71.
 18. Hajj Heydari Y, Castro EM, Lotfipour S, Leslie FM. Unraveling the Role of CHRNA6, the Neuronal $\alpha 6$ Nicotinic Acetylcholine Receptor Subunit. *Receptors*. 14 Ocak 2025;4(1):1.
 19. Lee CH, Hung SY. Physiologic Functions and Therapeutic Applications of $\alpha 7$ Nicotinic Acetylcholine Receptor in Brain Disorders. *Pharmaceutics*. 22 Aralık 2022;15(1):31.
 20. Elgoyhen AB, Katz E, Fuchs PA. The nicotinic receptor of cochlear hair cells: A possible pharmacotherapeutic target? *Biochemical Pharmacology*. Ekim 2009;78(7):712-9.
 21. Lipovsek M, Marcovich I, Elgoyhen AB. The Hair Cell $\alpha 9 \alpha 10$ Nicotinic Acetylcholine Receptor: Odd Cousin in an Old Family. *Front Cell Neurosci*. 15 Kasım 2021;15:785265.
 22. Guillem K, Bloem B, Poorthuis RB, Loos M, Smit AB, Maskos U, vd. Nicotinic Acetylcholine Receptor $\beta 2$ Subunits in the Medial Prefrontal Cortex Control Attention. *Science*. 12 Ağustos 2011;333(6044):888-91.
 23. Hoft NR, Corley RP, McQueen MB, Schlaepfer IR, Huizinga D, Ehringer MA. Genetic Association of the CHRNA6 and CHRNA3 Genes with Tobacco Dependence in a Nationally Representative Sample. *Neuropsychopharmacol*. Şubat 2009;34(3):698-706.
 24. Husson M, Harrington L, Tochon L, Cho Y, Ibañez-Tallon I, Maskos U, vd. $\beta 4$ -Nicotinic Receptors Are Critically Involved in Reward-Related Behaviors and Self-Regulation of Nicotine Reinforcement. *J Neurosci*. 22 Nisan 2020;40(17):3465-77.
 25. Herman M, Tarran R. E-cigarettes, nicotine, the lung and the brain: multi-level cascading pathophysiology. *The Journal of Physiology*. Kasım 2020;598(22):5063-71.
 26. Li HJ, Sun ZL, Pan YB, Xu MH, Feng DF. Effect of $\alpha 7$ nAChR on learning and memory dysfunction in a rat model of diffuse axonal injury. *Experimental Cell Research*. Ekim 2019;383(2):111546.
 27. Gordon L, Levkowitz G. Through the Open Window: How Does the Brain Talk to the Body? *Front Young Minds*. 24 Şubat 2021;9:534184.
 28. Cole RD, Poole RL, Guzman DM, Gould TJ, Parikh V. Contributions of $\beta 2$ subunit-containing nAChRs to chronic nicotine-induced alterations in cognitive flexibility in mice. *Psychopharmacology*. 01 Nisan 2015;232(7):1207-17.
 29. Rose JE. Multiple brain pathways and receptors underlying tobacco addiction. *Biochemical Pharmacology*. Ekim 2007;74(8):1263-70.
 30. Chellian R, Behnood-Rod A, Bruijnzeel DM, Wilson R, Pandey V, Bruijnzeel AW. Rodent models for nicotine withdrawal. *J Psychopharmacol*. Ekim 2021;35(10):1169-87.
 31. Mihailescu S, Drucker-Colin R. Nicotine, brain nicotinic receptors, and neuropsychiatric disorders. *Archives of medical research*. Nisan 2000;31:131.
 32. Albuquerque EX, Pereira EF, Castro NG, Alkondon M, Reinhardt S, Schröder H, vd. Nicotinic receptor function in the mammalian central nervous system. *Annals of the New York Academy of Sciences*. 757:48.
 33. Sheffler ZM, Reddy V, Pillarisetty LS. Physiology, Neurotransmitters. İçinde: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 [a.yer 13 Eylül 2025]. Erişim adresi: <http://www.ncbi.nlm.nih.gov/books/NBK539894/>
 34. Nimgampalle M, Chakravarthy H, Sharma S, Shree S, Bhat AR, Pradeepkiran JA, vd. Neurotransmitter systems in the etiology of major neurological disorders: Emerging insights and the-

- rapeutic implications. Ageing Research Reviews. Ağustos 2023;89:101994.
35. Goudet C, Magnaghi V, Landry M, Nagy F, Gereau RW, Pin JP. Metabotropic receptors for glutamate and GABA in pain. Brain Research Reviews. Nisan 2009;60(1):43-56.
 36. D'Souza MS, Markou A. Neuronal mechanisms underlying development of nicotine dependence: implications for novel smoking-cessation treatments. Addiction science & clinical practice. 6:4.
 37. Baranowska U, Wiśniewska RJ. The $\alpha 7$ -nACh nicotinic receptor and its role in memory and selected diseases of the central nervous system. Postępy higieny i medycyny doswiadczalnej (Online). 71:633.
 38. Terry AV, Jones K, Bertrand D. Nicotinic acetylcholine receptors in neurological and psychiatric diseases. Pharmacological Research. Mayıs 2023;191:106764.
 39. Wang Q, Du W, Wang H, Geng P, Sun Y, Zhang J, vd. Nicotine's effect on cognition, a friend or foe? Progress in Neuro-Psychopharmacology and Biological Psychiatry. Haziran 2023;124:110723.
 40. Zarrindast MR, Khakpai F. The modulatory role of nicotine on cognitive and non-cognitive functions. Brain Research. Mayıs 2019;1710:92-101.
 41. Benowitz NL. Cigarette smoking and nicotine addiction. Medical Clinics of North America. 01 Mart 1992;76(2):415-37.
 42. Kutlu MG, Gould TJ. Effects of drugs of abuse on hippocampal plasticity and hippocampus-dependent learning and memory: contributions to development and maintenance of addiction. Learn Mem. Ekim 2016;23(10):515-33.
 43. Simmons SJ, Gould TJ. Involvement of neuronal β_2 subunit-containing nicotinic acetylcholine receptors in nicotine reward and withdrawal: Implications for pharmacotherapies. J Clin Pharm Ther. Ekim 2014;39(5):457-67.
 44. Gozen O, Aypar B, Ozturk Bintepe M, Tuzcu F, Balkan B, Koylu EO, vd. Chronic Nicotine Consumption and Withdrawal Regulate Melanocortin Receptor, CRF, and CRF Receptor mRNA Levels in the Rat Brain. Brain Sciences. 09 Ocak 2024;14(1):63.
 45. Dandekar MP, Nakhate KT, Kokare DM, Subhedar NK. Effect of nicotine on feeding and body weight in rats: Involvement of cocaine- and amphetamine-regulated transcript peptide. Behav Brain Res. 16 Mayıs 2011;219(1):31-8.
 46. Brynildsen JK, Najar J, Hsu LM, Vaupel DB, Lu H, Ross TJ, vd. A novel method to induce nicotine dependence by intermittent drug delivery using osmotic minipumps. Pharmacology Biochemistry and Behavior. Mart 2016;142:79-84.
 47. Ashare RL, Falcone M, Lerman C. Cognitive function during nicotine withdrawal: Implications for nicotine dependence treatment. Neuropharmacology. Ocak 2014;76:581-91.
 48. Morris, R. (1981). *Spatial localization does not require the presence of local cues*. Learning and Motivation, 12(2), 239–260.
 49. Nesil T, Kanit L, Pogun S. Nicotine intake and problem solving strategies are modified during a cognitively demanding water maze task in rats. Pharmacology Biochemistry and Behavior. Kasım 2015;138:156-63.
 50. Barrett RM, Wood MA. Beyond transcription factors: The role of chromatin modifying enzymes in regulating transcription required for memory. Learn Mem. Temmuz 2008;15(7):460-7.
 51. Li Y, Li X, Fu Y, Mou W, Chen Z, Wu P, vd. Nicotine Improves Working Memory via Augmenting BDNF Levels Through $\alpha 7$ nAChR: Evidence from Clinical and Preclinical Studies. Nicotine and Tobacco Research. 15 Mart 2025;ntaf060.
 52. Kenney JW, Gould TJ. Modulation of Hippocampus-Dependent Learning and Synaptic Plasticity by Nicotine. Mol Neurobiol. Ağustos 2008;38(1):101-21.
 53. Leslie JH, Nedivi E. Activity-regulated genes as mediators of neural circuit plasticity. Progress in Neurobiology. Ağustos 2011;94(3):223-37.
 54. Hritcu L, Ciobica A, Gorgan L. Nicotine-induced memory impairment by increasing brain oxidative stress. Open Life Sciences. 01 Eylül 2009;4(3):335-42.
 55. Yamada K, Nabeshima T. Brain-derived neurotrophic factor/TrkB signaling in memory processes. J Pharmacol Sci. 2003;91(4):267–70. doi:10.1254/jphs.91.267.

56. Huang Z, Chang R, Peng J, Chen Y, Liao H, Zhao S, et al. Chronic nicotine up-regulates hippocampal BDNF-TrkB signaling pathway and ANA-12 inhibits nicotine conditioned place preference in mice. *Asian J Psychiatr.* 2022;71:103084. doi:10.1016/j.ajp.2022.10308
57. Gardoni F, Caputi A, Cimino M, Pastorino L, Cattabeni F, Di Luca M. Calcium/calmodulin-dependent protein kinase II is associated with NR2A/B subunits of NMDA receptor in postsynaptic densities. *J Neurochem.* 1998;71(4):1733–41. doi:10.1046/j.1471-4159.1998.71041733.x.
58. Strack S, McNeill RB, Colbran RJ. Mechanism and regulation of calcium/calmodulin-dependent protein kinase II targeting to the NR2B subunit of the N-methyl-D-aspartate receptor. *J Biol Chem.* 2000;275(16):11807–13. doi:10.1074/jbc.275.16.11807.
59. Colbran RJ. Targeting of calcium/calmodulin-dependent protein kinase II. *Biochem J.* 2004;378(Pt 1):1–16. doi:10.1042/BJ20031547.