DENEYSEL ALZHEİMER HASTALIĞI MODELLERİ

BÖLÜM 1

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Giriş

Demansın en yaygın şekli olarak da bilinen Alzheimer hastalığı, dünya çapında yaklaşık 50 milyon kişiyi etkiyen ilerleyici, nörodejeneratif bir hastalıktır. Yıllar içinde Alzheimer hastalığı için çeşitli tedaviler geliştirilmiş olsa da bu hastalık için mevcut iyileştirici tedaviler henüz bulunamamış, sadece semptomlar hafifletilmiştir. Alzheimer hastalığı, çok sayıda biyolojik yolu etkileyen, çeşitli etiyolojik faktörlere atfedilebilen karmaşık bir durumdur. Deneysel modeller hastalığın patogenezini daha iyi anlayabilmek ve klinik öncesi yeni tedavileri test edebilmek için önemlidir. Alzheimer hastalığının karmaşıklığını tamamen kapsayan bir araştırma modeli geliştirmek zor olsa da çeşitli yönleriyle ilgili bilgi edinmek için birçok model geliştirilmiştir.

Alzheimer hastalığının deneysel hayvan modelleri, hem transgenik hayvanları hem de doğal, transgenik olmayan Alzheimer hastalığı modellerini içerir. Tüm bu modeller, Alzheimer hastalığı patolojisinin altında yatan temel mekanizmaların araştırılması ve ayrıca bu hastalığa karşı hedeflenen yeni tedavilerin test edilmesi için değerlidir.

Her bir modelin belirli sınırlamaları olsa da araştırmacılar uygun deneysel modelli kullanarak, Alzheimer hastalığı hakkında önemli bilgilere ulaşabilirler. Bu bölümde, güncel modellerin nasıl kullanılacağına ve bu modellerin insan hastalıklarıyla benzerlik ve farklılıklarına odaklanılarak, mevcut deneysel Alzheimer hastalığı modelleri özetlenmektedir.

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delleri için ek bilgi sağlayarak hücre dışı ortamların doğru ve tekrarlanabilir kontrolünü sağlar. Tüm bu modeller, AH'nin patofizyolojisini araştırmak ve potansiyel tedavileri değerlendirmek için uygundur. Her model belirli avantajlar ve belirli sınırlamalar sunar. Deneysel bir modelin seçilmesi, hem araştırma hedeflerine hem de çalışmanın temel amaçlarına bağlıdır.

Bir bütün olarak, bu bölümde tartışılan deneysel AH modelleri AH'yi anlamamıza katkıda bulunmuştur. Bununla birlikte, bu modellerin hiçbiri, AH alt tiplerinin büyük çoğunluğunda hastalık ilerlemesinin tüm yönlerini yeniden üretemez. Bu nedenle, mevcut modeller, insan AH'sinin karmaşık koşullarını tam olarak çoğaltmak için ek modifikasyonlar gerektirir. Kuşkusuz, deneysel modeller gelecekteki AH araştırmalarında hayati bir rol oynamaya devam edecektir.

Kaynaklar

1. Mucke L. 2009. Alzheimer's disease. *Nature* 461:895-7
2. Small DH, Cappai R. 2006. Alois Alzheimer and Alzheimer's disease: a centennial perspective. *Journal of neurochemistry* 99:708-10
3. Drummond E, Wisniewski T. 2017. Alzheimer's disease: experimental models and reality. *Acta neuropathologica* 133:155-75
4. Nelson PT, Alafuzoff I, Bigio EH, Bouras C, Braak H, et al. 2012. Correlation of Alzheimer disease neuropathologic changes with cognitive status: a review of the literature. *Journal of Neuropathology & Experimental Neurology* 71:362-81
5. Li X, Bao X, Wang R. 2016. Experimental models of Alzheimer's disease for deciphering the pathogenesis and therapeutic screening. *International journal of molecular medicine* 37:271-83
6. Glenner G, Wong C. 1988. Alzheimer's disease: initial report of the purification and characterization of a novel cerebrovascular amyloid protein. *Alzheimer Disease & Associated Disorders* 2:134
7. Schindowski K, Bretteville A, Leroy K, Bégard S, Brion J-P, et al. 2006. Alzheimer's disease-like tau neuropathology leads to memory deficits and loss of functional synapses in a novel mutated tau transgenic mouse without any motor deficits. *The American journal of pathology* 169:599-616
8. Gonzalo-Ruiz A, Gonzalez I, Sanz-Anquela J. 2003. Effects of β-amyloid protein on serotoninergic, noradrenergic, and cholinergic markers in neurons of the pontomesencephalic tegmentum in the rat. *Journal of chemical neuroanatomy* 26:153-69
9. Moghul S, Wilkinson D. 2001. Use of acetylcholinesterase inhibitors in Alzheimer's disease. *Expert Review of Neurotherapeutics* 1:61-9
10. Cacace R, Sleegers K, Van Broeckhoven C. 2016. Molecular genetics of early-onset Alzheimer's disease revisited. *Alzheimer's & dementia* 12:733-48
11. Bertram L, Tanzi RE. 2012. The genetics of Alzheimer's disease. *Progress in molecular biology and translational science* 107:79-100
12. Cuyvers E, Sleegers K. 2016. Genetic variations underlying Alzheimer's disease: evidence from genome-wide association studies and beyond. *The Lancet Neurology* 15:857-68

13. Shinohara M, Fujioka S, Murray ME, Wojtas A, Baker M, et al. 2014. Regional distribution of synaptic markers and APP correlate with distinct clinicopathological features in sporadic and familial Alzheimer's disease. *Brain* 137:1533-49
14. Borenstein AR, Copenhaver CI, Mortimer JA. 2006. Early-life risk factors for Alzheimer disease. *Alzheimer Disease & Associated Disorders* 20:63-72
15. Knopman DS, Jack Jr CR, Lundt ES, Weigand SD, Vemuri P, et al. 2016. Evolution of neurodegeneration-imaging biomarkers from clinically normal to dementia in the Alzheimer disease spectrum. *Neurobiology of aging* 46:32-42
16. Elder GA, Gama Sosa MA, De Gasperi R. 2010. Transgenic mouse models of Alzheimer's disease. *Mount Sinai Journal of Medicine: A Journal of Translational and Personalized Medicine: A Journal of Translational and Personalized Medicine* 77:69-81
17. Games D, Adams D, Alessandrini R, Barbour R, Borthelette P, et al. 1995. Alzheimer-type neuropathology in transgenic mice overexpressing V717F β-amyloid precursor protein. *Nature* 373:523-7
18. Hsiao K, Chapman P, Nilsen S, Eckman C, Harigaya Y, et al. 1996. Correlative memory deficits, Aβ elevation, and amyloid plaques in transgenic mice. *Science* 274:99-103
19. STURCHLER-PIERRAT C, Staufenbiel M. 2000. Pathogenic mechanisms of Alzheimer's disease analyzed in the APP23 transgenic mouse model. *Annals of the New York Academy of Sciences* 920:134-9
20. Radde R, Bolmont T, Kaeser SA, Coomaraswamy J, Lindau D, et al. 2006. Aβ42-driven cerebral amyloidosis in transgenic mice reveals early and robust pathology. *EMBO reports* 7:940-6
21. Holcomb L, Gordon MN, McGowan E, Yu X, Benkovic S, et al. 1998. Accelerated Alzheimer-type phenotype in transgenic mice carrying both mutant amyloid precursor protein and presenilin 1 transgenes. *Nature medicine* 4:97-100
22. Oakley H, Cole SL, Logan S, Maus E, Shao P, et al. 2006. Intraneuronal β-amyloid aggregates, neurodegeneration, and neuron loss in transgenic mice with five familial Alzheimer's disease mutations: potential factors in amyloid plaque formation. *Journal of Neuroscience* 26:10129-40
23. Lewis J, Dickson DW, Lin W-L, Chisholm L, Corral A, et al. 2001. Enhanced neurofibrillary degeneration in transgenic mice expressing mutant tau and APP. *Science* 293:1487-91
24. Götz J, Probst A, Spillantini MG, Schäfer T, Jakes R, et al. 1995. Somatodendritic localization and hyperphosphorylation of tau protein in transgenic mice expressing the longest human brain tau isoform. *The EMBO journal* 14:1304-13
25. Allen B, Ingram E, Takao M, Smith MJ, Jakes R, et al. 2002. Abundant tau filaments and nonapoptotic neurodegeneration in transgenic mice expressing human P301S tau protein. *Journal of Neuroscience* 22:9340-51
26. Bolmont T, Clavaguera F, Meyer-Luehmann M, Herzig MC, Radde R, et al. 2007. Induction of tau pathology by intracerebral infusion of amyloid-β-containing brain extract and by amyloid-β deposition in APP× Tau transgenic mice. *The American journal of pathology* 171:2012-20
27. Grueninger F, Bohrmann B, Czech C, Ballard TM, Frey JR, et al. 2010. Phosphorylation of Tau at S422 is enhanced by Aβ in TauPS2APP triple transgenic mice. *Neurobiology of Disease* 37:294-306
28. Fryer JD, Simmons K, Parsadanian M, Bales KR, Paul SM, et al. 2005. Human apolipoprotein E4 alters the amyloid-β 40: 42 ratio and promotes the formation of cerebral amyloid angiopathy in an amyloid precursor protein transgenic model. *Journal of Neuroscience* 25:2803-10
29. Oddo S, Caccamo A, Shepherd JD, Murphy MP, Golde TE, et al. 2003. Triple-transgenic model of Alzheimer's disease with plaques and tangles: intracellular Aβ and synaptic dysfunction. *Neuron* 39:409-21

30. Janelsins MC, Mastrangelo MA, Oddo S, LaFerla FM, Federoff HJ, Bowers WJ. 2005. Early correlation of microglial activation with enhanced tumor necrosis factor-alpha and monocyte chemoattractant protein-1 expression specifically within the entorhinal cortex of triple transgenic Alzheimer's disease mice. *Journal of neuroinflammation* 2:1-12
31. Saito T, Matsuba Y, Mihira N, Takano J, Nilsson P, et al. 2014. Single App knock-in mouse models of Alzheimer's disease. *Nature neuroscience* 17:661-3
32. Do Carmo S, Cuello AC. 2013. Modeling Alzheimer's disease in transgenic rats. *Molecular neurodegeneration* 8:1-11
33. Cohen RM, Rezai-Zadeh K, Weitz TM, Rentsendorj A, Gate D, et al. 2013. A transgenic Alzheimer rat with plaques, tau pathology, behavioral impairment, oligomeric aβ, and frank neuronal loss. *Journal of Neuroscience* 33:6245-56
34. Leon WC, Canneva F, Partridge V, Allard S, Ferretti MT, et al. 2010. A novel transgenic rat model with a full Alzheimer's-like amyloid pathology displays pre-plaque intracellular amyloid-β-associated cognitive impairment. *Journal of Alzheimer's Disease* 20:113-26
35. Braidy N, Poljak A, Jayasena T, Mansour H, Inestrosa NC, Sachdev PS. 2015. Accelerating Alzheimer's research through 'natural'animal models. *Current opinion in psychiatry* 28:155-64
36. Camus S, Ko WKD, Pioli E, Bezard E. 2015. Why bother using non-human primate models of cognitive disorders in translational research? *Neurobiology of learning and memory* 124:123-9
37. Gearing M, Tigges J, Mori H, Mirra S. 1997. β-Amyloid (Aβ) deposition in the brains of aged orangutans. *Neurobiology of aging* 18:139-46
38. Rosen RF, Farberg AS, Gearing M, Dooyema J, M. Long P, et al. 2008. Tauopathy with paired helical filaments in an aged chimpanzee. *Journal of Comparative Neurology* 509:259-70
39. Perez SE, Raghanti MA, Hof PR, Kramer L, Ikonomovic MD, et al. 2013. Alzheimer's disease pathology in the neocortex and hippocampus of the western lowland gorilla (Gorilla gorilla gorilla). *Journal of Comparative Neurology* 521:4318-38
40. Schütt T, Helboe L, Pedersen LØ, Waldemar G, Berendt M, Pedersen JT. 2016. Dogs with cognitive dysfunction as a spontaneous model for early Alzheimer's disease: a translational study of neuropathological and inflammatory markers. *Journal of Alzheimer's Disease* 52:433-49
41. Smolek T, Madari A, Farbakova J, Kandrac O, Jadhav S, et al. 2016. Tau hyperphosphorylation in synaptosomes and neuroinflammation are associated with canine cognitive impairment. *Journal of Comparative Neurology* 524:874-95
42. Davis PR, Head E. 2014. Prevention approaches in a preclinical canine model of Alzheimer's disease: benefits and challenges. *Frontiers in pharmacology* 5:47
43. Bao S, Zheng H, Chen C, Zhang Y, Bao L, et al. 2021. Nfe2l1 deficiency mitigates streptozotocin-induced pancreatic β-cell destruction and development of diabetes in male mice. *Food and Chemical Toxicology* 158:112633
44. Voronkov D, Stavrovskaya A, Stelmashook E, Genrikhs E, Isaev N. 2019. Neurodegenerative Changes in Rat Brain in Streptozotocin Model of Alzheimer's Disease. *Bulletin of Experimental Biology & Medicine* 166
45. Kamat PK. 2015. Streptozotocin induced Alzheimer's disease like changes and the underlying neural degeneration and regeneration mechanism. *Neural regeneration research* 10:1050
46. Gao C, Liu Y, Jiang Y, Ding J, Li L. 2014. Geniposide Ameliorates Learning Memory Deficits, Reduces Tau Phosphorylation and Decreases Apoptosis via GSK 3β Pathway in Streptozotocin-Induced A lzheimer Rat Model. *Brain pathology* 24:261-9
47. Kamat PK, Rai S, Swarnkar S, Shukla R, Nath C. 2014. Mechanism of synapse redox stress in okadaic acid (ICV) induced memory impairment: role of NMDA receptor. *Neurochemistry international* 76:32-41

48. Paxinos G, Watson C. 2006. *The rat brain in stereotaxic coordinates: hard cover edition*. Elsevier
49. Moreira-Silva D, Carrettiero DC, Oliveira AS, Rodrigues S, dos Santos-Lopes J, et al. 2018. Anandamide effects in a streptozotocin-induced Alzheimer's disease-like sporadic dementia in rats. *Frontiers in neuroscience* 12:653
50. Hacımüftüoğlu A, Okkay U, Sağsöz M, Taşpınar M. 2021. DENEYSEL ALZHEİMER MODELİNDE HİPOKAMPÜSTE GLUTAMAT GERİ ALINIM PARAMETRELERİNİN DEĞERLENDİRİLMESİ.
51. Woods SC, Seeley RJ, Rushing PA, D'Alessio D, Tso P. 2003. A controlled high-fat diet induces an obese syndrome in rats. *The Journal of nutrition* 133:1081-7
52. Demetrius LA, Driver J. 2013. Alzheimer's as a metabolic disease. *Biogerontology* 14:641-9
53. Herculano B, Tamura M, Ohba A, Shimatani M, Kutsuna N, Hisatsune T. 2013. β-alanyl-L-histidine rescues cognitive deficits caused by feeding a high fat diet in a transgenic mouse model of Alzheimer's disease. *Journal of Alzheimer's Disease* 33:983-97
54. Haley RW, Dietschy JM. 2000. Is there a connection between the concentration of cholesterol circulating in plasma and the rate of neuritic plaque formation in Alzheimer disease? *Archives of neurology* 57:1410-2
55. Wood WG, Eckert GP, Igbavboa U, Müller WE. 2003. Amyloid beta-protein interactions with membranes and cholesterol: causes or casualties of Alzheimer's disease. *Biochimica et Biophysica Acta (BBA)-Biomembranes* 1610:281-90
56. Wu Y-Y, Wang X, Tan L, Liu D, Liu X-H, et al. 2013. Lithium attenuates scopolamine-induced memory deficits with inhibition of GSK-3β and preservation of postsynaptic components. *Journal of Alzheimer's Disease* 37:515-27
57. Vandal M, White PJ, Tremblay C, St-Amour I, Chevrier G, et al. 2014. Insulin reverses the high-fat diet–induced increase in brain Aβ and improves memory in an animal model of Alzheimer disease. *Diabetes* 63:4291-301
58. Pinton S, Brüning CA, Oliveira CES, Prigol M, Nogueira CW. 2013. Therapeutic effect of organoselenium dietary supplementation in a sporadic dementia of Alzheimer's type model in rats. *The Journal of nutritional biochemistry* 24:311-7
59. Nakamura S, Murayama N, Noshita T, Annoura H, Ohno T. 2001. Progressive brain dysfunction following intracerebroventricular infusion of beta1–42-amyloid peptide. *Brain research* 912:128-36
60. Winslow J, Camacho F. 1995. Cholinergic modulation of a decrement in social investigation following repeated contacts between mice. *Psychopharmacology* 121:164-72
61. Sain H, Sharma B, Jaggi A, Singh N. 2011. Pharmacological investigations on potential of peroxisome proliferator-activated receptor-gamma agonists in hyperhomocysteinemia-induced vascular dementia in rats. *Neuroscience* 192:322-33
62. Kamat PK, Rai S, Nath C. 2013. Okadaic acid induced neurotoxicity: an emerging tool to study Alzheimer's disease pathology. *Neurotoxicology* 37:163-72
63. Zhang J, Li P, Wang Y, Liu J, Zhang Z, et al. 2013. Ameliorative effects of a combination of baicalin, jasminoidin and cholic acid on ibotenic acid-induced dementia model in rats. *PLoS One* 8:e56658
64. Bonda DJ, Lee H-g, Blair JA, Zhu X, Perry G, Smith MA. 2011. Role of metal dyshomeostasis in Alzheimer's disease. *Metallomics* 3:267-70
65. Squire LR, Zola-Morgan S. 1988. Memory: brain systems and behavior. *Trends in neurosciences* 11:170-5
66. Liu J, Zhang Z, Li J-T, Zhu Y-H, Zhou H-L, et al. 2009. Effects of NT-4 gene modified fibroblasts transplanted into AD rats. *Neuroscience letters* 466:1-5
67. Savage LM, Sweet AJ, Castillo R, Langlais PJ. 1997. The effects of lesions to thalamic lateral internal medullary lamina and posterior nuclei on learning, memory and habituation in the rat. *Behavioural brain research* 82:133-47

68. V Colom L, T Castaneda M, Hernandez S, Perry G, Jaime S, Touhami A. 2011. Intrahippocampal amyloid-β (1-40) injections injure medial septal neurons in rats. *Current Alzheimer Research* 8:832-40
69. Sadigh-Eteghad S, Sabermarouf B, Majdi A, Talebi M, Farhoudi M, Mahmoudi J. 2015. Amyloid-beta: a crucial factor in Alzheimer's disease. *Medical principles and practice* 24:1-10
70. McLarnon JG, Ryu JK. 2008. Relevance of abeta1-42 intrahippocampal injection as an animal model of inflamed Alzheimer's disease brain. *Curr Alzheimer Res* 5:475-80
71. Yankner BA, Duffy LK, Kirschner DA. 1990. Neurotrophic and neurotoxic effects of amyloid beta protein: reversal by tachykinin neuropeptides. *Science* 250:279-82
72. Avaliani N, Sørensen AT, Ledri M, Bengzon J, Koch P, et al. 2014. Optogenetics reveal delayed afferent synaptogenesis on grafted human-induced pluripotent stem cell-derived neural progenitors. *Stem Cells* 32:3088-98
73. Green K, Smith I, Laferla F. 2007. Role of calcium in the pathogenesis of Alzheimer's disease and transgenic models. *Calcium Signalling and Disease*:507-21
74. Akhter R, Sanphui P, Biswas SC. 2014. The essential role of p53-up-regulated modulator of apoptosis (Puma) and its regulation by FoxO3a transcription factor in β-amyloid-induced neuron death. *Journal of Biological Chemistry* 289:10812-22
75. Nepovimova E, Uliassi E, Korabecny J, Pena-Altamira LE, Samez S, et al. 2014. Multitarget drug design strategy: quinone–tacrine hybrids designed to block amyloid-β aggregation and to exert anticholinesterase and antioxidant effects. *Journal of medicinal chemistry* 57:8576-89
76. Gong C-X, Lidsky T, Wegiel J, Grundke-Iqbal I, Iqbal K. 2001. Metabolically active rat brain slices as a model to study the regulation of protein phosphorylation in mammalian brain. *Brain research protocols* 6:134-40
77. Jang J, Yoo J-E, Lee J-A, Lee DR, Kim JY, et al. 2012. Disease-specific induced pluripotent stem cells: a platform for human disease modeling and drug discovery. *Experimental & molecular medicine* 44:202-13
78. Takahashi K, Okita K, Nakagawa M, Yamanaka S. 2007. Induction of pluripotent stem cells from fibroblast cultures. *Nature protocols* 2:3081-9
79. Yagi T, Ito D, Okada Y, Akamatsu W, Nihei Y, et al. 2011. Modeling familial Alzheimer's disease with induced pluripotent stem cells. *Human molecular genetics* 20:4530-9
80. Israel MA, Yuan SH, Bardy C, Reyna SM, Mu Y, et al. 2012. Probing sporadic and familial Alzheimer's disease using induced pluripotent stem cells. *Nature* 482:216-20
81. Macias MP, Gonzales AM, Siniard AL, Walker AW, Corneveaux JJ, et al. 2014. A cellular model of amyloid precursor protein processing and amyloid-β peptide production. *Journal of neuroscience methods* 223:114-22
82. Meng P, Yoshida H, Tanji K, Matsumiya T, Xing F, et al. 2015. Carnosic acid attenuates apoptosis induced by amyloid-β 1–42 or 1–43 in SH-SY5Y human neuroblastoma cells. *Neuroscience Research* 94:1-9
83. Raja WK, Mungenast AE, Lin Y-T, Ko T, Abdurrob F, et al. 2016. Self-organizing 3D human neural tissue derived from induced pluripotent stem cells recapitulate Alzheimer's disease phenotypes. *PLoS One* 11:e0161969
84. Paquet D, Bhat R, Sydow A, Mandelkow E-M, Berg S, et al. 2009. A zebrafish model of tauopathy allows in vivo imaging of neuronal cell death and drug evaluation. *The Journal of clinical investigation* 119:1382-95