DEHB'DA TRANSGENETİK HAYVAN MODELLERİNE BİR BAKIŞ

28 BÖLÜM

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GİRİŞ

Dikkat Eksikliği ve Hiperaktivite Bozukluğu (DEHB), çocukluk çağında bulgu veren, kişinin gelişimsel düzeyiyle uyumlu olmayan, toplum, okul veya işle ilgili alanları olumsuz etkileyen dikkatsizlik, aşırı hareketlilik ve dürtüsellikle karakterize bir nörogelişimsel bozukluktur (1).

DEHB çocukluk çağında sık görülen psikiyatrik bozukluklarından biri olup, dünya genelindeki prevalansı %8-12 arasında bildirilmiştir (2, 3, 4). Ülkemizde yapılan bir çalışmada ise DEHB prevalansı %13,8 olarak bildirilmiştir (5). DEHB olan çocukların yetişkinlik döneminde yaklaşık %30 ila 50'sinin bozukluk belirtilerini göstermeye devam edebileceği belirtilmiştir (6). DEHB ilerleyen yıllarda kişide kaygı, depresyon, uyuşturucu bağımlılığı, suça karışma, okul başarısızlığı, sosyal ret ve zayıf özgüven gibi birçok olumsuz sonuçlarla sonlanabilir (7, 8). Bu nedenle bu bozukluğun, hasta ve hastanın aile üyeleri için önemli bir yüke neden olabilecek ciddi akademik, finansal ve sosyal etkileri vardır (9).

DEHB belirtileri genellikle farmakolojik tedavi ile tedavi edilir. DEHB için en sık kullanılan ve onaylanan ilaçlar metilfenidat, amfetamin ve atomoksetindir. Alternatif olarak ise Guanfasin, bupropion ve klonidin gibi ilaçlar kullanılmaktadır (10). Metilfenidat DEHB tedavisi gören hastaların yaklaşık %70'inde en çok reçete edilen stimülan ilaçtır (11). Amfetamin ayrıca çocuklarda DEHB semptomlarının tedavisinde etkili olduğu kanıtlanmış bir psikostimülan ilaçtır (12) Ayrıca, bu ilaçların serotonerjik sistemi etkilediğine dair kanıtlar vardır (13-14). Atomoksetin farmakolojik olarak bir norepinefrin geri alım inhibitörü olarak sınıflandırılan stimülan olmayan bir ilaçtır. Psikostimülanlara benzer şekilde, atomoksetin beyindeki hücre dışı norepinefrin ve dopamin düzeylerini de arttırır (15). DEHB ilaçlarının beyin monoamin düzeylerini artırarak etki göstermesi, monoaminerjik nörotransmisyondaki bozuklukların DEHB patofizyolojisinde rol oynadığını açıkça göstermektedir (9). Bu bilgilere rağmen, DEHB'nin kesin nedeni bilinmemektedir. DEHB için hala bilinen herhangi bir objektif biyobelirteç saptanmamıştır. Tanı ağırlıklı olarak Davranışsal ve Ruhsal Bozuklukların Tanısal ve İstatistiksel El Kitabına (DSM) dayanmaktadır (1).

Metilfenidat ve amfetamin, dopamin ve norepinefrin taşıyıcılarının etkisini antagonize ederek, hücre dışı dopamin ve norepinefrin düzeylerini arttırarak çalışır.

Hayvan modelleri tam olarak insan psikiyatrik hastalıklarını yansıtmasa da hastalıklar

Kısaltmalar

DEHB	Dikkat Eksikliği ve Hiperaktivite Bozukluğu
DSM	Davranışsal ve Ruhsal Bozuklukların Tanısal ve İstatistiksel El Kitabına
DA	Dopamin
DAT	Dopamine Transporter
DAT-1	Dopamin Transporter -1
NE	Norepinefrin
DBH	Dopamin beta hidroksilaz enzimİ
MPH	Metilfenidat
AMPH	Amfetamin
5-HTT	Seratonin transporter enzimi
SNAP-25	25 kDa'lık sinaptozomal ilişkili protein
WW-25	Sinaptozomal- ilişkili protein -25 KDA
SHR	Spontan hipertansif sıçan
PFK	Prefrontal korteks
NHE	Yüksek Uyarılabilen Napoli sıçanı
DAT-KO	DAT knock out faresi
5-CSRT	5 Seçim seri reaksiyon süresi
NK1R	Nörokininin1 reseptörü
Tacr1	Taşikinin 1reseptörü
6-OHDA	6-hidroksidopamin
WKY	Wistar-Kyoto suşu
SNARE	Çözünür N-Etilmaleimide duyarlı faktör bağlanma protein reseptörü
LTP	Long-Term-Potentiation
LTD	Long-Term-Depression
NK1R-KO-faresi	Nörokininin1 reseptörü (NK1R) veya Tacr1 (taşikinin1reseptörü) geninin fonksiyonel ablasyonu olan fareler.
TACR1-Geni	Taşikinin reseptor 1 geni
TRβPV	Mutant insan tiroid hormonu reseptörü beta geni
TRβPV-KI	TRβPV knockin faresi
T3	Triiyodotironin
T4	Tiroksin
RTH	Dirençli tiroid hormonu

Anahtar Kelimeler: DEHB, Hayvan Modelleri, Transgenetik, Genetik modeller, Hiperaktivite, İmpulsivite, Dikkat, Psikostimülanlar, Metilfenidat, Atomoksetin

KAYNAKLAR

1. American Psychiatric Association, Diagnostic and statistical manual of mental disorders. 5th edn. 2013, Washington, DC.
2. Faraone SV, Sergeant J, Gillberg C, Biederman J The worldwide prevalence of ADHD: Is it an American condition? World Psychiatry. 2003; 2:104–113.
3. Biederman J and Faraone SV, Attention deficit hyperactivity disorder. Lancet 2005; 366:237-248.
4. Polanczyk G, Rohde LA, Epidemiology of attention deficit/hyperactivity disorder across the lifespan. Curr Opin Psychiatry 2007; 20: 386-392.
5. Ercan ES, Kandulu R, Uslu E ve ark. Prevalance and diagnostic stability of ADHD and ODD in Turkish children: A 4-year longitudinal study. Child Adolesc Psychiatry Ment Health. Aug 2013; 7: 7(1):30.
6. Kooij SJ, Bejerot S, Blackwell A, Caci H, Casas-Brugue M, Carpentier PJ, Edvinsson D, Fayyad J et al, European consensus statement on diagnosis and treatment of adultADHD: the European Network Adult ADHD. BMC Psychiatry 2010; 10:67.
7. Barkley RA, Behavioral inhibition, sustained attention, and executive functions:constructing a unifying theory of ADHD. Psychol Bull 1997; 121:65–94
8. Biederman J, Attention-deficit/hyperactivity disorder: a selective overview. BiolPsychiatry 2005; 57(11):1215–1220.
9. De la Peña, J. B., dela Peña, I. J., Custodio, R. J., Botanas, C. J., Kim, H. J., & Cheong, J. H. Exploring the Validity of Proposed Transgenic Animal Models of Attention-Deficit Hyperactivity Disorder (ADHD). Molecular Neurobiology. 2017.doi:10.1007/s12035-017-0608-1
10. Wigal SB, Efficacy and safety limitations of attentiondeficit hyperactivity disorderpharmacotherapy in children and adults. CNS Drugs, 2009; 23(Suppl 1):21–31.
11. Kuczenski R, Segal DS, Locomotor effects of acute and repeated threshold doses of amphetamine and methylphenidate: relative roles of dopamine and norepinephrine. J Pharmacol Exp Ther, 2001; 296(3):876–883
12. A 14-Month Randomized Clinical Trial of Treatment Strategies for Attention-Deficit/Hyperactivity Disorder, *Archives of General Psychiatry, 56(12), 1073.* doi:10.1001/archpsyc.1999; 56.12.1073
13. Gainetdinov RR, Wetsel WC, Jones SR, Levin ED, Jaber M, Caron MG, Role of serotonin in the paradoxical calming effect of psychostimulants on hyperacti-

vity. Science 1999; 283(5400): 397–401
14. Oades RD, Dopamine-serotonin interactions in attention deficit hyperactivity disorder (ADHD). Prog Brain Res 2008; 172:543– 565.
15. Bymaster FP, Katner JS, Nelson DL, Hemrick-Luecke SK, Threlkeld PG, Heiligenstein JH, Morin SM, Gehlert DR et al, Atomoxetine increases extracellular levels of norepinephrine and dopamine in prefrontal cortex of rat: a potential mechanism for efficacy in attention deficit/hyperactivity disorder. Neuropsychopharmacology 2002; 27(5):699–711
16. Bari A and Robbins TW, Animal Models of ADHD, Hagan, J. J. (Ed.) Molecular and Functional Models in Neuropsychiatry. Current Topics in Behavioral Neurosciences, 2011; 151-173.
17. Faraone SV, Perlis RH, Doyle AE, Smoller JW, Goralnick JJ, Holmgren MA, Sklar P (2005) Molecular genetics of attention-deficit/hyperactivity disorder. Biol Psychiatry2005; 57:1313–1323
18. Thapar A, Langley K, Asherson P and Gill M (2007) Gene-environment interplay in attentiondeficit hyperactivity disorder and the importance of a developmental perspective.Br. J. Psychiatry 2007; 190:1-3.
19. Faraone SV and Khan SA (2006) Candidate gene studies of attention-deficit/hyperactivity disorder. J. Clin. Psychiatry, 2006; 67:13-20.
20. Smalley SL, Genetic influences in childhood-onset psychiatric disorders: Autism and attention-deficit/ hyperactivity disorder. Am. J. Hum. Genet.1997; 60:1276-1282.
21. Faraone SV, Genetics of adult attentiondeficit/hyperactivity disorder. Psychiatr. Clin. North Am. 2004; 27:303-321.
22. Biederman J, Faraone SV, Mick E, Spencer T, Wilens T, Kiely K, Guite J, Ablon JS, Reed E, Warburton R, High risk for attention deficit hyperactivity disorder among children of parents with childhood onset of the disorder: a pilot study. Am J Psychiatry 1995; 152:431–435
23. Mick E, Biederman J, Faraone SV, Sayer J, and Kleinman S, Case-control study of attention-deficit hyperactivity disorder and maternal smoking, alcohol use, and druguse during pregnancy. J. Am. Acad. Child Adolesc. Psychiatry 2002; 41:378-385.
24. Russell VA, Overview of Animal Models of Attention Deficit HyperactivityDisorder (ADHD). Current Protocols in Neuroscience, 2011; 54(1), 9.35.1–9.35.25.
25. Castellanos FX, Giedd JN, Marsh WL, Hamburger SD, Vaituzis AC, Dickstein DP, Sarfatti SE, Vauss YC, Snell JW, Lange N, Kaysen D, Krain AL, Ritchie GF, Rajapakse JC and Rapoport JL, Quantitative brain magnetic resonance imaging in attention-deficit hyperactivity disorder. Arch. Gen. Psychiatry 1996; 53:607-616.
26. Castellanos FX, Lee PP, Sharp W, Jeffries NO, Greenstein DK, Clasen LS, Blumenthal JD, James RS, Ebens CL,Walter JM, Zijdenbos A, Evans AC, Giedd JN, and Rapoport JL, 2002, Developmental trajectories of brain volume abnormalities in children and adolescents with attention-deficit/hyperactivity disorder. JAMA288:1740-1748.
27. Filipek PA, Semrud-Clikeman M, Steingard RJ, Renshaw PF, Kennedy DN, and Biederman J, Volumetric MRI analysis comparing subjects having attention-deficit hyperactivity disorder with normal controls. Neurology 1997; 48:589-601.
28. Hill DE, Yeo RA, Campbell RA, Hart B, Vigil J, and Brooks W, Magnetic resonance imaging correlates of attentiondeficit/ hyperactivity disorder in children. Neuropsychology 2003; 17:496-506.
29. Durston S, Hulshoff Pol HE, Schnack HG, Buitelaar JK, Steenhuis MP, Minderaa RB, Kahn RS and van Engeland H 2004, Magnetic resonance imaging of boys with attention-deficit/hyperactivity disorder and their unaffected siblings. J. Am. Acad. Child Adolesc. Psychiatry 2004; 43:332-340.
30. Valera EM, Faraone SV, Murray KE and Seidman LJ, Meta-analysis of structural imaging findings in attentiondeficit/ hyperactivity disorder. Biol. Psychiatry 2007; 61:1361-1369.
31. Clark L, Blackwell AD, Aron AR, Turner DC, Dowson J, Robbins TW, and Sahakian BJ, Association between response inhibition and working memory in adult ADHD: A link to right frontal cortex pathology? Biol. Psychiatry 2006; 61:1395-1401
32. Faraone SV, Biederman J, Neurobiology of attention-deficit hyperactivity disorder. Biol Psychiatry 1998; 44:951–958
33. Bradley C, The behavior of children receiving benzedrine. Am J Psychiatry 1937; 9:577–585
34. Oades RD, Attention deficit disorder with hyperactivity (ADDH): the contribution of catecholaminergic activity. Prog Neurobiol 1987; 29:365–391
35. Dickstein SG, Bannon K, Xavier CF, and Milham MP, The neural correlates of attention deficit hyperactivity disorder: An ALE meta-analysis. J. Child Psychol. Psychiatry 2006; 47:1051-1062.
36. Moll GH, Heinrich H, Trott G, Wirth S, and Rothenberger A, Deficient intracortical inhibition in drug-naive children with attention deficit hyperactivity disorder is enhanced by methylphenidate. Neurosci. Lett, 2000; 284:121-125
37. Kim BN, Lee JS, Shin MS, Cho SC, and Lee DS, Regional cerebral perfusion abnormalities in attention deficit/hyperactivity disorder: Statistical parametric mapping analysis. Eur. Arch. Psychiatry Clin. Neurosci. 2002; 252:219- 225
38. Bush G, Attention-deficit/hyperactivity disorder and attention networks.Neuropsychopharmacology 2010; 35:278-300.
39. Sagvolden T, Russell VA, Aase H, Johansen EB, Farshbaf M, Rodent models ofattention- deficit/hyperactivity disorder. Biol. Psychiatry 2005a; 57: 1239-1247.
40. Johansen EB, Killeen PR, Russell VA, Tripp G, Wickens JR, Tannock R, Williams J, and Sagvolden T, Origins of altered reinforcement effects in ADHD. Behav. BrainFunct. 2009; 5:7.
41. Russell VA, Sagvolden T and Johansen EB, Animal models of attention-deficithyperactivity disorder. Behav. Brain Funct. 2005; 1:9.
42. Sontag A S, Tucha O, Walitza S, Lange KW, Animal models of attention deficit/hyperactivity disorder, ADHD Atten Def Hyp Disord 2010; 2:1–20
43. Okamoto K, Aoki K, Development of a strain of spon-

taneously hypertensive rats. JpnCirc J, 1963, 27:282–293
44. Sagvolden T, Behavioral validation of the spontaneously hypertensive rat (SHR) as an animal model of attention-deficit/hyperactivity disorder (AD/HD). Neurosci. Biobehav. Rev. 2000; 24:31- 39.
45. Russell VA, The nucleus accumbens motor-limbic interface of the spontaneously hypertensive rat as studied in vitro by the superfusion slice technique. Neurosci Biobehav Rev 2000; 24:133–136.
46. De Villiers AS, Russell VA, Sagvolden T, Searson A, Jaffer A, Taljaard JJ (1995) Alpha 2-adrenoceptor mediated inhibition of [3H] dopamine release from nucleus accumbens slices and monoamine levels in a rat model for attention-deficit hyperactivity disorder. Neurochem Res 20:427–433
47. Sagvolden, T, Johansen EB, Woien G, Walaas SI, Storm-Mathisen J, Bergersen LH, Hvalby O, Jensen V, Aase H, Russell VA, Killeen PR, Dasbanerjee T, Middleton FA and Faraone SV, The spontaneously hypertensive rat model of ADHD—the importance of selecting the appropriate reference strain. Neuropharmacology 2009; 57:619-626.
48. Mill J, Sagvolden T, Asherson P, Sequence analysis of Drd2, Drd4, and Dat1 in SHRand WKY rat strains. Behavioral and Brain Functions, 2005;1: 24
49. Leo D, Sorrentino E, Volpicelli F, Eyman M, Greco D, Viggiano D, Altered midbrain dopaminergic neurotransmission during development in an animal model of ADHD.Neurosci Biobehav Rev, 2003; 27: 661– 669.
50. Bendel P, Eilam R, Quantitation of ventricular size in normal and spontaneously hypertensive rats by magnetic resonance imaging. Brain Res 1992; 574 (1-2): 224 228.
51. Sabbatini M, Strocchi P, Vitaioli L, Amenta F, The hippocampus in spontaneously hypertensive rats: A quantitative microanatomical study. Neuroscience, 2000; 100: 251-258.
52. Mignini F, Vitaioli L, Sabbatini M, Tomassoni D, and Amenta F, The cerebral cortex of spontaneously hypertensive rats: A quantitative microanatomical study. Clin ExpHypertens 2004; 26: 287-303
53. Russell VA. Dopamine hypofunction possibly results from a defect in glutamate-stimulated release of dopamine in the nucleus accumbens shell of a rat model for attention deficit hyperactivity disorder—the spontaneously hypertensive rat, NeurosciBiobehav Rev, 2003; 27: 671– 682.
54. Marcil J, Thibault C, Anand-Srivastava MB. Enhanced expression of Gi-protein precedes the development of blood pressure in spontaneously hypertensive rats. J Mol Cell Cardiol 1997; 29: 1009 –1022.
55. Lehohla M, Kellaway L, Russell V. NMDA receptor function in the prefrontal cortex of a rat model for attention-deficit/hyperactivity disorder. Metab Brain Dis 2004; 19:35– 42.
56. Myers MM, Musty RE, Hendley ED, Attenuation of hyperactivity in the spontaneously hypertensive rat by amphetamine. Behav Neural Biol, 1982; 34 (1):4254
57. Sagvolden T, Johansen EB. Rat models of ADHD. Curr Top Behav Neurosci, 2012; 9: 301-15.
58. Leo D, Gainetdinov RR, Transgenic mouse models for ADHD. Cell Tissue Res 2013; 354(1):259–271.
59. Gainetdinov RR, Caron MG, Genetics of childhood disorders: XXIV. ADHD, part 8: hyperdopaminergic mice as an animal model of ADHD. J Am Acad Child AdolescPsychiatry 2001; 40(3): 380–382
60. Schenk JO, The functioning neuronal transporter for dopamine: kinetic mechanisms and effects of amphetamines, cocaine and methylphenidate. In: Progress in drug research, Springer, 2002; pp 111–131.
61. Gainetdinov RR, Jones SR, Caron MG, Functional hyperdopaminergia in dopamine transporter knock-out mice. Biol Psychiatry 1999; 46(3):303–311
62. Hawi Z, Cummins TD, Tong J, Johnson B, Lau R, Samarrai W, Bellgrove MA, The molecular genetic architecture of attention deficit hyperactivity disorder. Mol Psychiatry, 2015; 20(3):289–297.
63. Li Z, Chang SH, Zhang LY, Gao L, Wang J, Molecular genetic studies of ADHD and its candidate genes: a review. Psychiatry Res, 2014; 219(1):10–24.
64. Sakrikar D, Mazei-Robison MS, Mergy MA, Richtand NW, Han Q, Hamilton PJ, Bowton E, Galli A et al, Attention deficit/ hyperactivity disorder-derived coding variation in the dopamine transporter disrupts microdomain targeting and traffickingregulation. J Neurosci, 2012; 32(16):5385–5397.
65. Hesse S, Ballaschke O, Barthel H, Sabri O, Dopamine transporter imaging in adult patients with attention-deficit/hyperactivity disorder. Psychiatry Res, 2009; 171(2):120–128.
66. Volkow ND, Wang GJ, Newcorn J, Fowler JS, Telang F, Solanto MV, Logan J, Wong C et al, Brain dopamine transporter levels in treatment and drug naive adultswith ADHD. NeuroImage, 2007; 34(3):1182–1190.
67. Cheon KA, Ryu YH, Kim YK, Namkoong K, Kim CH, Lee JD, Dopamine transporter density in the basal ganglia assessed with [123I] IPT SPET in children with attention deficit hyperactivity disorder. Eur J NuclMed Mol Imaging 2003; 30(2):306–311.
68. Krause KH, Dresel SH, Krause J, Kung HF, Tatsch K, Increased striatal dopamine transporter in adult patients with attention deficit hyperactivity disorder: effects of methylphenidate as measured by single photon emission computed tomography.Neurosci Lett, 2000; 285(2):107–110
69. Wilson MC, Coloboma mouse mutant as an animal model of hyperkinesis and attention deficit hyperactivity disorder. Neurosci Biobehav Rev, 2000; 24(1):51–57
70. Barr CL, Feng Y, Wigg K, Bloom S, Roberts W, Malone M, Schachar R, Tannock R, and Kennedy J, Identification of DNA variants in the SNAP-25 gene and linkage study of these polymorphisms and attention-deficit hyperactivity disorder. Mol. Psychiatry, 2000; 5:405-409.
71. Mill J, Curran S, Kent L, Gould A, Huckett L, Richards S, Taylor E, and Asherson P, Association study of a SNAP-25 microsatellite and attention deficit hyperactivity disorder. Am. J. Med. Genet, 2002; 114:269-271.
72. Hess EJ, Collins KA, Wilson MC, Mouse model of hyperkinesis implicates SNAP-25 in behavioral regulati-

on. J Neurosci, 1996; 16(9):3104–3111
73. Hess EJ, Jinnah HA, Kozak CA, Wilson MC, Spontaneous locomotor hyperactivity in a mouse mutant with a deletion including the Snap gene on chromosome 2. J Neurosci, 1992; 12(7):2865–2874
74. Bruno KJ, Freet CS, Twining RC, Egami K, Grigson PS, Hess EJ, Abnormal latent inhibition and impulsivity in coloboma mice, a model of ADHD. Neurobiol Dis, 2007;25(1):206–216.
75. Steffensen SC, Henriksen SJ, Wilson MC, Transgenic rescue of SNAP-25 restores dopamine-modulated synaptic transmission in the coloboma mutant. Brain Res, 1999; 847(2):186–195
76. Raber J, Mehta PP, Kreifeldt M, Parsons LH, Weiss F, Bloom FE, Wilson MC, Coloboma hyperactive mutant mice exhibit regional and transmitter-specific deficits inneurotransmission. J Neurochem, 1997; 68(1):176–186
77. Jones MD, Williams ME, Hess EJ, Expression of catecholaminergic mRNAs in the hyperactive mouse mutant coloboma. Brain Res Mol Brain Res, 2001a; 96(1–2):114–121
78. Jones MD, Williams ME, Hess EJ, Abnormal presynaptic catecholamine regulation in a hyperactive SNAP-25-deficient mouse mutant. Pharmacol Biochem Behav, 2001b; 68(4):669–676
79. Maggi CA, The mammalian tachykinin receptors. Gen Pharmacol 1995; 26:911–944
80. Yan TC, Hunt SP, Stanford SC, Behavioural and neurochemical abnormalities in mice lacking functional tachykinin-1 (NK1) receptors: a model of attention deficit hyperactivity disorder. Neuropharmacology 2009; 57(7–8):627–635. ---57
81. Ljungdahl A, Hökfelt T, Nilsson G, Goldstein M, Distribution of substance P-like immunoreactivity in the central nervous system of the rat–II. Light microscopic localization in relation to catecholamine-containing neurons. Neuroscience 1978; 3:945–976
82. Ribeiro-da-Silva A, Hökfelt T, Neuroanatomical localisation of Substance P in the CNS and sensory neurons. Neuropeptides 2000; 34:256–271
83. Sharp SI, McQuillin A, Marks M, Hunt SP, Stanford SC, Lydall GJ, Morgan MY, Asherson P et al, Genetic association of the tachykinin receptor 1 TACR1 gene in bipolar disorder, attention deficit hyperactivity disorder, and the alcohol dependence syndrome. Am J Med Genet B Neuropsychiatr Genet 2014; 165B(4): 373–380. –56
84. Yan TC, McQuillin A, Thapar A, Asherson P, Hunt SP, Stanford SC, Gurling H, NK1 (TACR1) receptor gene 'knockout' mouse phenotype predicts genetic association with ADHD. J Psychopharmacol 2010; 24(1):27–38.—61
85. Yan TC, Dudley JA, Weir RK, Grabowska EM, Pena-Oliver Y, Ripley TL, Hunt SP, Stephens DN et al, Performance deficits of NK1 receptor knockout mice in the 5-choice serial reaction-time task: effects of d-amphetamine, stress and time of day. PLoS One 2011; 6(3):e17586. –65
86. Pillidge K, Porter AJ, Vasili T, Heal DJ, Stanford SC, Atomoxetine reduces hyperactive/impulsive behaviours in neurokinin-1 receptor 'knockout' mice. Pharmacol Biochem Behav 2014; 127:56–61.—66
87. Herpfer I, Hunt SP, Stanford SC, A comparison of neurokinin 1 receptor knock-out (NK1−/−) and wildtype mice: exploratory behaviour and extracellular noradrenaline concentration in the cerebral cortex of anaesthetised subjects. Neuropharmacology 2005; 48(5):706–719.
88. Froger N, Gardier AM, Moratalla R, Alberti I, Lena I, Boni C, De Felipe C, Rupniak NM et al, 5-Hydroxytryptamine (5-HT)1A autoreceptor adaptive changes in substance P (neurokinin 1) receptor knock-out mice mimic antidepressant-induced desensitization. J Neurosci 2001; 21(20):8188–8197---67
89. Murtra P, Sheasby AM, Hunt SP, De Felipe C. Rewarding effects of opiates are absentin mice lacking the receptor for substance P. Nature 2000; 405(6783):180–183.-
90. Burd L, Klug MG, Coumbe MJ, and Kerbeshian J. Children and adolescents with attention deficit-hyperactivity disorder: 1. Prevalence and cost of care. J. Child Neurol. 2003; 18:555-561.
91. Siesser WB, Cheng SY, McDonald MP, Hyperactivity, impaired learning on a vigilance task, and a differential response to methylphenidate in the TRbetaPV knock-in mouse. Psychopharmacology 2005; 181(4):653–663.
92. Siesser WB, Zhao J, Miller LR, Cheng SY, McDonald MP, Transgenic mice expressing a human mutant beta1 thyroid receptor are hyperactive, impulsive, and inattentive.Genes Brain Behav 2006; 5(3):282–297.
93. Hauser P, Zametkin AJ, Martinez P, Vitiello B, Matochik JA, Mixson AJ, Weintraub BD, Attention deficit-hyperactivity disorder in people with generalized resistance to thyroid hormone. N Engl J Med 1993; 328(14):997–1001.
94. Russell VA, Oades RD, Tannock R, Killeen PR, Auerbach JG, Johansen EB, and Sagvolden T, Response variability in attention-deficit hyperactivity disorder: Aneuronal and glial energetics hypothesis. Behav. Brain Funct. 2006; 2:30.
95. Bernal J, Action of thyroid hormone in brain. J Endocrinol Investig 2002; 25(3):268–288.
96. Modesto T, Tiemeier H, Peeters RP, Jaddoe VW, Hofman A, Verhulst FC, Ghassabian A, Maternal mild thyroid hormone insufficiency in early pregnancy and attention-deficit/hyperactivity disorder symptoms in children. JAMA Pediatr 2015; 169(9): 838–845.
97. Brucker-Davis F, Skarulis MC, Grace MB, Benichou J, Hauser P, Wiggs E,Weintraub BD, Genetic and clinical features of 42 kindreds with resistance to thyroid hormone. The National Institutes of Health Prospective Study. Ann Intern Med 1995; 123(8): 572–583