

BİPOLAR BOZUKLUKTA HAYVAN MODELLERİ

24 BÖLÜM

Burcu KÖK KENDİRLİOĞLU

GİRİŞ

Bipolar Bozukluk (BPB), belirgin psikososyal bozulma ve yeti yitimine neden olan, süreğen, duygudurum atakları ile seyreden ve sık görülen bir psikiyatrik morbidite nedenidir. Yakın zamana kadar bipolar bozukluğun yaşam boyu prevalansı %1 olarak kabul edilmekte iken; son yıllarda BPB I ve II'yi kapsayan çalışmalarda %5'e varan oranlar verilmektedir (1). BPB yani iki uçlu duygudurum bozukluğu manik, depresif ve karma dönemler içerir. Manik dönem en az 1 hafta veya hasta yatırılmak zorunda kalırsa daha kısa süren, olağandışı ve uzun süreli yükselmiş, kabarmış veya iritabl duygudurum dönemidir. Manik dönemde kişide artmış benlik saygısı, uyku ihtiyacında azalma, aşırı uyarılmışlık hali, aşırı fiziksel ve zihinsel aktivite, amaca yönelik etkinliklerde artış saptanır (2). Depresif dönemde en az iki hafta süren moral bozukluğu, karamsarlık, anhedoni, avolusyon, vejetatif değişiklikler (uyku, iştah ve cinsel aktivite), özsaygıda azalma, enerji azlığı ve suicid fikirleri görülmektedir. Karma dönem ise hem manik hem de depresif belirtilerden birkaçını içeren en az 1 haftalık süreyi ifade eder (2). BPB'nin tedavisinde duygudurum dengeleyici ilaçlar, antipsikotikler ve kimi zaman antidepresanlar kullanılır.

Psikiyatrik bozukluklarda hayvan modellerinin genel durumu diğer hastalıkların ideal modellerinden geride kalmış olmasına karşın, psikiyatrik araştırmalar arasında bile BPB modellerinin durumu en yetersizlerindedir. BPB'de hayvan modeli oluşturmada zorluk yaratan nedenlerden birincisi; hastalık durumunu veya tedavinin etkilerini gözlemek için yerleşik bir biyolojik belirteç bulunmamasıdır. İkincisi; bir insanın "afektif" hastalığı için genel bir hayvan modeli kavramı her zaman sorunludur, çünkü hayvanların 'afekti' olduğu varsayılmaz (3). BPB modellemesinin en belirgin yarattığı üçüncü sıkıntı ise; hastalığın doğal döngüsel yapısından kaynaklanmaktadır (4). Literatürde hastalığın bu döngüsel yapısının modellenmesi çokça tartışılmıştır. Kimi yazarlar, BPB modelinin mutlaka döngüsel özellik göstermesi gerektiğini savunmuşken (5); kimi yazarlar ise bu döngüsel durumun üstesinden gelmek için manik ve depresif dönemlerin ayrı ayrı modellenebileceğini öne sürmüştür (6). Hala BPB'yi tamamen yansıtan bir model geliştirilememiş olmasına karşın; hastalığın manik ve depresif dönemlerinin ayrı ayrı çalışıldığı yeni hayvan modelleri duygudurum bozukluklarının altında yatan mekanizmaların anlaşılmasını sağlamak için kullanılmaktadır.

liği olarak tüm bu üç kriteri de kapsayan ideal bir modele ulaşamadığı görülmektedir. Bu tür ideal modeller nadir olmakla birlikte psikiyatrik bozukluklarda hiç yoktur. BPB' de ideal modeli oluşturmadaki en büyük sorunlardan biri hastalığın doğal iki uç duygudurum arasındaki döngüsellidir. Bunun yanında BPB için en önemli belirti olan afektte gözlenen değişimin hayvanlarda gözlenemiyor oluşu da ikinci büyük sorunu oluşturmaktadır. BPB' de ideal model ancak hastalığın nörobiyolojisi anlaşıldıktan sonra ortaya çıkabilecektir. Şimdilik elimizde ideal bir BPB hayvan modeli olmasa da; mevcut modellerin araştırmalara katkısı yadsınmaz.

KAYNAKLAR

1. Rihmer Z, Angst J. Mood Disorders Epidemiology Comprehensive Textbook of Psychiatry: Sadock BJ, Sadock VA (editors). Cilt I, 8.baskı Philadelphia: Lippincott Williams & Wilkins., 2005, 1575-1582.
2. Sadock BJ, Sadock VA, Ruiz P. (2016) Kaplan & Sadock's Synopsis of Psychiatry Behavioral Sciences/Clinical Psychiatry (Prof. Dr. Ali Bozkurt, Çev. Ed.), Ankara: Güneş Tıp Kitapevi
3. Gould TD, Einat H. Animal models of bipolar disorder and mood stabilizer efficacy: a critical need for improvement. *Neurosci Biobehav Rev.* 2007;31(6):825-831.
4. Einat H. Different behaviors and different strains: Potential new ways to model bipolar disorder. *Neuroscience and Biobehavioral Reviews.* 2007;31 (6): 850-857
5. Machado-Vieira R, Kapczinski F, Soares JC. Perspectives for the development of animal models of bipolar disorder. *Progress in Neuropsychopharmacology and Biological Psychiatry.* 2004; 28 (2):209-224
6. Malatynska E, Knapp RJ. Dominant-submissive behavior as models of mania and depression. *Neuroscience and Biobehavioral Reviews* 2005;29 (45):715-737.
7. Ellenbroek BA, Cools AR. Animal models with construct validity for schizophrenia. *Behav Pharmacol.* 1990;1:469-490.
8. Atay İM. (2016). Psikiyatrik Bozukluklarda Deney Hayvan Modelleri. Ankara: Derman Medical Publishing.
9. Kato T, Kubota M, Kasahara T. Animal models of bipolar disorder. *Neurosci Biobehav Rev.* 2007;31(6):832-842.
10. Valvassori SS, Budni J, Varela RB. Et al. Contributions of animal models to the study of mood disorders. *Braz J Psychiatry.* 2013;35 Suppl 2:S121-131.
11. Hoffman BB, Lefkowitz RJ. (1996) Catecholamines, sympathomimetic drugs, and adrenergic receptor antagonists. In: Hardman JG, Limbird LE, Molinoff PB, et al. (Eds.). Goodman & Gilman's the pharmacological basis of therapeutics. (9th ed. p. 199-248) New York: McGraw-Hill.
12. Frey BN, Andrezza AC, Cereser KM, et al. Effects of mood stabilizers on hippocampus BDNF levels in an animal model of mania. *Life Sci.* 2006;79:281-286.
13. Frey BN, Valvassori SS, Reus GZ, et al. Effects of lithium and valproate on amphetamine induced oxidative stress generation in an animal model of mania. *J Psychiatry Neurosci.* 2006;31:326-332.
14. Shaldivin A, Kaptan A, Belmaker RH, et al. Transcranial magnetic stimulation in an amphetamine hyperactivity model of mania. *Bipolar Disorders* 2001;3:30-34.
15. Gould TJ, Keith RA, Bhat RV. Differential sensitivity to lithium's reversal of amphetamine-induced open-field activity in two inbred strains of mice. *Behavioural Brain Research.* 2001;118:95-105.
16. Shaldubina A, Einat H, Szechtman H, et al. Preliminary evaluation of oral anticonvulsant treatment in the quinpirole model of bipolar disorder. *Journal of Neural Transmission.* 2002;109:433-440.
17. Antelman SM, Caggiula AR, Kucinski BJ, et al. The effects of lithium on a potential cycling model of bipolar disorder. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry.* 1998;22:495-510.
18. Kucinski BJ, Antelman SM, Caggiula AR, et al. Oscillatory effects of repeated morphine on shock-induced hypoalgesia and betaendorphin. *Synapse.* 1998;30:30-37.
19. Vale AL, Ratcliffe F. Effect of lithium administration on rat brain 5-hydroxyindole levels in a possible animal model for mania. *Psychopharmacology (Berlin).* 1987;91:352-355.
20. Arban R, Maraia G, Brackenborough K, et al. Evaluation of the effects of lamotrigine, valproate and carbamazepine in a rodent model of mania. *Behavioural Brain Research.* 2005;158:123-132.
21. Schwartz JM, Ksir C, Koob GF, et al. Changes in locomotor response to beta-endorphin microinfusion during and after opiate abstinence syndrome—a proposal for a model of the onset of mania. *Psychiatry Research.* 1982;7:153-161.
22. Macedo DS, Medeiros CD, Cordeiro RC, et al. Effects of alpha-lipoic acid in an animal model of mania induced by D-amphetamine. *Bipolar Disord.* 2012;14:707-718.
23. Park H, Poo MM. Neurotrophin regulation of neural circuit development and function. *Nat Rev Neurosci.* 2013;14:7-23.
24. Andrezza AC, Cassini C, Rosa AR, et al. Serum S100B and antioxidant enzymes in bipolar patients. *J Psychiatry Res.* 2007;41:523-529.
25. Kapczinski F, Frey BN, Andrezza AC, et al. Increased oxidative stress as a mechanism for decreased BDNF levels in acute manic episodes. *Rev Bras Psiquiatr.* 2008;30:243-245.
26. Hibbeln, JR. Seafood consumption, the DHA content of mothers'milk and prevalence rates of postpartum depression: a cross-national, ecological analysis. *Journal of Affective Disorders.* 2002;69:15-29.
27. Parker G, Gibson NA, Brotchie H, et al. Omega-3 fatty acids and mood disorders. *American Journal of Psych-*

- hiatry 2006;163:969–978.
28. DeMar Jr. JC, Ma K, Bell JM, et al. One generation of n-3 polyunsaturated fatty acid deprivation increases depression and aggression test scores in rats. *Journal of Lipid Research*. 2006; 47:172–180.
 29. Gessa GL, Pani L, Fadda P, et al. 1995. Sleep deprivation in the rat: an animal model of mania. *European Neuropsychopharmacology* 1995;5 (Suppl):89–93.
 30. Kroes RA, Panksepp J, Burgdorf J, et al. Modeling depression: social dominance-submission gene expression patterns in rat neocortex. *Neuroscience* 2006;137:37–49.
 31. McClung CA, Sidiropoulou K, Vitaterna M, et al. Regulation of dopaminergic transmission and cocaine reward by the Clock gene. *Proceedings of the National Academy of Sciences of USA*. 2005;102:9377–9381.
 32. Roybal K, Theobald D, DiNieri JA, et al. Mania-like behavior induced by disruption of CLOCK. *Proceedings of the National Academy of Sciences of USA*. 2007 Apr 10;104(15):6406–6411.
 33. Nievergelt CM, Kripke DF, Barrett TB, et al. Suggestive evidence for association of the circadian genes PERIOD3 and ARNTL with bipolar disorder. *American Journal of Medical Genetics—B Neuropsychiatric Genetics*. 2006;141, 234–241.
 34. Dokucu ME, Yu L, Taghert PH. Lithium- and valproate induced alterations in circadian locomotor behavior in *Drosophila*. *Neuropsychopharmacology* 2005;30:2216–2224.
 35. Klein PS, Melton DA. A molecular mechanism for the effect of lithium on development. *Proceedings of the National Academy of Sciences of USA* 1996;93:8455–8459.
 36. Prickaerts J, Moechars D, Cryns K, et al. Transgenic mice overexpressing glycogen synthase kinase 3beta: a putative model of hyperactivity and mania. *Journal of Neuroscience*. 2006;26:9022–9029.
 37. Nishiguchi N, Breen G, Russ C. Association analysis of the glycogen synthase kinase-3beta gene in bipolar disorder. *Neuroscience Letters*. 2006;394: 243–245.
 38. Razafsha M, Behforuzi H, Harati H, et al. An updated overview of animal models in neuropsychiatry. *Neuroscience*. 2013;240:204–218.
 39. Porsolt RD, Le Pichon M, Jalfre M. Depression: a new animal model sensitive to antidepressant treatments. *Nature*. 1977;266: 730– 732.
 40. Steru L, Chermat R, Thierry B, et al. The tail suspension test: a new method for screening antidepressants in mice. *Psychopharmacology (Berl)*. 1985;85:367–370.
 41. Strelakova T, Steinbusch HW. Measuring behavior in mice with chronic stress depression paradigm. *Prog Neuropsychopharmacol Biol Psychiatry*. 2010;34:348–361.
 42. Kelly JP, Wrynn AS, Leonard BE. The olfactory bulbectomized rat as a model of depression: an update. *Pharmacol. Ther*. 1997;74: 299–316.
 43. Connor TJ, Song C, Leonard BE, et al. Stressor-induced alterations in serotonergic activity in an animal model of depression. *NeuroReport*. 1999;10: 523– 528.
 44. Wrynn AS, Mac Sweeney CP, Franconi F, et al. An in-vivo magnetic resonance imaging study of the olfactory bulbectomized rat model of depression. *Brain Res*. 2000 Oct 6;879(1-2):193–199.
 45. Kastin AJ, Scollan EL, Ehrensing RH, et al. Enkephalin and other peptides reduce passiveness. *Pharmacol. Biochem. Behav*. 1978;9:515– 519.
 46. Skuza G, Rogoz Z, Quack G, et al. Memantine, amantadine, and L-deprenyl potentiate the action of L-dopa in monoaminodepleted rats. *J. Neural Transm. Gen. Sect*. 1994; 98: 57– 67.
 47. Nagayama H, Hingtgen JN, Aprison MH. Postsynaptic action by four antidepressive drugs in an animal model of depression. *Pharmacol. Biochem. Behav*. 1981;15:125–130.
 48. Aprison MH, Hingtgen JN, Nagayama H. (1982) Testing a new theory of depression with an animal model: neurochemical– behavioural evidence for postsynaptic serotonergic receptor involvement. In: Langer SZ, Takahashi R, Segawa T, et al. (Eds.). *New Vistas in Depression*. (pp. 171– 178) New york: Pergamon.
 49. Leith NJ, Barret RJ. Amphetamine and the reward system: evidence for tolerance and post-drug depression. *Psychopharmacology (Berl)*.1976;46:19– 25.
 50. Simpson DM, Annau Z. Behavioral withdrawal following several psychoactive drugs. *Pharmacol. Biochem. Behav*. 1977; 7:59– 64.
 51. Kehoe P, Shoemaker WJ, Triano L, et al. Isolation in the neonatal period in rat produces alterations in behavior and ventral striatal dopamine release after in the juvenile rat after amphetamine challenge. *Behav. Neurosci*. 1996;110:61435– 61444.
 52. Willner P. Validity, reliability and utility of the chronic mild stress model of depression: a 10-year review and evaluation. *Psychopharmacology (Berl)*. 1997;134:319– 329.
 53. D’Aquila PS, Brain P, Willner P. Effects of chronic mild stress on performance in behavioural tests relevant to anxiety and depression. *Physiol. Behav*. 1994; 56:861– 867.
 54. Cheeta S, Ruigt G, van Proosdij J, et al. Changes in sleep architecture following chronic mild stress. *Biol. Psychiatry*. 1997;41:419–427.
 55. Papp M, Klimek V, Willner P. Effects of imipramine on serotonergic and beta-adrenergic receptor binding in a realistic animal model of depression. *Psychopharmacology (Berl)*. 1994a;114:309– 314.
 56. Papp M, Klimek V, Willner P. Parallel changes in dopamine D2 receptor binding in limbic forebrain associated with chronic mild stress-induced anhedonia and its reversal by imipramine. *Psychopharmacology(-Berl)*.1994b;115:441– 446.
 57. Murakami S, Imbe H, Morikawa Y, et al. Chronic stress, as well as acute stress, reduces BDNF mRNA expression in the rat hippocampus but less robustly. *Neurosci Res*. 2005;53:129–139.
 58. Zhang L, Zhang J, Sun H, et al. Exposure to enriched environment restores the mRNA expression of mineralocorticoid and glucocorticoid receptors in the hippocampus and ameliorates depressive-like symptoms in chronically stressed rats. *Curr Neurovasc Res*. 2011;8:286–293.
 59. Seligman ME, Beagley G. Learned helplessness in the

- rat. *J. Comp. Physiol. Psychol.* 1975; 88:534– 541.
60. Rosellini RA, de Cola JP. Inescapable shock interferes with the acquisition of a low-activity response in an appetitive context. *Anim. Learn Behav.* 1981;9:487–490.
 61. Jacobsen JP, Medvedev IO, Caron MG. The 5-HT deficiency theory of depression: perspectives from a naturalistic 5-HT deficiency model, the tryptophan hydroxylase 2Arg439His knockin mouse. *Philos Trans R Soc Lond B Biol Sci.* 2012;367:2444-2459.
 62. Beaulieu JM, Zhang X, Rodriguiz RM, et al. Role of GSK3 beta in behavioral abnormalities induced by serotonin deficiency. *Proc Natl Acad Sci USA.* 2008;105:1333-1338.
 63. Valverde O, Torrens M. CB1 receptor-deficient mice as a model for depression. *Neuroscience.* 2012;204:193-206.
 64. Bunney WE, Bunney BG. Molecular clock genes in man and lower animals possible implications for circadian abnormalities in depression. *Neuropsychopharmacology.* 2000; 22:335–345.
 65. Takahashi JS, Hong H-K, Ko CH, et al. The genetics of mammalian circadian order and disorder: implications for physiology and disease. *Nat Rev Genet.* 2008;9(10):764–775.
 66. Logan RW, McClung CA. Animal models of bipolar mania: the past, present and future. *Neuroscience.* 2016;3(321):163–188.