

# Bölüm 8

## Kopma: Depresyonun Sürdürülmesinde Homeostatik Yönlendiricinin Rolü

Çeviri: Dr. Yusuf TAMAM

### Özet

Beyin nörokimyası ve davranışı modülasyona uğratan düzenleyici etkileşimlerin kompleks olmasının nedeni, çok sayıda stabil yanıtların desteklenebilmesi ve bazı alternatif düzenleyici programların inatçı psikolojik disfonksiyonun sürdürülmesinde bir rol sahibi olabilmesidir. Bu öneriyi araştırmak için literatürde birbirlerinden ayrı mantık devreleri olarak bildirilmiş olan major nörotransmisyon ve davranış mekanizmalarını temsil eden bir ağ modeli üretti. Bu biyodavranış devresindeki bağlantılar ve bilginin devre üzerinde akışı iki ayrı ve stabil düzenleyici programı destekler. Böyle bir program, düşük serotonin dahil karakteristik bir nörokimyasal imza ile depresif bir tabloyu sürdürtür. Daha ileri analizler glutamat düzeylerindeki ufak tefek düzensizliklerin bu patolojiyi daha da doğrudan ulaşılabilir hale getirebildiğini telkin etmektedir. Hergün karşılaşılan stresörlerin varlığında selektif serotonin geri kapılma inhibitörü (SSRI) tedavisini taklit eden bilgisayar simülasyonları klinikten rapor edilene benzer tekrar etme hızını ön-gördürür ve eş zamanlı yapılan davranış stres yönetme terapisinin potansiyel olarak önemli yararına ışık tutar.

**Anahtar sözcükler** Bilgisayar modelleme, Homeostatik düzenleme, Depresyon, SSRI, Stres, Nörotransmiterler, Glutamat, Serotonin, Ağ kompleksitesi, Düzenleyici mantık, Multi-stabilite

---

### 1 Giriş

2012'de ABD'deki 16 milyon erişkinin en azından bir kere major depresif nöbet geçirdiği hesaplanmıştır [1]. Olaya daha yakın bir bakış çok daha geniş ve kompleks bir durumun varlığını ortaya çıkartmış olup bir yıllık bir süre içinde ABD'deki erişkinlerin %6,9'u 2 hafta veya daha uzun süre devam etmiş depresif bir duygusal durum yaşadığı veya ilgi ve hız almayı yitirdiğini ve uykuya, yemek yeme, enerji, konsantrasyon olma ve özeleştirici gibi işlevde bir değişikliği yansitan en az dört diğer semptom yaşadığını ortaya çıkarmıştır [2]. Bunun bir diğer anlamı, her yıl 14 erişkinden 1 tanesinde, ABD'deki ölüm nedenleri listesinde onuncu olan özkiyim riskinin artmış olduğunudır. Depresyonda olmanın açıkça görülecek kişisel sorunlar yaratması bir

yar Bilimi Merkezindeki (CCS) yüksek performanslı bilgisayar ekipinin işbirliği ile yürütülmüştür (CCS) (<http://ccs.miami.edu>).

*İkaz Notu:* Burada zikredilen fikir ve görüşler yazarların şahsi fikirleri olup Savunma Bakanlığı'nın resmi görüşü degildir ve bakanlığın hiçbir görüşünü yansıtmez.

## Kaynaklar

1. Substance Abuse and Mental Health Services Administration (2013) Results from the 2012 National Survey on Drug Use and Health: Mental Health Findings, NSDUH Series H-47, HHS Publication No. (SMA) 13-4805. Substance Abuse and Mental Health Services Administration, Rockville, MD
2. American Psychiatric Association (2013) Diagnostic and statistical manual of mental disorders: DSM-V. 5. American Psychiatric Association, Washington, DC
3. Greenberg PE, Fournier A, Sisitsky T, Pike CT, Kessler RC (2014) The economic burden of adults with major depressive disorder in the United States (2005 and 2010). *J Clin Psychiatry* 76(2):155–162
4. Antonuccio DO, Danton WG, DeNelsky GY (1995) Psychotherapy versus medication for depression: challenging the conventional wisdom with data. *J Psychother Pract Res* 26 (6):574–585
5. Sałat K, Podkowa A, Kowalczyk P, Kulig K, Dziubina A, Filipek B, Librowski T (2015) Anticonvulsant active inhibitor of GABA transporter subtype 1, tiagabine, with activity in mouse models of anxiety, pain and depression. *Pharmacol Rep* 67(3):465–472
6. Cuijpers P, van Straten A, Andersson G, van Oppen P (2008) Psychotherapy for depression in adults: a meta-analysis of comparative outcome studies. *J Consult Clin Psychol* 76 (6):909
7. Burcusa SL, Iacono WG (2007) Risk for recurrence in depression. *Clin Psychol Rev* 27 (8):959–985
8. Wurtman RJ, Pohorecky LA, Baliga BS (1972) Adrenocortical control of the biosynthesis of epinephrine and proteins in the adrenal medulla. *Pharmacol Rev* 24(2):411–426
9. Piazza PV, Rouge'-Pont F, Deroche V, Maccaire S, Simon H, Le Moal M (1996) Glucocorticoids have state-dependent stimulant effects on the mesencephalic dopaminergic transmission. *Proc Natl Acad Sci* 93 (16):8716–8720
10. Yuen EY, LiuW, Karatsoreos IN, Feng J, McEwen BS, Yan Z (2009) Acute stress enhances glutamatergic transmission in prefrontal cortex and facilitates working memory. *Proc Natl Acad Sci* 106(33):14075–14079
11. Tafet GE, Toister-Achituv M, Shnitzky M (2001) Enhancement of serotonin uptake by cortisol: a possible link between stress and depression. *Cogn Affect Behav Neurosci* 1 (1):96–104
12. Janssen SA, Arntz A, Bouts S (1998) Anxiety and pain: epinephrine-induced hyperalgesia and attentional influences. *Pain* 76 (3):309–316
13. Bergstrom DA, Walters JR (1984) Dopamine attenuates the effects of GABA on single unit activity in the globus pallidus. *Brain Res* 310 (1):23–33
14. Daw ND, Kakade S, Dayan P (2002) Opponent interactions between serotonin and dopamine. *Neural Netw* 15(4):603–616
15. Gillard ER, Dang DQ, Stanley BG (1993) Evidence that neuropeptide Y and dopamine in the perifornical hypothalamus interact antagonistically in the control of food intake. *Brain Res* 628(1):128–136
16. El Mansari M, Guiard BP, Chernoloz O, Ghanbari R, Katz N, Blier P (2010) Relevance of norepinephrine-dopamine interactions in the treatment of major depressive disorder. *CNS Neurosci Ther* 16(3):e1–e17
17. Calabresi P, Picconi B, Parnetti L, Di FilippoM (2006) A convergent model for cognitive dysfunctions in Parkinson's disease: the critical dopamine-acetylcholine synaptic balance. *Lancet Neurol* 5(11):974–983
18. Biello SM, Golombok DA, Harrington ME (1997) Neuropeptide Y and glutamate block each other's phase shifts in the supra-

- chiasmatic nucleus in vitro. *Neuroscience* 77 (4):1049–1057
19. Serfozo P, Bartfai T, Vizi ES (1986) Presynaptic effects of neuropeptide Y on [3 H] noreadrenaline and [3 H] acetylcholine release. *Regul Pept* 16(2):117–123
  20. Dryden S, McCarthy HD, Malabu UH, Ware M, Williams G (1993) Increased neuropeptide Y concentrations in specific hypothalamic nuclei of the rat following treatment with methysergide: evidence that NPY may mediate serotonin's effects on food intake. *Peptides* 14 (4):791–796
  21. Herman JP, Renda A, Bodie B (2003) Nor-epinephrine-gamma-aminobutyric acid (GABA) interaction in limbic stress circuits: effects of reboxetine on GABAergic neurons. *Biol Psychiatry* 53(2):166–174
  22. Wahlestedt CLAES, Hakanson ROLE, Vaz CA, Zukowska-Grojec ZOFIA (1990) Norepinephrine and neuropeptide Y: va-soconstrictor cooperation in vivo and in vitro. *Am J Phys Regul Integr Comp Phys* 258(3):R736–R742
  23. Bremner JD, Krystal JH, Southwick SM, Charney DS (1996) Noradrenergic mechanisms in stress and anxiety: II. Clinical studies. *Synapse* 23(1):39–51
  24. Southwick SM, Bremner JD, Rasmussen A, Morgan CA, Arnsten A, Charney DS (1999) Role of norepinephrine in the pathophysiology and treatment of posttraumatic stress disorder. *Biol Psychiatry* 46(9):1192–1204
  25. Bymaster FP, Katner JS, Nelson DL, Hemrick-Luecke SK, Threlkeld PG, Heiligenstein JH, Morin SM, Gehlert DR, Perry KW (2002) Atomoxetine increases extracellular levels of norepinephrine and dopamine in prefrontal cortex of rat: a potential mechanism for efficacy in attention deficit/hyperactivity disorder. *Neuropsychopharmacology* 27(5):699–711
  26. Zhang K, Grady CJ, Tsapakis EM, Andersen SL, Tarazi FI, Baldessarini RJ (2004) Regulation of working memory by dopamine D4 receptor in rats. *Neuropsychopharmacology* 29(9):1648
  27. Delgado PL, Moreno FA (1999) Role of norepinephrine in depression. *J Clin Psychiatry* 61:5–12,
  28. Casey DE, Gerlach J, Christensson E (1980) Behavioral aspects of GABA-dopamine interrelationships in the monkey. *Brain Res Bull* 5:269–273
  29. Moises HC, Woodward DJ (1980) Potentiation of GABA inhibitory action in cerebellum by locus coeruleus stimulation. *Brain Res* 182 (2):327–344
  30. Bankson MG, Yamamoto BK (2004) Serotonin- GABA interactions modulate MD-MAinduced mesolimbic dopamine release. *J Neurochem* 91(4):852–859
  31. Edden RA, Crocetti D, Zhu H, Gilbert DL, Mostofsky SH (2012) Reduced GABA concentration in attention-deficit/hyperactivity disorder. *Arch Gen Psychiatry* 69(7):750–753
  32. Russell VA, Wiggins TM (2000) Increased glutamate-stimulated norepinephrine release from prefrontal cortex slices of spontaneously hypertensive rats. *Metab Brain Dis* 15 (4):297–304
  33. Mathew SJ, Coplan JD, Smith EL, Schoepp DD, Rosenblum LA, Gorman JM (2001) Glutamate—hypothalamic-pituitary-adrenal Axis interactions: implications for mood and anxiety disorders. *CNS Spectr* 6(07):555–564
  34. Carlsson A, Waters N, Holm-Waters S, Tedroff J, Nilsson M, Carlsson ML (2001) Interactions between monoamines, glutamate, and GABA in schizophrenia: new evidence. *Annu Rev Pharmacol Toxicol* 41(1):237–260
  35. Aultman JM, Moghaddam B (2001) Distinct contributions of glutamate and dopamine receptors to temporal aspects of rodent working memory using a clinically relevant task. *Psychopharmacology* 153(3):353–364
  36. Paul IA, Skolnick P (2003) Glutamate and depression. *Ann N Y Acad Sci* 1003 (1):250–272
  37. Carrey NJ, MacMaster FP, Gaudet L, Schmidt MH (2007) Striatal creatine and glutamate/ glutamine in attention-deficit/ hyperactivity disorder. *J Child Adolesc Psychopharmacol* 17 (1):11–17
  38. Van Praag HM, Kahn RS, Asnis GM, Wetzler S, Brown SL, Bleich A, Korn ML (1987) Denosologization of biological psychiatry or the specificity of 5-HT disturbances in psychiatric disorders. *J Affect Disord* 13(1):1–8
  39. Aghajanian GK, Marek GJ (1999) Serotonin-glutamate interactions: a new target for antipsychotic drugs. *Neuropsychopharmacology* 21:S122–S133

40. MacDermot J, Higashida H, Wilson SP, Matsuzawa H, Minna J, Nirenberg M (1979) Adenylate cyclase and acetylcholine release regulated by separate serotonin receptors of somatic cell hybrids. *Proc Natl Acad Sci* 76 (3):1135–1139
41. Guiard BP, El Mansari M, Merali Z, Blier P (2008) Functional interactions between dopamine, serotonin and norepinephrine neurons: an in-vivo electrophysiological study in rats with monoaminergic lesions. *Int J Neuropsychopharmacol* 11(5):625–639
42. Korsgaard S, Gerlach J, Christensson E (1985) Behavioral aspects of serotonin-dopamine interaction in the monkey. *Eur J Pharmacol* 118(3):245–252
43. O'hara R, Schroder CM, Mahadevan R, Schatzberg AF, Lindley S, Fox S, Weiner M, Kraemer HC, Noda A, Lin X, Gray HL, Hallmayer JF (2007) Serotonin transporter polymorphism, memory and hippocampal volume in the elderly: association and interaction with cortisol. *Mol Psychiatry* 12(6):544–555 142 J. Tory Toole et al.
44. Connor KM, Davidson JR (1998) The role of serotonin in posttraumatic stress disorder: neurobiology and pharmacotherapy. *CNS Spectr* 3 (S2):42–51
45. Charney DS, Woods SW, Goodman WK, Heninger GR (1987) Serotonin function in anxiety. *Psychopharmacology* 92(1):14–24
46. Owens MJ, Nemeroff CB (1994) Role of serotonin in the pathophysiology of depression: focus on the serotonin transporter. *Clin Chem* 40(2):288–295
47. Roelandts B, Meeusen R (2010) Alterations in central fatigue by pharmacological manipulations of neurotransmitters in normal and high ambient temperature. *Sports Med* 40 (3):229–246
48. Keely SL, Lincoln TM, Corbin JD (1978) Interaction of acetylcholine and epinephrine on heart cyclic AMP-dependent protein kinase. *Am J Phys Heart Circ Phys* 234(4): H432–H438
49. Dixon JS, Jen PY, Gosling JA (2000) The distribution of vesicular acetylcholine transporter in the human male genitourinary organs and its co-localization with neuropeptide Y and nitric oxide synthase. *Neurourol Urodyn* 19 (2):185–194
50. Walker SW, Strachan MWJ, Lightly ERT, Williams BC, Bird IM (1990) Acetylcholine stimulates cortisol secretion through the M3 muscarinic receptor linked to a polyphosphoinositide-specific phospholipase C in bovine adrenal fasciculata/reticularis cells. *Mol Cell Endocrinol* 72(3):227–238
51. Kalsner S, Quillan M (1988) Presynaptic interactions between acetylcholine and adrenergic antagonists on norepinephrine release. *J Pharmacol Exp Ther* 244(3):879–891
52. Leboulenger F, Benyamina M, Delarue C, Netchitailo P, Saint-Pierre S, Vaudry H (1988) Neuronal and paracrine regulation of adrenal steroidogenesis: interactions between acetylcholine, serotonin and vasoactive intestinal peptide (VIP) on corticosteroid production by frog interrenal tissue. *Brain Res* 453 (1):103–109
53. Czermak C, Staley JK, Kasserman S, Bois F, Young T, Henry S, Tamagnan GD, Seibyl JP, Krystal JH, Neumeister A (2008)  $\beta 2$  Nicotinic acetylcholine receptor availability in posttraumatic stress disorder. *Int J Neuropsychopharmacol* 11(3):419–424
54. Botly LC, De Rosa E (2008) A cross-species investigation of acetylcholine, attention, and feature binding. *Psychol Sci* 19 (11):1185–1193
55. Daniel JM, Dohanich GP (2001) Acetylcholine mediates the estrogen-induced increase in NMDA receptor binding in CA1 of the hippocampus and the associated improvement in working memory. *J Neurosci* 21 (17):6949–6956
56. Mendoza L, Xenarios I (2006) A method for the generation of standardized qualitative dynamical systems of regulatory networks. *Theor Biol Med Model* 3:13
57. Thomas R (1991) Regulatory networks seen as asynchronous automata: a logical description. *J Theor Biol* 153(1):1–23
58. Craddock TJ, Fritsch P, Rice MA Jr, del Rosario RM, Miller DB, Fletcher MA, Klimas NG, Broderick G (2014) A role for homeostatic drive in the perpetuation of complex chronic illness: gulf war illness and chronic fatigue syndrome. *PLoS One* 9(1):e84839
59. Fritsch P, Craddock TJ, del Rosario RM, Rice MA, Smylie A, Folcik VA, de Vries G, Fletcher MA, Klimas NG, Broderick G (2013) Succumbing to the laws of attraction: exploring the sometimes pathogenic versatility of discrete immune logic. *Sys Biomed* 1(3):179–194

60. Whitley D, Garrett D, Watson JP (2003, January) Quad search and hybrid genetic algorithms. In: Genetic and evolutionary computation—GECCO 2003. Springer, Berlin, pp 1469–1480
61. Müller N, Schwarz MJ (2007) The immunemediated alteration of serotonin and glutamate: towards an integrated view of depression. *Mol Psychiatry* 12:988–1000
62. Nicu MJ, Henter ID, Luckenbaugh DA, Zarrate CA Jr, Charney DS (2014) Glutamate receptor antagonists as fast-acting therapeutic alternatives for the treatment of depression: ketamine and other compounds. *Annu Rev Pharmacol Toxicol* 54:119–139
63. Morgan CA, Rasmussen AM, Wang S, Hoyt G, Hauger RL, Hazlett G (2002) Neuropeptide-Y, cortisol, and subjective distress in humans exposed to acute stress: replication and extension of previous report. *Biol Psychiatry* 52 (2):136–142
64. Thorsell A (2010) Brain neuropeptide Y and corticotropin-releasing hormone in mediating stress and anxiety. *Exp Biol Med* 235 (10):1163–1167
65. Schubert KO, Clark SR, Van LK et al (2017) Depressive symptom trajectories in late adolescence and early adulthood: A systematic review. *Aust N Z J Psychiatry* 51(5):477–499
66. Anderson IM (1998) SSRIs versus tricyclic antidepressants in depressed inpatients: a meta-analysis of efficacy and tolerability. *Depress Anxiety* 7(S1):11–17
67. Reiche EMV, Nunes SOV, Morimoto HK (2004) Stress, depression, the immune system, and cancer. *Lancet Oncol* 5(10):617–625
68. Yirmiya R, Rimmerman N, Reshef R (2015) Depression as a microglial disease. *Trends Neurosci* 38(10):637–658
69. Louveau A, Smirnov I, Keyes TJ, Eccles JD, Rouhani SJ, Peske JD, Derecki NC, Castle D, Mandell JW, Lee KS, Harris TH, Kipnis J (2015) Structural and functional features of central nervous system lymphatic vessels. *Nature* 523(7560):337–341
70. Hammen C (2005) Stress and depression. *Annu Rev Clin Psychol* 1:293–319
71. Furlong M, Oei TP (2002) Changes to automatic thoughts and dysfunctional attitudes in group CBT for depression. *Behav Cogn Psychother* 30(03):351–360
72. Farrer L, Christensen H, Griffiths KM, Mackinnon A (2011) Internet-based CBT for depression with and without telephone tracking in a national helpline: randomised controlled trial. *PLoS One* 6(11):e28099
73. Chisholm D, Sanderson K, Ayuso-Mateos JL, Saxena S (2004) Reducing the global burden of depression. *Br J Psychiatry* 184(5):393–403
74. March J, Silva S, Petrycki S, Curry J, Wells K, Fairbank J, Burns B, Domino M, McNulty S, Vitiello B, Severe J (2004) Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: treatment for adolescents with depression study (TADS) randomized controlled trial. *JAMA* 292(7):807–820
75. Soeteman DI, Miller M, Kim JJ (2012) Modeling the risks and benefits of depression treatment for children and young adults. *Value Health* 15(5):724–729
76. Gruwez B, Poirier MF, Dauphin A, Olie JP, Tod M (2007) A kinetic-pharmacodynamic model for clinical trial simulation of antidepressant action: application to clomipramine–lithium interaction. *Contemp Clin Trials* 28 (3):276–287
77. Peacock BN, Scheiderer DJ, Kellermann GH (2017) Biomolecular aspects of depression: a retrospective analysis. *Compr Psychiatry* 73:168–180