

Zeynep AYKIN YİĞMAN¹

1. Giriş

Ağrı, organizmayı yaklaşıma olana veya devam eden doku hasarı hakkında uyarıcı, koruyucu bir mekanizma işlevi gören, hoş olmayan duyusal, bilişsel veya duygusal deneyimlerin karmaşık bir kümesidir. Ağrı, süreye (akut ve kronik), lokasyona (yüzeysel veya derin; deri, kemik/eklem, kas veya iç organlar) ve nedene (inflamatuar, nöropatik) göre kategorize edilebilir (1). Genel olarak, primer afferent nöronlarda meydana gelen aktiviteler ağrı deneyiminin temelini oluşturur. Buna bağlı olarak, primer afferentler (duyu nöronları) ağrı mekanizmalarını anlamada ve ağrıyı yönetmede kilit oyunculardır. Ağrı oldukça bireysel ve özneldir. Nosisepsyonun ağrı algısına dönüştürülmesi beklenen ile şiddetlenebilir. Ağrı algısı stres tarafından artabilir veya tehlike anınlardaki savaş-kaç tepkisinde olduğu gibi azalması da mümkün olabilir (1). Nihayetinde ağrı, işlev bozukluğuna, fiziksel semptomlara, bilişsel bozukluklara veya duygusal tepkilere neden olabilir. Daha da önemlisi, kronikleşen ağrı hastaların hem günlük yaşam aktivitelerini hem de yaşam kalitesini olumsuz etkiler ve uzun süreli disabilitenin en sık nedenidir (2).

Ağrıyı sınırlandırmanın birçok yolu (kaynaklandığı bölge, fizyolojik mekanizma veya süre

gibi) vardır. Ağrı mekanizmasına (patogenezine göre) göre nosiseptif ve nörojenik ağrı olarak ikiye ayrılmaktadır (2). Nosiseptif ağrı, zararlı stimülasyon veya doku iltihabı/yaralanmasından kaynaklanır. Nöropatik ağrı, nosiseptif sistemin nöronlarının kendisinde meydana gelen hasar sonucunda gelişir ve nedenleri arasında sinir hasarı, metabolik hastalıklar (örneğin, diabetes mellitus) ve herpes zoster bulunur. Nöropatik ağrı zararlı doku uyarımı sinyali vermez, genellikle anormal (yanma veya elektriksel karakter) hissedilir ve kalıcı veya kısa ataklar halinde ortaya çıkabilir (trigeminal nevralji gibi). Hiperaljezi (ağrılı uyarana verilen aşırı ağrı cevabı), allodini (normalde ağrı hissi oluşturmayacak uyarınların hasta ağrı oluşturması durumu) veya duyu kaybı ile birlikte olabilir (3). Nöropatik ağrı mekanizmaları kısmen nosiseptif ağrınınkinden farklıdır.

2. Periferik Ağrı Mekanizmaları

2.1. Bir Ağrı Uyarısı Sonrası Nosiseptif Süreç

Nosisepsyon, zararlı/agrılı uyarılardan kaynaklanan doku hasarı hakkındaki bilgilerin algılandığı ve beyne iletiliği sınırsız süreçtir (1, 4). Ço-

¹ Uzm. Dr., Mamak Devlet Hastanesi, Fiziksel Tıp ve Rehabilitasyon Kliniği, zynpaykn@gmail.com

KAYNAKLAR

1. Dubin AE, Patapoutian A. Nociceptors: the sensors of the pain pathway. *The Journal of clinical investigation.* 2010;120(11):3760-72. doi:10.1172/JCI42843
2. Anwar K. Pathophysiology of pain. *Disease-a-month.* 2016;9(62):324-9. doi: 10.1016/j.disamonth.2016.05.015
3. Gold MS, Gebhart GF. Nociceptor sensitization in pain pathogenesis. *Nature medicine.* 2010;16(11):1248-57. doi: 10.1038/nm.2235
4. Garland EL. Pain processing in the human nervous system: a selective review of nociceptive and bio-behavioral pathways. *Primary Care: Clinics in Office Practice.* 2012;39(3):561-71. doi: 10.1016/j.pop.2012.06.013
5. Kruger L, Kavookjian AM, Kumazawa T, et al. Nociceptor structural specialization in canine and rodent testicular "free" nerve endings. *Journal of Comparative Neurology.* 2003;463(2):197-211. doi:10.1002/cne.10754
6. Basbaum AI, Bautista DM, Scherrer G, et al. Cellular and molecular mechanisms of pain. *Cell.* 2009;139(2):267-84. doi:10.1016/j.cell.2009.09.028
7. Cohen SP, Mao J. Neuropathic pain: mechanisms and their clinical implications. *Bmj.* 2014;348. doi:10.1136/bmj.f7656
8. Woolf CJ, Ma Q. Nociceptors—noxious stimulus detectors. *Neuron.* 2007;55(3):353-64. doi:10.1016/j.neuron.2007.07.016
9. Costigan M, Scholz J, Woolf CJ. Neuropathic pain: a maladaptive response of the nervous system to damage. *Annual review of neuroscience.* 2009;32:1. doi: 10.1146/annurev.neuro.051508.135531
10. Al-Chalabi M, Reddy V, Gupta S. Neuroanatomy, spinothalamic tract. 2018.
11. Ossipov MH, Morimura K, Porreca F. Descending pain modulation and chronification of pain. *Current opinion in supportive and palliative care.* 2014;8(2):143. doi: 10.1097/SPC.0000000000000055
12. McGuire C, Boundouki G, Hockley JR, et al. Ex vivo study of human visceral nociceptors. *Gut.* 2018;67(1):86-96. doi: 10.1136/gutjnl-2016-311629
13. Hockley JR, Tranter MM, McGuire C, et al. P2Y receptors sensitize mouse and human colonic nociceptors. *Journal of Neuroscience.* 2016;36(8):2364-76. doi: 10.1523/JNEUROSCI.3369-15.2016
14. Weidner C, Schmelz M, Schmidt R, et al. Functional attributes discriminating mechano-insensitive and mechano-responsive C nociceptors in human skin. *Journal of Neuroscience.* 1999;19(22):10184-90. doi: 10.1523/JNEUROSCI.19-22-10184.1999
15. Thut P, Wrigley D, Gold M. Cold transduction in rat trigeminal ganglia neurons in vitro. *Neuroscience.* 2003;119(4):1071-83. doi: 10.1016/S0306-4522(03)00225-2
16. Vilceanu D, Stucky CL. TRPA1 mediates mechanical currents in the plasma membrane of mouse sensory neurons. *PloS one.* 2010;5(8):e12177. doi: 10.1371/journal.pone.0012177
17. Bevan S, Yeats J. Protons activate a cation conductance in a sub-population of rat dorsal root ganglion neurones. *The Journal of physiology.* 1991;433(1):145-61. doi:10.1113/jphysiol.1991.sp018419
18. Bautista DM, Jordt S-E, Nikai T, et al. TRPA1 mediates the inflammatory actions of environmental irritants and proalgesic agents. *Cell.* 2006;124(6):1269-82. doi: 10.1016/j.cell.2006.02.023
19. Stein C, Clark JD, Oh U, et al. Peripheral mechanisms of pain and analgesia. *Brain research reviews.* 2009;60(1):90-113. doi: 10.1016/j.brainresrev.2008.12.017
20. Levine JD, Alessandri-Haber N. TRP channels: targets for the relief of pain. *Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease.* 2007;1772(8):989-1003. doi: 10.1016/j.bbadi.2007.01.008
21. Linley JE, Rose K, Ooi L, et al. Understanding inflammatory pain: ion channels contributing to acute and chronic nociception. *Pflügers Archiv-European Journal of Physiology.* 2010;459(5):657-69. doi: 10.1007/s00424-010-0784-6
22. Mizumura K, Sugiura T, Katanosaka K, et al. Excitation and sensitization of nociceptors by bradykinin: what do we know? *Experimental brain research.* 2009;196(1):53-65. doi: 10.1007/s00221-009-1814-5
23. Mrozkova P, Spicarova D, Palecek J. Hypersensitivity induced by activation of spinal cord PAR2 receptors is partially mediated by TRPV1 receptors. *PLoS One.* 2016;11(10):e0163991. doi: 10.1371/journal.pone.0163991
24. Jänig W, Grossmann L, Gorodetskaya N. Mechano-and thermosensitivity of regenerating cutaneous afferent nerve fibers. *Experimental brain research.* 2009;196(1):101-14. doi: 10.1007/s00221-008-1673-5
25. Carr RW, Pianova S, Brock JA. The effects of polarizing current on nerve terminal impulses recorded from polymodal and cold receptors in the guinea-pig cornea. *The Journal of general physiology.* 2002;120(3):395-405. doi: 10.1085/jgp.20028628

26. Zhang X-F, Gopalakrishnan M, Shieh C-C. Modulation of action potential firing by iberiotoxin and NS1619 in rat dorsal root ganglion neurons. *Neuroscience*. 2003;122(4):1003-11. doi: 10.1016/j.neuroscience.2003.08.035
27. Catterall WA, Hulme JT, Jiang X, et al. Regulation of sodium and calcium channels by signaling complexes. *Journal of Receptors and Signal Transduction*. 2006;26(5-6):577-98. doi: 10.1080/10799890600915100
28. Gold MS, Gebhart G. Peripheral pain mechanisms and nociceptor sensitization. Bonica's pain management: Lippincott Williams & Wilkins (LWW); 2010. p. 25-34.
29. Pinto V, Derkach VA, Safronov BV. Role of TTX-sensitive and TTX-resistant sodium channels in A δ - and C-fiber conduction and synaptic transmission. *Journal of neurophysiology*. 2008;99(2):617-28. doi: 10.1152/jn.00944.2007
30. Gold MS. Na $^+$ channel blockers for the treatment of pain: context is everything, almost. *Experimental neurology*. 2008;210(1):1. doi: 10.1016/j.expneurol.2007.12.001
31. Djouhri L, Fang X, Okuse K, et al. The TTX-resistant sodium channel Nav1. 8 (SNS/PN3): expression and correlation with membrane properties in rat nociceptive primary afferent neurons. *The Journal of physiology*. 2003;550(3):739-52. doi:10.1113/jphysiol.2003.042127
32. Elliott A, Elliott J. Characterization of TTX-sensitive and TTX-resistant sodium currents in small cells from adult rat dorsal root ganglia. *The Journal of physiology*. 1993;463(1):39-56. doi: 10.1113/jphysiol.1993.sp019583
33. Gold MS, Zhang L, Wrigley DL, et al. Prostaglandin E2 modulates TTX-R I $_{Na}$ in rat colonic sensory neurons. *Journal of Neurophysiology*. 2002;88(3):1512-22. doi: 10.1152/jn.2002.88.3.1512
34. Zimmermann K, Leffler A, Babes A, et al. Sensory neuron sodium channel Nav1. 8 is essential for pain at low temperatures. *Nature*. 2007;447(7146):856-9. doi: 10.1038/nature05880
35. Rush AM, Dib-Hajj SD, Liu S, et al. A single sodium channel mutation produces hyper- or hypoexcitability in different types of neurons. *Proceedings of the National Academy of Sciences*. 2006;103(21):8245-50. doi: 10.1073/pnas.0602813103
36. Wittmack EK, Rush AM, Craner MJ, et al. Fibroblast growth factor homologous factor 2B: association with Nav1. 6 and selective colocalization at nodes of Ranvier of dorsal root axons. *Journal of Neuroscience*. 2004;24(30):6765-75. doi: 10.1523/JNEUROSCI.1628-04.2004
37. Alexandrou AJ, Brown AR, Chapman ML, et al. Subtype-selective small molecule inhibitors reveal a fundamental role for Nav1. 7 in nociceptor electrogenesis, axonal conduction and presynaptic release. *PloS one*. 2016;11(4):e0152405. doi: 10.1371/journal.pone.0152405
38. Dolphin AC. Voltage-gated calcium channels and their auxiliary subunits: physiology and pathophysiology and pharmacology. *The Journal of physiology*. 2016;594(19):5369-90. doi: 10.1113/JP272262
39. Rycroft BK, Vikman KS, Christie MJ. Inflammation reduces the contribution of N-type calcium channels to primary afferent synaptic transmission onto NK1 receptor-positive lamina I neurons in the rat dorsal horn. *The Journal of physiology*. 2007;580(3):883-94. doi:10.1113/jphysiol.2006.125880
40. Schaible H-G, Richter F. Pathophysiology of pain. *Langenbeck's archives of surgery*. 2004;389(4):237-43. doi: 10.1007/s00423-004-0468-9
41. Sandkuhler J. Models and mechanisms of hyperalgesia and allodynia. *Physiological reviews*. 2009;89(2):707-58. doi: 10.1152/physrev.00025.2008
42. Hucho T, Levine JD. Signaling pathways in sensitization: toward a nociceptor cell biology. *Neuron*. 2007;55(3):365-76. doi: 10.1016/j.neuron.2007.07.008
43. Schaible HG, Von Banchet GS, Boettger M, et al. The role of proinflammatory cytokines in the generation and maintenance of joint pain. *Annals of the New York Academy of Sciences*. 2010;1193(1):60-9. doi:10.1111/j.1749-6632.2009.05301.x
44. Üçeyler N, Schäfers M, Sommer C. Mode of action of cytokines on nociceptive neurons. *Experimental brain research*. 2009;196(1):67-78. doi: 10.1007/s00221-009-1755-z
45. Willrich MA, Murray DL, Snyder MR. Tumor necrosis factor inhibitors: clinical utility in autoimmune diseases. *Translational Research*. 2015;165(2):270-82. doi: 10.1016/j.trsl.2014.09.006
46. Denk F, Bennett DL, McMahon SB. Nerve growth factor and pain mechanisms. *Annual review of neuroscience*. 2017;40:307-25. doi: 10.1146/annurev-neuro-072116-031121
47. Lane NE, Schnitzer TJ, Birbara CA, et al. Tanezumab for the treatment of pain from osteoarthritis of the knee. *New England Journal of Medicine*. 2010;363(16):1521-31. doi: 10.1056/NEJMoa0901510
48. Price TJ, Cervero F, Gold MS, et al. Chloride regulation in the pain pathway. *Brain research re*

- views. 2009;60(1):149-70. doi: 10.1016/j.brainresrev.2008.12.015
49. Zhu Y, Lu S, Gold MS. Persistent inflammation increases GABA-induced depolarization of rat cutaneous dorsal root ganglion neurons in vitro. *Neuroscience*. 2012;220:330-40. doi: 10.1016/j.neuroscience.2012.06.025
50. Zhu Y, Dua S, Gold MS. Inflammation-induced shift in spinal GABA signaling is associated with a tyrosine kinase-dependent increase in GABA current density in nociceptive afferents. *Journal of Neurophysiology*. 2012;108(9):2581-93. doi: 10.1152/jn.00590.2012
51. Salvemini D, Doyle T, Kress M, et al. Therapeutic targeting of the ceramide-to-sphingosine 1-phosphate pathway in pain. *Trends in pharmacological sciences*. 2013;34(2):110-8. doi: 10.1016/j.tips.2012.12.001
52. Kelleher JH, Tewari D, McMahon SB. Neurotrophic factors and their inhibitors in chronic pain treatment. *Neurobiology of Disease*. 2017;97:127-38. doi: 10.1016/j.nbd.2016.03.025
53. Gold MS, Caterina M. Molecular biology of the nociceptor/transduction. *Pain: Elsevier Inc.*; 2008. p. 43-73. doi: 10.1016/B978-012370880-9.00141-9
54. Niederberger E, Resch E, Parnham MJ, et al. Drugging the pain epigenome. *Nature Reviews Neurology*. 2017;13(7):434-47. doi: 10.1038/nrneurol.2017.68
55. Ji R-R, Samad TA, Jin S-X, et al. p38 MAPK activation by NGF in primary sensory neurons after inflammation increases TRPV1 levels and maintains heat hyperalgesia. *Neuron*. 2002;36(1):57-68. doi: 10.1016/S0896-6273(02)00908-X
56. Melemedjian OK, Asiedu MN, Tillu DV, et al. IL-6-and NGF-induced rapid control of protein synthesis and nociceptive plasticity via convergent signaling to the eIF4F complex. *Journal of Neuroscience*. 2010;30(45):15113-23. doi: 10.1523/JNEUROSCI.3947-10.2010
57. Moy JK, Khoutorsky A, Asiedu MN, et al. The MNK-eIF4E signaling axis contributes to injury-induced nociceptive plasticity and the development of chronic pain. *Journal of Neuroscience*. 2017;37(31):7481-99. doi: 10.1523/JNEUROSCI.0220-17.2017
58. Aley K, Messing RO, Mochly-Rosen D, et al. Chronic hypersensitivity for inflammatory nociceptor sensitization mediated by the ε isozyme of protein kinase C. *Journal of Neuroscience*. 2000;20(12):4680-5. doi: 10.1523/JNEUROSCI.20-12-04680.2000
59. Reichling DB, Levine JD. Critical role of nociceptor plasticity in chronic pain. *Trends in neurosciences*. 2009;32(12):611-8. doi: 10.1016/j.tins.2009.07.007
60. Kim J-YV, Tillu DV, Quinn TL, et al. Spinal dopaminergic projections control the transition to pathological pain plasticity via a D1/D5-mediated mechanism. *Journal of Neuroscience*. 2015;35(16):6307-17. doi: 10.1523/JNEUROSCI.3481-14.2015
61. Joseph EK, Levine J. Hyperalgesic priming is restricted to isolectin B4-positive nociceptors. *Neuroscience*. 2010;169(1):431-5. doi: 10.1016/j.neuroscience.2010.04.082
62. Araldi D, Ferrari LF, Levine JD. Hyperalgesic priming (type II) induced by repeated opioid exposure: maintenance mechanisms. *Pain*. 2017;158(7):1204. doi: 10.1097/j.pain.0000000000000898