

Použitá literatura

1. Bentley, K. W. Sir Robert Robinson—his contribution to alkaloid chemistry. *Nat. Prod. Rep.* **4**, 13–23 (1987).
2. Gulland, J. M. & Robinson, R. CXII.—The morphine group. Part I. A discussion of the constitutional problem. *J. Chem. Soc. Trans.* **123**, 980–998 (1923).
3. *Hodgson, B. *In the arms of morpheus: The tragic history of laudanum, morphine, and patent medicines.* (Firefly Books Limited, 2001).
4. *Remington, J. P. *Remington: The science and practice of pharmacy.* vol. 1 (Lippincott Williams & Wilkins, 2006).
5. *Wink, M. & Van Wyk, B.-E. *Mind-altering and poisonous plants of the world.* (Timber Press, 2008).
6. *Sumner, J. *The natural history of medicinal plants.* (Timber press, 2000).
7. Blakemore, P. R. & White, J. D. Morphine, the Proteus of organic molecules. *Chem. Commun.* 1159–1168 (2002).
8. *Davenport-Hines, R. *The pursuit of oblivion: A global history of narcotics.* (WW Norton & Company, 2003).
9. *Trease, G. E. *Pharmacy in history.* vol. 784 (Baillière, Tindall and Cox, 1964).
10. *Michael J. Brownstein. A brief history of opiates, opioid peptides, and opioid receptors. *Proc. Natl. Acad. Sci. U. S. A.* **90**, 5391–5393 (1993).
11. *Serturmer, F. W. Darstellung der reinen Mohnsaure (Opiumsaeure) nebst einer chemischen Untersuchung des Opiums mit vorzuglicher Hinsicht auf einen darin neu entdeckten Stoff und die darin gehorigen Bemerkungen. *Trommsdorffs J. der Pharm.* **14**, 47–98 (1805).
12. *Ebadi, M. *Pharmacodynamic basis of herbal medicine.* (CRC press, 2006).
13. Max, M.. World Health Organization cancer pain relief program: Network news. *Journal of Pain and Symptom Management* **1**, 53–57 (1986).
14. Ruiz-Garcia, V. & Lopez-Briz, E. Morphine remains gold standard in breakthrough cancer pain. *Bmj* **337**, a3104 (2008).
15. Stein, C., Schäfer, M. & Machelska, H. Why is morphine not the ultimate analgesic and what

- can be done to improve it? *J. Pain* **1**, 51–56 (2000).
16. Ventafridda, V., Ripamonti, C., Bianchi, M., Sbanotto, A. & De Conno, F. A randomized study on oral administration of morphine and methadone in the treatment of cancer pain. *J. Pain Symptom Manage.* **1**, 203–207 (1986).
 17. Hanks, G. W. Antiemetics for terminal cancer patients. *Lancet (London, England)* **319**, 1410 (1982).
 18. Ventafridda, V., Oliveri, E., Caraceni, A., Spoldi, E., De Conno, F., Saita, L. & Ripamonti, C. A retrospective study on the use of oral morphine in cancer pain. *J. Pain Symptom Manage.* **2**, 77–81 (1987).
 19. *Twycross, R. G. & Lack, S. A. *Control of alimentary symptoms in far advanced cancer.* (Churchill Livingstone, 1986).
 20. Sjøgren, P., Banning, A. M., Christensen, C. B. & Pedersen, O. Continuous reaction time after single dose, long-term oral and epidural opioid administration. *Eur. J. Anaesthesiol.* **11**, 95–100 (1994).
 21. Bruera, E., Macmillan, K., Hanson, J. & MacDonald, R. N. The cognitive effects of the administration of narcotic analgesics in patients with cancer pain. *Pain* **39**, 13–16 (1989).
 22. Vainio, A., Rosenberg, P., Kalso, E., Ollila, J. & Matikainen, E. Driving ability in cancer patients receiving long-term morphine analgesia. *Lancet* **346**, 667–670 (1995).
 23. Sjøgren, P. & Banning, A. Pain, sedation and reaction time during long-term treatment of cancer patients with oral and epidural opioids. *Pain* **39**, 5–11 (1989).
 24. Sjøgren, P., Banning, A., Larsen, T. K., Sørensen, C. G. & Jansen, E. C. Postural stability during long-term treatment of cancer patients with epidural opioids. *Acta Anaesthesiol. Scand.* **34**, 410–412 (1990).
 25. Sjøgren, P. & Eriksen, J. Opioid toxicity. *Curr. Opin. Anaesthesiol.* **7**, 465–469 (1994).
 26. Ripamonti, C. & Bruera, E. CNS adverse effects of opioids in cancer patients. *CNS Drugs* **8**, 21–37 (1997).
 27. Bruera, E., Brenneis, C., Paterson, A. H. & MacDonald, R. N. Use of methylphenidate as an adjuvant to narcotic analgesics in patients with advanced cancer. *J. Pain Symptom Manage.* **4**, 3–6 (1989).

28. Paix, A., Coleman, A., Lees, J., Grigson, J., Brooksbank, M., Thorne, D. and Ashby, M. Subcutaneous fentanyl and sufentanil infusion substitution for morphine intolerance in cancer pain management. *PAIN*® **63**, 263–269 (1995).
29. Caraceni, A., Martini, C., De Conno, F. & Ventafridda, V. Organic brain syndromes and opioid administration for cancer pain. *J. Pain Symptom Manage.* **9**, 527–533 (1994).
30. Rane, A., Säwe, J., Dahlström, B., Paalzow, L. & Kager, L. Pharmacological treatment of cancer pain with special reference to the oral use of morphine. *Acta Anaesthesiol. Scand.* **26**, 97–103 (1982).
31. *Bodnar, R. J. & Klein, G. E. Endogenous opiates and behavior: 2005. *Peptides* **27**, 3391–3478 (2006).
32. Tsou, K. & Jang, C. S. Studies on the site of analgesic action of morphine by intracerebral micro-injection. *Sci. Sin.* **13**, 1099–1109 (1964).
33. *Stein, C. & Machelska, H. Modulation of peripheral sensory neurons by the immune system: implications for pain therapy. *Pharmacol. Rev.* **63**, 860–881 (2011).
34. *Zöllner, C. & Stein, C. Opioids. in *analgesia* 31–63 (Springer, 2006).
35. Pert, C. B. & Snyder, S. H. Opiate receptor: demonstration in nervous tissue. *Science* (80-). **179**, 1011–1014 (1973).
36. Terenius, L. Stereospecific interaction between narcotic analgesics and a synaptic plasma membrane fraction of rat cerebral cortex. *Acta Pharmacol. Toxicol. (Copenh).* **32**, 317–320 (1973).
37. Wittert, G., Hope, P. & Pyle, D. Tissue distribution of opioid receptor gene expression in the rat. *Biochem. Biophys. Res. Commun.* **218**, 877–881 (1996).
38. Villemagne, P. S., Dannals, R. F., Ravert, H. T. & Frost, J. J. PET imaging of human cardiac opioid receptors. *Eur. J. Nucl. Med. Mol. Imaging* **29**, 1385–1388 (2002).
39. *Barry, U. & Zuo, Z. Opioids: old drugs for potential new applications. *Curr. Pharm. Des.* **11**, 1343–1350 (2005).
40. Satoh, M., Seki, T. & Minami, M. Opioid receptors. *Tanpakushitsu Kakusan Koso.* **45**, 985–990 (2000).
41. *Katritch, V., Cherezov, V. & Stevens, R. C. Structure-function of the G protein–coupled

- receptor superfamily. *Annu. Rev. Pharmacol. Toxicol.* **53**, (2013).
42. *Waldhoer, M., Bartlett, S. E. & Whistler, J. L. Opioid receptors. *Annu. Rev. Biochem.* **73**, 953–990 (2004).
 43. Martin, W., Eades, C. G., Thompson, Ja., Huppler, R. E. & Gilbert, P. E. The effects of morphine-and nalorphine-like drugs in the nondependent and morphine-dependent chronic spinal dog. *J. Pharmacol. Exp. Ther.* **197**, 517–532 (1976).
 44. Lord, J. A. H., Waterfield, A. A., Hughes, J. & Kosterlitz, H. W. Endogenous opioid peptides: multiple agonists and receptors. *Nature* **267**, 495–499 (1977).
 45. *Stein, C. Opioid Receptors. - PubMed - NCBI. *Annu. Rev. Med.* **67**, 433–451 (2016).
 46. * Quock, R. M., Burkey, T. H., Varga, E., Hosohata, Y., Hosohata, K., Cowell, S. M., Slate, C. A., Ehlert, F. J., Roeske, W. R., & Yamamura, H. I. The δ -opioid receptor: molecular pharmacology, signal transduction, and the determination of drug efficacy. *Pharmacol. Rev.* **51**, 503–532 (1999).
 47. Pogozheva, I. D., Lomize, A. L. & Mosberg, H. I. Opioid receptor three-dimensional structures from distance geometry calculations with hydrogen bonding constraints. *Biophys. J.* **75**, 612–634 (1998).
 48. Minami, M. & Satoh, M. Molecular biology of the opioid receptors: structures, functions and distributions. *Neurosci. Res.* **23**, 121–145 (1995).
 49. Law, P.-Y. & Loh, H. H. Regulation of opioid receptor activities. *J. Pharmacol. Exp. Ther.* **289**, 607–624 (1999).
 50. Chavkin, C., McLaughlin, J. P. & Cerver, J. P. Regulation of opioid receptor function by chronic agonist exposure: constitutive activity and desensitization. *Mol. Pharmacol.* **60**, 20–25 (2001).
 51. *von Zastrow, M., Svingos, A., Haberstock-Debic, H. & Evans, C. Regulated endocytosis of opioid receptors: cellular mechanisms and proposed roles in physiological adaptation to opiate drugs. *Curr. Opin. Neurobiol.* **13**, 348–353 (2003).
 52. *Tedford, H. W. & Zamponi, G. W. Direct G protein modulation of Cav2 calcium channels. *Pharmacol. Rev.* **58**, 837–862 (2006).
 53. *Lüscher, C. & Slesinger, P. A. Emerging roles for G protein-gated inwardly rectifying potassium (GIRK) channels in health and disease. *Nat. Rev. Neurosci.* **11**, 301–315 (2010).

54. *Vanderah, T. W. Delta and kappa opioid receptors as suitable drug targets for pain. *Clin. J. Pain* **26**, 10–15 (2010).
55. Wang, H.-B., Zhao, B., Zhong, Y.-Q., Li, K.-C., Li, Z.-Y., Wang, Q., Lu, Y.-J., Zhang, Z.-N., He, S.-Q., Zheng, H.-C., Wu, S.-X., Hokfelt, T.G.M., Bao, L. & Zhang, X. Coexpression of δ - and μ -opioid receptors in nociceptive sensory neurons. *Proc. Natl. Acad. Sci.* **107**, 13117–13122 (2010).
56. Nockemann, D., Rouault, M., Labuz, D., Hublitz, P., Mcknelly, K., Reis, F.C., Stein, C. & Heppenstall, P.A. The K⁺ channel GIRK2 is both necessary and sufficient for peripheral opioid-mediated analgesia. *EMBO Mol. Med.* **5**, 1263–1277 (2013).
57. Gold, M. S. & Levine, J. D. DAMGO inhibits prostaglandin E₂-induced potentiation of a TTX-resistant Na⁺ current in rat sensory neurons in vitro. *Neurosci. Lett.* **212**, 83–86 (1996).
58. Ingram, S. L. & Williams, J. T. Opioid inhibition of I_h via adenylyl cyclase. *Neuron* **13**, 179–186 (1994).
59. Cai, Q., Qiu, C.-Y., Qiu, F., Liu, T.-T., Qu, Z.-W., Liu, Y.-M. & Hu, W.-P. Morphine inhibits acid-sensing ion channel currents in rat dorsal root ganglion neurons. *Brain Res.* **1554**, 12–20 (2014).
60. Spahn, V., Fischer, O., Endres-Becker, J., Schäfer, M., Stein, C. & Zöllner, C. Opioid withdrawal increases transient receptor potential vanilloid 1 activity in a protein kinase A-dependent manner. *Pain* **154**, 598–608 (2013).
61. Endres-Becker, J., Heppenstall, P. A., Mousa, S. A., Labuz, D., Oksche, A., Schäfer, M., Stein, C., & Zöllner, C. μ -Opioid receptor activation modulates transient receptor potential vanilloid 1 (TRPV1) currents in sensory neurons in a model of inflammatory pain. *Mol. Pharmacol.* **71**, 12–18 (2007).
62. * Williams, J.T., Ingram, S.L., Henderson, G., Chavkin, C., Von Zastrow, M., Schulz, S., Koch, T., Evans, C.J. & Christie, M.J. Regulation of μ -opioid receptors: desensitization, phosphorylation, internalization, and tolerance. *Pharmacol. Rev.* **65**, 223–254 (2013).
63. Basbaum, A. I. The perception of pain, Principles of Neural Science, Edited by Kandel ER, Schwartz JH, Jessell TM. (2000).
64. *Basbaum, A. I., Bautista, D. M., Scherrer, G. & Julius, D. Cellular and Molecular Mechanisms of Pain. *Cell* **139**, 267–284 (2009).
65. Apkarian, A. V., Bushnell, M. C., Treede, R.-D. & Zubieta, J.-K. Human brain mechanisms of

- pain perception and regulation in health and disease. *Eur. J. pain* **9**, 463–484 (2005).
66. *Lipton, P. Ischemic cell death in brain neurons. *Physiol. Rev.* **79**, 1431–1568 (1999).
 67. Meng, F., Li, Y., Chi, W. & Li, J. Morphine preconditioning downregulates MicroRNA-134 expression against oxygen-glucose deprivation injuries in cultured neurons of mice. *J. Neurosurg. Anesthesiol.* **28**, 195–202 (2016).
 68. Martin, J. A., Smith, B. L., Mathews, T. J. & Ventura, S. J. Births and deaths: preliminary data for 1998. (1999).
 69. Lim, Y. J., Zheng, S. & Zuo, Z. Morphine Preconditions Purkinje Cells against Cell Death under in Vitro Simulated Ischemia-Reperfusion Conditions. *Anesthesiology* **100**, 562–568 (2004).
 70. Huh, J., Gross, G. J., Nagase, H. & Liang, B. T. Protection of cardiac myocytes via δ 1-opioid receptors, protein kinase C, and mitochondrial KATP channels. *Am. J. Physiol. Circ. Physiol.* **280**, H377–H383 (2001).
 71. McPherson, B. C. & Yao, Z. Signal transduction of opioid-induced cardioprotection in ischemia-reperfusion. *Anesthesiol. J. Am. Soc. Anesthesiol.* **94**, 1082–1088 (2001).
 72. McPherson, B. C. & Yao, Z. Morphine mimics preconditioning via free radical signals and mitochondrial KATP channels in myocytes. *Circulation* **103**, 290–295 (2001).
 73. Liang, B. T. & Gross, G. J. Direct preconditioning of cardiac myocytes via opioid receptors and KATP channels. *Circ. Res.* **84**, 1396–1400 (1999).
 74. Schultz, J. E. J., Hsu, A. K. & Gross, G. J. Ischemic preconditioning in the intact rat heart is mediated by δ 1-but not μ -or κ -opioid receptors. *Circulation* **97**, 1282–1289 (1998).
 75. *Fanjun, M., Junfa, L., Bingxi, Z. & Fang, J. nPKC ϵ and NMDA receptors participate in neuroprotection induced by morphine pretreatment. *J. Neurosurg. Anesthesiol.* **18**, 119–124 (2006).
 76. Zhao, P., Huang, Y. & Zuo, Z. Opioid preconditioning induces opioid receptor-dependent delayed neuroprotection against ischemia in rats. *J. Neuropathol. Exp. Neurol.* **65**, 945–952 (2006).
 77. Park, D., Jhon, D.-Y., Lee, C. W., Lee, K.-H. & Rhee, S. G. Activation of phospholipase C isozymes by G protein beta gamma subunits. *J. Biol. Chem.* **268**, 4573–4576 (1993).
 78. *Akita, Y. Protein kinase C- ϵ (PKC- ϵ): Its unique structure and function. *J. Biochem.* **132**, 847–

- 852 (2002).
79. Cheung, H. H., Teves, L., Wallace, M. C. & Gurd, J. W. Increased phosphorylation of the NR1 subunit of the NMDA receptor following cerebral ischemia. *J. Neurochem.* **78**, 1179–1182 (2001).
 80. Bickler, P. E., Fahlman, C. S. & Ferriero, D. M. Hypoxia increases calcium flux through cortical neuron glutamate receptors via protein kinase C. *J. Neurochem.* **88**, 878–884 (2004).
 81. Kraft, A. S. & Anderson, W. B. Phorbol esters increase the amount of Ca²⁺, phospholipid-dependent protein kinase associated with plasma membrane. *Nature* **301**, 621–623 (1983).
 82. Katsura, K.-I., Kurihara, J., Kato, H. & Katayama, Y. Ischemic pre-conditioning affects the subcellular distribution of protein kinase C and calcium/calmodulin-dependent protein kinase II in the gerbil hippocampal CA1 neurons. *Neurol. Res.* **23**, 751–754 (2001).
 83. Huang, H., Weng, C., Ou, S. & Hwang, T. Selective subcellular redistributions of protein kinase C isoforms by chemical hypoxia. *J. Neurosci. Res.* **56**, 668–678 (1999).
 84. Liu, C., Peng, Z., Zhang, N., Yu, L., Han, S., Li, D. & Li, J. Identification of differentially expressed microRNAs and their PKC-isoform specific gene network prediction during hypoxic pre-conditioning and focal cerebral ischemia of mice. *J. Neurochem.* **120**, 830–841 (2012).
 85. Chao, D., He, X., Yang, Y., Bazy-Asaad, A., Lazarus, L.H., Balboni, G., Kim, D.H. & Xia, Y. DOR activation inhibits anoxic/ischemic Na⁺ influx through Na⁺ channels via PKC mechanisms in the cortex. *Exp. Neurol.* **236**, 228–239 (2012).
 86. Liu, Y., Li, J., Yang, J., Ji, F., Bu, X., Zhang, N. & Zhang, B. Inhibition of PKC γ membrane translocation mediated morphine preconditioning-induced neuroprotection against oxygen-glucose deprivation in the hippocampus slices of mice. *Neurosci. Lett.* **444**, 87–91 (2008).
 87. Ma, M.-C., Qian, H., Ghassemi, F., Zhao, P. & Xia, Y. Oxygen-sensitive δ -opioid receptor-regulated survival and death signals novel insights into neuronal preconditioning and protection. *J. Biol. Chem.* **280**, 16208–16218 (2005).
 88. *Chen, Y. M., He, X. Z., Wang, S. M. & Xia, Y. δ -Opioid Receptors, microRNAs, and Neuroinflammation in Cerebral Ischemia/Hypoxia. *Front. Immunol.* **11**, 1–11 (2020).
 89. Guo, L., Zhao, Y., Yang, S., Zhang, H. & Chen, F. An integrated analysis of miRNA, lncRNA, and mRNA expression profiles. *Biomed Res. Int.* **2014**, (2014).
 90. Friedländer, M.R., Lizano, E., Houben, A.J., Bezdan, D., Báñez-Coronel, M., Kudla, G., Mateu-

- Huertas, E., Kagerbauer, B., González, J., Chen, K.C., Leproust, E.M., Martí, E. & Estivill, X. Evidence for the biogenesis of more than 1,000 novel human microRNAs. *Genome Biol.* **15**, 1–17 (2014).
91. *Bartel, D. P. MicroRNAs: target recognition and regulatory functions. *Cell* **136**, 215–233 (2009).
92. Yang, Y., Zhi, F., He, X., Moore, M.L., Kang, X., Chao, D., Wang, R., Kim, D.H. & Xia, Y. δ -opioid receptor activation and microRNA expression of the rat cortex in hypoxia. *PLoS One* **7**, e51524 (2012).
93. *Yang, Y., K Sandhu, H., Zhi, F., Hua, F., Wu, M., & Xia, Y. Effects of hypoxia and ischemia on microRNAs in the brain. *Curr. Med. Chem.* **22**, 1292–1301 (2015).
94. *Nallamshetty, S., Chan, S. Y. & Loscalzo, J. Hypoxia: a master regulator of microRNA biogenesis and activity. *Free Radic. Biol. Med.* **64**, 20–30 (2013).
95. Bardua, M., Haftmann, C., Durek, P., Westendorf, K., Buttgereit, A., Tran, C.L., Mcgrath, M., Weber, M., Lehmann, K., Addo, R.K., Heinz, G.A., Stittrich, A.-B., Maschmeyer, P., Radbruch, H., Lohoff, M., Chang, H.-D., Radbruch, A. & Mashreghi, M.-F. MicroRNA-31 reduces the motility of proinflammatory T helper 1 lymphocytes. *Front. Immunol.* **9**, 2813 (2018).
96. Johansson, A., Nyberg, W.A., Sjöstrand, M., Moruzzi, N., Bergman, P., Khademi, M., Andersson, M., Piehl, F., Berggren, P.-O., Covacu, R., Jagodic, M. & Espinosa, A. miR-31 regulates energy metabolism and is suppressed in T cells from patients with Sjögren's syndrome. *Eur. J. Immunol.* **49**, 313–322 (2019).
97. Granger, D. N. & Kvietys, P. R. Reperfusion injury and reactive oxygen species: the evolution of a concept. *Redox Biol.* **6**, 524–551 (2015).
98. Xing, B., Chen, H., Zhang, M., Zhao, D., Jiang, R., Liu, X. & Zhang, S. Ischemic postconditioning inhibits apoptosis after focal cerebral ischemia/reperfusion injury in the rat. *Stroke* **39**, 2362–2369 (2008).
99. Olianas, M. C., Dedoni, S. & Onali, P. Regulation of PI3K/Akt signaling by N-desmethylclozapine through activation of δ -opioid receptor. *Eur. J. Pharmacol.* **660**, 341–350 (2011).
100. Lv, M.-R., Li, B., Wang, M.-G., Meng, F.-G., Yu, J.-J., Guo, F. & Li, Y. Activation of the PI3K-Akt pathway promotes neuroprotection of the δ -opioid receptor agonist against cerebral ischemia-reperfusion injury in rat models. *Biomed. Pharmacother.* **93**, 230–237 (2017).

101. Glowinski, J., Marin, P., Tence, M., Stella, N., Giaume, C. & Premont, J. Glial receptors and their intervention in astrocyto–astrocytic and astrocyto–neuronal interactions. *Glia* **11**, 201–208 (1994).
102. *Danbolt, N. C., Furness, D. N. & Zhou, Y. Neuronal vs glial glutamate uptake: resolving the conundrum. *Neurochem. Int.* **98**, 29–45 (2016).
103. *Coyle, J. T. & Puttfarcken, P. Oxidative stress, glutamate, and neurodegenerative disorders. *Science (80-.).* **262**, 689–695 (1993).
104. *Belov Kirdajova, D., Kriska, J., Tureckova, J. & Anderova, M. Ischemia-Triggered Glutamate Excitotoxicity From the Perspective of Glial Cells. *Front. Cell. Neurosci.* **14**, 1–27 (2020).
105. *Schousboe, A. & Waagepetersen, H. S. Role of astrocytes in glutamate homeostasis: implications for excitotoxicity. *Neurotox. Res.* **8**, 221–225 (2005).
106. Gupta, K., Hardingham, G. E. & Chandran, S. NMDA receptor-dependent glutamate excitotoxicity in human embryonic stem cell-derived neurons. *Neurosci. Lett.* **543**, 95–100 (2013).
107. Girling, K.D., Demers, M.-J., Laine, J., Zhang, S., Wang, Y.T. & Graham, R.K. Activation of caspase-6 and cleavage of caspase-6 substrates is an early event in NMDA receptor–mediated excitotoxicity. *J. Neurosci. Res.* **96**, 391–406 (2018).
108. Warren, D.E., Bickler, P.E., Clark, J.P., Gregersen, M., Brosnan, H., Mckleroy, W. & Gabatto, P. Hypothermia and rewarming injury in hippocampal neurons involve intracellular Ca²⁺ and glutamate excitotoxicity. *Neuroscience* **207**, 316–325 (2012).
109. Kumagai, A., Sasaki, T., Matsuoka, K., Abe, M., Tabata, T., Itoh, Y., Fuchino, H., Wugangerile, S., Suga, M., Yamaguchi, T., Kawahara, H., Nagaoka, Y., Kawabata, K., Furue, M.K. & Takemori, H. Monitoring of glutamate-induced excitotoxicity by mitochondrial oxygen consumption. *Synapse* **73**, e22067 (2019).
110. Koriauli, S., Natsvlishvili, N., Barbakadze, T. & Mikeladze, D. Knockdown of interleukin-10 induces the redistribution of sigma1-receptor and increases the glutamate-dependent NADPH-oxidase activity in mouse brain neurons. *Biol. Res.* **48**, 1–5 (2015).
111. Lu, X., Al-Aref, R., Zhao, D., Shen, J., Yan, Y. & Gao, Y. Astrocyte-conditioned medium attenuates glutamate-induced apoptotic cell death in primary cultured spinal cord neurons of rats. *Neurol. Res.* **37**, 803–808 (2015).

112. Zhang, C., Wang, C., Ren, J., Guo, X. & Yun, K. Morphine protects spinal cord astrocytes from glutamate-induced apoptosis via reducing endoplasmic reticulum stress. *Int. J. Mol. Sci.* **17**, (2016).
113. Eriksson, P. S., Hansson, E. & Rönnbäck, L. δ and κ opiate receptors in primary astroglial cultures part II: Receptor sets in cultures from various brain regions and interactions with β -receptor activated cyclic AMP. *Neurochem. Res.* **17**, 545–551 (1992).
114. Suwanjang, W., Holmström, K. M., Chetsawang, B. & Abramov, A. Y. Glucocorticoids reduce intracellular calcium concentration and protects neurons against glutamate toxicity. *Cell Calcium* **53**, 256–263 (2013).
115. Chao, C.-C., Huang, C.-C., Lu, D.-Y., Wong, K.-L., Chen, Y.-R., Cheng, T.-H. & Leung, Y.-M. Ca^{2+} store depletion and endoplasmic reticulum stress are involved in P2X7 receptor-mediated neurotoxicity in differentiated NG108-15 cells. *J. Cell. Biochem.* **113**, 1377–1385 (2012).
116. *Li, Y., Guo, Y., Tang, J., Jiang, J. & Chen, Z. New insights into the roles of CHOP-induced apoptosis in ER stress. *Acta Biochim. Biophys. Sin. (Shanghai)*. **46**, 629–640 (2014).
117. Cunha, D.A., Ladriere, L., Ortis, F., Igoillo-Esteve, M., Gurzov, E.N., Lupi, R., Marchetti, P., Eizirik, D.L. & Cnop, M. Glucagon-like peptide-1 agonists protect pancreatic β -cells from lipotoxic endoplasmic reticulum stress through upregulation of BiP and JunB. *Diabetes* **58**, 2851–2862 (2009).
118. *Ron, D. & Walter, P. Signal integration in the endoplasmic reticulum unfolded protein response. *Nat. Rev. Mol. cell Biol.* **8**, 519–529 (2007).
119. Benjelloun, N., Joly, L., Palmier, B., Plotkine, M. & Charriaut-Marlangue, C. Apoptotic mitochondrial pathway in neurones and astrocytes after neonatal hypoxia-ischaemia in the rat brain. *Neuropathol. Appl. Neurobiol.* **29**, 350–360 (2003).
120. Kim, H.-E., Jiang, X., Du, F. & Wang, X. PHAPI, CAS, and Hsp70 promote apoptosome formation by preventing Apaf-1 aggregation and enhancing nucleotide exchange on Apaf-1. *Mol. Cell* **30**, 239–247 (2008).
121. Lee, J., Kim, M., Park, C., Jung, E., Choi, D., Kim, T., Moon, S. & Park, R. Morphine Prevents Glutamate-Induced Death of Primary Rat Neonatal Astrocytes Through Modulation of Intracellular Redox. *Immunopharmacol. Immunotoxicol.* **26**, 17–28 (2004).
122. Murphy, T. H., Miyamoto, M., Sastre, A., Schnaar, R. L. & Coyle, J. T. Glutamate toxicity in a neuronal cell line involves inhibition of cystine transport leading to oxidative stress. *Neuron* **2**,

- 1547–1558 (1989).
123. Thor, H., Moldéus, P. & Orrenius, S. Metabolic activation and hepatotoxicity: effect of cysteine, N-acetylcysteine, and methionine on glutathione biosynthesis and bromobenzene toxicity in isolated rat hepatocytes. *Arch. Biochem. Biophys.* **192**, 405–413 (1979).
124. Meyer, M., Schreck, R. & Baeuerle, P. A. H₂O₂ and antioxidants have opposite effects on activation of NF-kappa B and AP-1 in intact cells: AP-1 as secondary antioxidant-responsive factor. *EMBO J.* **12**, 2005–2015 (1993).
125. Qian, L., Tan, K.S., Wei, S.-J., Wu, H.-M., Xu, Z., Wilson, B., Lu, R.-B., Hong, J.-S. & Flood, P.M. Microglia-Mediated Neurotoxicity Is Inhibited by Morphine through an Opioid Receptor-Independent Reduction of NADPH Oxidase Activity. *J. Immunol.* **179**, 1198–1209 (2007).
126. Stefano, G. B., Zhu, W., Cadet, P., Bilfinger, T. V & Mantione, K. MORPHINE ENHANCES NITRIC OXIDE RELEASE IN THE. *J. Physiol. Pharmacol.* **55**, 279–288 (2004).
127. Pak, T., Cadet, P., Mantione, K. J. & Stefano, G. B. Morphine via nitric oxide modulates β -amyloid metabolism: A novel protective mechanism for Alzheimer's disease. *Med. Sci. Monit.* **11**, 357–366 (2005).
128. Singhal, P. C., Reddy, K., Franki, N., Sanwal, V. & Gibbons, N. Morphine induces splenocyte apoptosis and enhanced mRNA expression of cathepsin-B. *Inflammation* **21**, 609–617 (1997).
129. Sei, Y., Yoshimoto, K., McIntyre, T., Skolnick, P. & Arora, P. K. Morphine-induced thymic hypoplasia is glucocorticoid-dependent. *J. Immunol.* **146**, 194–198 (1991).
130. Razaq, M., Balicas, M. & Mankan, N. Use of hydromorphone (Dilaudid) and morphine for patients with hepatic and renal impairment. *Am. J. Ther.* **14**, 414–416 (2007).
131. Jaume, M., Jacquet, S., Cavallès, P., Macé, G., Stephan, L., Blanpied, C., Demur, C., Brousset, P. & Dietrich, G. Opioid receptor blockade reduces Fas-induced hepatitis in mice. *Hepatology* **40**, 1136–1143 (2004).
132. Atici, S., Cinel, L., Cinel, I., Doruk, N., Aktekin, M., Akca, A., Camdeviren, H. & Oral, U. Opioid neurotoxicity: Comparison of morphine and tramadol in an experimental model. *Int. J. Neurosci.* **114**, 1001–1011 (2004).
133. *Hodgson, P. S., Neal, J. M., Pollock, J. E. & Liu, S. S. The neurotoxicity of drugs given intrathecally (Spinal). *Anesth. Analg.* **88**, 797–809 (1999).
134. *Yuan, J. & Yankner, B. A. Apoptosis in the nervous system. *Nature* **407**, 802–809 (2000).

135. McArthur, K., Whitehead, L.W., Heddlestone, J.M., Li, L., Padman, B.S., Oorschot, V., Geoghegan, N.D., Chappaz, S., Davidson, S., San Chin, H., Lane, R.M., Dramicanin, M., Saunders, T.L., Sugiana, C., Lessene, R., Osellame, L.D., Chew, T.-L., Dewson, G., Lazarou, M., Ramm, G., Lessene, G., Ryan, M.T., Rogers, K.L., Van Delft, M.F. & Kile, B.T. BAK/BAX macropores facilitate mitochondrial herniation and mtDNA efflux during apoptosis. *Science (80-)*. **359**, (2018).
136. Singhal, P. C., Sharma, P., Kapasi, A. A., Reddy, K., Franki, N., & Gibbons, N. Morphine enhances macrophage apoptosis. *J. Immunol.* **160**, 1886–1893 (1998).
137. Toshiyuki, M. & Reed, J. C. Tumor suppressor p53 is a direct transcriptional activator of the human bax gene. *Cell* **80**, 293–299 (1995).
138. Miyashita, T., Krajewski, S., Krajewska, M., Wang, H. G., Lin, H. K., Liebermann, D. A., Hoffman, B., & Reed, J. C. Tumor suppressor p53 is a regulator of bcl-2 and bax gene expression in vitro and in vivo. *Oncogene* **9**, 1799–1805 (1994).
139. Stefano, G. B., Liu, Y. & Goligorsky, M. S. Cannabinoid receptors are coupled to nitric oxide release in invertebrate immunocytes, microglia, and human monocytes. *J. Biol. Chem.* **271**, 19238–19242 (1996).
140. Joshi, J. C., Ray, A. & Gulati, K. Effects of morphine on stress induced anxiety in rats: role of nitric oxide and Hsp70. *Physiol. Behav.* **139**, 393–396 (2015).
141. *Brüne, B. Nitric oxide: NO apoptosis or turning it ON? *Cell Death Differ.* **10**, 864–869 (2003).
142. Yin, D., Mufson, R. A., Wang, R. & Shi, Y. Fas-mediated cell death promoted by opioids. *Nature* **397**, 218 (1999).
143. *Wajant, H. The Fas signaling pathway: more than a paradigm. *Science (80-)*. **296**, 1635–1636 (2002).
144. Chen, L. & Marine, L.-Y. M. H. Sustained potentiation of NMDA receptor-mediated glutamate responses through activation of protein kinase C by a μ opioid. *Neuron* **7**, 319–326 (1991).
145. Zeitz, K. P., Malmberg, A. B., Gilbert, H. & Basbaum, A. I. Reduced development of tolerance to the analgesic effects of morphine and clonidine in PKC γ mutant mice. *Pain* **94**, 245–253 (2001).
146. Mao, J., Sung, B., Ji, R. R. & Lim, G. Neuronal apoptosis associated with morphine tolerance: Evidence for an opioid-induced neurotoxic mechanism. *J. Neurosci.* **22**, 7650–7661 (2002).

147. Fjellidal, M. F., Hadera, M. G., Kongstorp, M., Austdal, L. P. E., Šulović, A., Andersen, J. M., & Paulsen, R. E. Opioid receptor-mediated changes in the NMDA receptor in developing rat and chicken. *Int. J. Dev. Neurosci.* **78**, 19–27 (2019).
148. Terman, G. W., Drake, C. T., Simmons, M. L., Milner, T. A. & Chavkin, C. Opioid modulation of recurrent excitation in the hippocampal dentate gyrus. *J. Neurosci.* **20**, 4379–4388 (2000).
149. *Martinez Jr, J. L. & Derrick, B. E. Long-term potentiation and learning. *Annu. Rev. Psychol.* **47**, 173–203 (1996).
150. *Morris, B. J. & Johnston, H. M. A role for hippocampal opioids in long-term functional plasticity. *Trends Neurosci.* **18**, 350–355 (1995).
151. Spain, J. W. & Newsom, G. C. Chronic opioids impair acquisition of both radial maze and Y-maze choice escape. *Psychopharmacology (Berl)*. **105**, 101–106 (1991).
152. *Deng, W., Aimone, J. B. & Gage, F. H. New neurons and new memories: how does adult hippocampal neurogenesis affect learning and memory? *Nat. Rev. Neurosci.* **11**, 339–350 (2010).
153. * Aimone, J. B., Li, Y., Lee, S. W., Clemenson, G. D., Deng, W., & Gage, F. H. Regulation and function of adult neurogenesis: from genes to cognition. *Physiol. Rev.* **94**, 991–1026 (2014).
154. *Abrous, D. N., Koehl, M. & Le Moal, M. Adult neurogenesis: from precursors to network and physiology. *Physiol. Rev.* **85**, 523–569 (2005).
155. *Eisch, A. J. & Harburg, G. C. Opiates, psychostimulants, and adult hippocampal neurogenesis: Insights for addiction and stem cell biology. *Hippocampus* **16**, 271–286 (2006).
156. Eisch, A. J., Barrot, M., Schad, C. A., Self, D. W. & Nestler, E. J. Opiates inhibit neurogenesis in the adult rat hippocampus. *Proc. Natl. Acad. Sci.* **97**, 7579–7584 (2000).
157. Harburg, G. C., Hall, F. S., Harrist, A. V., Sora, I., Uhl, G. R. and Eisch, A. J. Knockout of the mu opioid receptor enhances the survival of adult-generated hippocampal granule cell neurons. *Neuroscience* **144**, 77–87 (2007).
158. Kaplan, T. J., Skyers, P. R., Tabori, N. E., Drake, C. T. & Milner, T. A. Ultrastructural evidence for mu-opioid modulation of cholinergic pathways in rat dentate gyrus. *Brain Res.* **1019**, 28–38 (2004).
159. Akaishi, T., Saito, H., Ito, Y., Ishige, K. & Ikegaya, Y. Morphine augments excitatory synaptic transmission in the dentate gyrus through GABAergic disinhibition. *Neurosci. Res.* **38**, 357–363

(2000).

160. Matsumoto, M., Yoshioka, M., Togashi, H., Hirokami, M., Tochihara, M., Ikeda, T., Smith, C. B. and Saito, H. mu-Opioid receptors modulate noradrenaline release from the rat hippocampus as measured by brain microdialysis. *Brain Res.* **636**, 1–8 (1994).
161. Mohapel, P., Leanza, G., Kokaia, M. & Lindvall, O. Forebrain acetylcholine regulates adult hippocampal neurogenesis and learning. *Neurobiol. Aging* **26**, 939–946 (2005).
162. Cooper-Kuhn, C. M., Winkler, J. & Kuhn, H. G. Decreased neurogenesis after cholinergic forebrain lesion in the adult rat. *J. Neurosci. Res.* **77**, 155–165 (2004).
163. Kotani, S., Yamauchi, T., Teramoto, T. & Ogura, H. Pharmacological evidence of cholinergic involvement in adult hippocampal neurogenesis in rats. *Neuroscience* **142**, 505–514 (2006).
164. Rizk, P., Salazar, J., Raisman-Vozari, R., Marien, M., Ruberg, M., Colpaert, F. and Debeir, T. The alpha 2-adrenoceptor antagonist dexefaroxan enhances hippocampal neurogenesis by increasing the survival and differentiation of new granule cells. *Neuropsychopharmacology* **31**, 1146–1157 (2006).
165. Lapchak, P. A., Araujo, D. M. & Collier, B. Regulation of endogenous acetylcholine release from mammalian brain slices by opiate receptors: hippocampus, striatum and cerebral cortex of guinea-pig and rat. *Neuroscience* **31**, 313–325 (1989).
166. Zhang, Y., Xu, C., Zheng, H., Loh, H. H. & Law, P.-Y. Morphine modulates adult neurogenesis and contextual memory by impeding the maturation of neural progenitors. *PLoS One* **11**, e0153628 (2016).
167. Oybon, L., Hjalt, T., Stott, S., Guillemot, F., Li, J.-Y. and Brundin, P. Neurogenin2 directs granule neuroblast production and amplification while NeuroD1 specifies neuronal fate during hippocampal neurogenesis. *PLoS One* **4**, e4779 (2009).
168. Gao, Z., Ure, K., Ables, J. L., Lagace, D. C., Nave, K.-A., Goebbels, S., Eisch, A. J. and Hsieh, J. Neurod1 is essential for the survival and maturation of adult-born neurons. *Nat. Neurosci.* **12**, 1090–1092 (2009).
169. Zheng, H., Zeng, Y., Chu, J., Kam, A. Y., Loh, H. H. and Law, P.-Y. Modulations of NeuroD activity contribute to the differential effects of morphine and fentanyl on dendritic spine stability. *J. Neurosci.* **30**, 8102–8110 (2010).
170. Zheng, H., Zhang, Y., Li, W., Loh, H. H. & Law, P.-Y. NeuroD modulates opioid agonist-selective

- regulation of adult neurogenesis and contextual memory extinction.
Neuropsychopharmacology **38**, 770–777 (2013).
171. Tegeder, I., Grösch, S., Schmidtko, A., Häussler, A., Schmidt, H., Niederberger, E., Scholich, K., & Geisslinger, G. G protein-independent G1 cell cycle block and apoptosis with morphine in adenocarcinoma cells: involvement of p53 phosphorylation. *Cancer Res.* **63**, 1846–1852 (2003).
172. Yeager, M. P. & Colacchio, T. A. Effect of morphine on growth of metastatic colon cancer in vivo. *Arch. Surg.* **126**, 454–456 (1991).
173. Hatzoglou, A., Bakogeorgou, E. & Castanas, E. The antiproliferative effect of opioid receptor agonists on the T47D human breast cancer cell line, is partially mediated through opioid receptors. *Eur. J. Pharmacol.* **296**, 199–207 (1996).
174. Mathew, B., Lennon, F. E., Siegler, J., Gerhold, L., Mambetsariev, N., Moreno-Vinasco, L., Garcia, J. G. N., Salgia, R., Moss, J., & Singleton, P. Abstract C78: The mu opioid receptor regulates Lewis lung carcinoma tumor growth and metastasis. (2009).
175. Lin, X., Wang, Y.-J., Li, Q., Hou, Y.-Y., Hong, M.-H., Cao, Y.-L., Chi, Z.-Q. and Liu, J.-G. Chronic high-dose morphine treatment promotes SH-SY5Y cell apoptosis via c-Jun N-terminal kinase-mediated activation of mitochondria-dependent pathway. *FEBS J.* **276**, 2022–2036 (2009).
176. Zagon, I. S. & McLaughlin, P. J. Opioids and the apoptotic pathway in human cancer cells. *Neuropeptides* **37**, 79–88 (2003).
177. Hatsukari, I., Hitosugi, N., Ohno, R. I. E., Hashimoto, K., Nakamura, S., Satoh, K., Nagasaka, H., Matsumoto, I., & Sakagami, H. Induction of apoptosis by morphine in human tumor cell lines in vitro. *Anticancer Res.* **27**, 857–864 (2007).

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