

Resumen

Abstract

Bibliography

- [1] H. J. Kloosterboer. Tibolone: A steroid with a tissue-specific mode of action. In *Journal of Steroid Biochemistry and Molecular Biology*, volume 76, pages 231–238, 2001.
- [2] Kazuhiro Takuma, Akemichi Baba, and Toshio Matsuda. Astrocyte apoptosis: Implications for neuroprotection. *Progress in Neurobiology*, 72:111–127, 2004.
- [3] Sofie C. Lange, Lasse K. Bak, Helle S. Waagepetersen, Arne Schousboe, and Michael D. Norenberg. Primary cultures of astrocytes: Their value in understanding astrocytes in health and disease. *Neurochemical Research*, 37:2569–2588, 2012.
- [4] Harold K Kimelberg. Functions of Mature Mammalian Astrocytes: A Current View. *The Neuroscientist*, 16(1):79–106, feb 2010.
- [5] Nicola J Allen and Ben Barres. Neuroscience: Glia - more than just brain glue. *Nature*, 457(7230):675–677, 2009.
- [6] Michael M Halassa and Philip G Haydon. Integrated brain circuits: astrocytic networks modulate neuronal activity and behavior. *Annual review of physiology*, 72(2):335–355, 2010.
- [7] Christian Giaume, Annette Koulakoff, Lisa Roux, David Holcman, and Nathalie Rouach. Astroglial networks: a step further in neuroglial and gliovascular interactions. *Nature reviews. Neuroscience*, 11(fEbRuARy):87–99, 2010.
- [8] Cora H. Nijboer, Cobi J. Heijnen, Vincent Degos, Hanneke L M Willemsen, Pierre Gressens, and Annemieke Kavelaars. Astrocyte GRK2 as a novel regulator of glutamate transport and brain damage. *Neurobiology of Disease*, 54:206–215, 2013.
- [9] Ben Barres. The mystery and magic of glia: a perspective on their roles in health and disease. *Neuron*, 60(3):430–40, nov 2008.
- [10] Jun Shen. Modeling the glutamate-glutamine neurotransmitter cycle. *Frontiers in Neuroenergetics*, 5(JAN):1–13, 2013.
- [11] Francesco Petrelli and Paola Bezzi. Novel insights into gliotransmitters. *Current Opinion in Pharmacology*, 26(Table 1):138–145, 2016.

-
- [12] Andrea R Durrant and Uriel Heresco-Levy. D-Serine in Neuropsychiatric Disorders: New Advances. *Advances in Psychiatry*, 2014:1–16, 2014.
 - [13] Tunahan Cakir, Selma Alsan, Hale Saybaşılı, Ata Akin, and Kutlu O Ulgen. Reconstruction and flux analysis of coupling between metabolic pathways of astrocytes and neurons: application to cerebral hypoxia. *Theoretical biology & medical modelling*, 4(1):48, 2007.
 - [14] Stephen P. Raps, James C K Lai, Leif Hertz, and Arthur J L Cooper. Glutathione is present in high concentrations in cultured astrocytes but not in cultured neurons. *Brain Research*, 493(2):398–401, 1989.
 - [15] Mithilesh Kumar Jha, Dong Ho Park, Hyun Kook, In-Kyu Lee, Won-Ha Lee, and Kyoungso Suk. Metabolic Control of Glia-Mediated Neuroinflammation. *Current Alzheimer research*, 13(4):387–402, 2016.
 - [16] Igor Allaman, Mireille Bélanger, and Pierre J. Magistretti. Astrocyte–neuron metabolic relationships: for better and for worse. *Trends in Neurosciences*, 34(2):76–87, feb 2011.
 - [17] Xue Feng Wang and Max S. Cynader. Astrocytes provide cysteine to neurons by releasing glutathione. *Journal of Neurochemistry*, 74(4):1434–1442, 2000.
 - [18] Nicholas J Maragakis and Jeffrey D Rothstein. Mechanisms of Disease: astrocytes in neurodegenerative disease. *Nature clinical practice. Neurology*, 2(12):679–689, 2006.
 - [19] Marco Avila-Rodriguez, Luis Miguel Garcia-Segura, Ricardo Cabezas, Daniel Torrente, Francisco Capani, Janneth Gonzalez, and George E. Barreto. Tibolone protects T98G cells from glucose deprivation. *The Journal of Steroid Biochemistry and Molecular Biology*, 144(8):294–303, 2014.
 - [20] Ghulam Hussain, Florent Schmitt, Jean-Philippe Loeffler, and Jose-Luis Gonzalez de Aguilar. Fattening the brain: a brief of recent research. *Frontiers in cellular neuroscience*, 7(September):144, 2013.
 - [21] Brent E Masel and Douglas S DeWitt. Traumatic brain injury: a disease process, not an event. *Journal of neurotrauma*, 27(8):1529–1540, 2010.
 - [22] Qing Yan. *Systems Biology in Drug Discovery and Development*, volume 662 of *Methods in Molecular Biology*. Humana Press, Totowa, NJ, 2010.
 - [23] Michael T. Fitch and Jerry Silver. CNS injury, glial scars, and inflammation: Inhibitory extracellular matrices and regeneration failure. *Experimental Neurology*, 209(2):294–301, 2008.

- [24] James a. Dowell, Jeffrey a. Johnson, and Lingjun Li. Identification of astrocyte secreted proteins with a combination of shotgun proteomics and bioinformatics. *Journal of Proteome Research*, 8(8):4135–4143, 2009.
- [25] Anna V. Molofsk, Robert Krennick, Erik Ullian, Hui Hsin Tsai, Benjamin Deneen, William D. Richardson, Ben. Barres, and David H. Rowitch. Astrocytes and disease: A neurodevelopmental perspective. *Genes and Development*, 26:891–907, 2012.
- [26] Marta Sidoryk-Wegrzynowicz and Michael Aschner. Role of astrocytes in manganese mediated neurotoxicity. *BMC pharmacology & toxicology*, 14:23, 2013.
- [27] Sunita Gupta, Alecia G. Knight, Shruti Gupta, Jeffrey N. Keller, and Annadora J. Bruce-Keller. Saturated long-chain fatty acids activate inflammatory signaling in astrocytes. *Journal of Neurochemistry*, 120(6):1060–1071, 2012.
- [28] Sudarshana Purkayastha and Dongsheng Cai. Neuroinflammatory basis of metabolic syndrome. *Molecular Metabolism*, 2(4):356–363, 2015.
- [29] Kyoungcho Suk. Proteomics-based discovery of biomarkers and therapeutic targets in neurodegenerative diseases: perspective of microglia and neuroinflammation. *Expert Opinion on Therapeutic Patents*, 16(3):237–247, mar 2006.
- [30] Yoram Vodovotz. Translational systems biology of inflammation and healing. *Wound Repair and Regeneration*, 18(1):3–7, 2010.
- [31] Yoram Vodovotz, Yoram Vodovotz, Marie Csete, Marie Csete, John Bartels, John Bartels, Steven Chang, Steven Chang, Gary An, and Gary An. Translational Systems Biology of Inflammation. *PLoS Comput Biol*, 4(4), 2008.
- [32] Gary An, John Bartels, and Yoram Vodovotz. In silico augmentation of the drug development pipeline: Examples from the study of acute inflammation. *Drug Development Research*, 72(2):187–200, 2011.
- [33] Qi Mi, Nicole Yee-Key Li, Cordelia Ziraldo, Ali Ghuma, Maxim Mikheev, Robert Squires, David O Okonkwo, Katherine Verdolini-Abbott, Gregory Constantine, Gary An, and Yoram Vodovotz. Translational systems biology of inflammation: potential applications to personalized medicine. *Personalized Medicine*, 7(5):549–559, 2010.
- [34] Durgaprasad Laveti, Manoj Kumar, R Hemalatha, Ramakrishna Sistla, V G M Naidu, Venu Talla, Vinod Verma, Navrinder Kaur, and Ravinder Nagpal. Anti-inflammatory treatments for chronic diseases: a review. *Inflammation & allergy drug targets*, 12(5):349–61, 2013.
- [35] Paola Albertazzi, Raffaele Di Micco, and Ettore Zanardi. Tibolone: A review, 1998.

-
- [36] Katarzyna Wojtal, Michał K. Trojnar, and Stanisław J. Czuczwar. Endogenous neuro-protective factors: Neurosteroids, 2006.
- [37] Sudhaa Sharma, Annil Mahajan, Sudesh Kumar, and Vishal R. Tandon. Tibolone: A selective tissue estrogenic activity regulator, 2006.
- [38] Cees J. Timmer, H. A M Verheul, and D. P. Doorstam. Pharmacokinetics of tibolone in early and late postmenopausal women. *British Journal of Clinical Pharmacology*, 54(2):101–106, 2002.
- [39] M A Altinoz, S B Albayrak, A Karasu, P A Sabanci, M Imer, and A Bilir. The effects of tibolone on the human primary glioblastoma multiforme cell culture and the rat C6 glioma model. *Neurol Res*, 31(9):923–927, 2009.
- [40] Helenius J. Kloosterboer. Tissue-selectivity: the mechanism of action of tibolone. *Maturitas*, 48(SUPPL. 1):30–40, aug 2004.
- [41] Ron Edgar, Michael Domrachev, and Alex E Lash. Gene Expression Omnibus: NCBI gene expression and hybridization array data repository. *Nucleic Acids Res*, 30(1):207–210, 2002.
- [42] Ye Zhang, Steven A. Sloan, Laura E. Clarke, Christine Caneda, Colton A. Plaza, Paul D. Blumenthal, Hannes Vogel, Gary K. Steinberg, Michael S B Edwards, Gordon Li, John A. Duncan, Samuel H. Cheshier, Lawrence M. Shuer, Edward F. Chang, Gerald A. Grant, Melanie G Hayden Gephart, and Ben A. Barres. Purification and Characterization of Progenitor and Mature Human Astrocytes Reveals Transcriptional and Functional Differences with Mouse. *Neuron*, 89(1):37–53, 2016.
- [43] Michael Rebhan, Vered Chalifa-Caspi, Jaime Prilusky, and Doron Lancet. GeneCards: integrating information about genes, proteins and diseases. *Trends in Genetics*, 13(4):163, 1997.
- [44] Donna Maglott, Jim Ostell, Kim D Pruitt, and Tatiana Tatusova. Entrez Gene: gene-centered information at NCBI. *Nucleic acids research*, 33(suppl 1):D54—D58, 2005.
- [45] Marc Carlson. *UniProt.ws: R Interface to UniProt Web Services*, 2016.
- [46] Ines Thiele, Neil Swainston, Ronan M T Fleming, Andreas Hoppe, Swagatika Sahoo, Maike K Aurich, Hulda Haraldsdottir, Monica L Mo, Ottar Rolfsson, Miranda D Stobbe, and Others. A community-driven global reconstruction of human metabolism. *Nature biotechnology*, 31(5):419–425, 2013.
- [47] Kelly Botero, Daniel Osorio, Janneth Gonzalez, and Andres Pinzon. *g2f: Find and Fill Gaps in Metabolic Networks*, 2016.

-
- [48] Daniel Osorio, Janneth Gonzalez, and Andres Pinzon. minval: MINimal VALidation for Stoichiometric Reactions, 2016.
 - [49] Ines Thiele and Bernhard Ø Palsson. A protocol for generating a high-quality genome-scale metabolic reconstruction. *Nature Protocols*, 5(1):93–121, jan 2010.
 - [50] Daniel Osorio, Kelly Botero, Janneth Gonzalez, and Andres Pinzon. *exp2flux: Convert Gene EXPression Data to FBA FLUXes*, 2016.
 - [51] Gabriel Gelius-Dietrich, Abdelmoneim Desouki, Claus Fritzscheier, and Martin J Lercher. sybil – Efficient constraint-based modelling in R. *BMC Systems Biology*, 7(1):125, 2013.
 - [52] R Core Team. *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing, Vienna, Austria, 2016.
 - [53] Jeffrey D Orth, Ines Thiele, and B O Palsson. What is flux balance analysis? *Nature Biotechnology*, 28(3):245–248, 2010.
 - [54] Karthik Raman and Nagasuma Chandra. Flux balance analysis of biological systems: Applications and challenges. *Briefings in Bioinformatics*, 10(4):435–449, 2009.
 - [55] M Kanehisa. KEGG: Kyoto Encyclopedia of Genes and Genomes. *Nucleic Acids Research*, 28(1):27–30, jan 2000.
 - [56] M T Fitch and J Silver. Activated macrophages and the blood-brain barrier: inflammation after CNS injury leads to increases in putative inhibitory molecules. *Experimental Neurology*, 148(2):587–603, 1997.
 - [57] R. Ciccarelli, P. Ballerini, G. Sabatino, M. P. Rathbone, M. D’Onofrio, F. Caciagli, and P. Di Iorio. Involvement of astrocytes in purine-mediated reparative processes in the brain. *International Journal of Developmental Neuroscience*, 19(4):395–414, 2001.
 - [58] Mustafa Sertbaş, Kutlu Ülgen, and Tunahan Çakir. Systematic analysis of transcription-level effects of neurodegenerative diseases on human brain metabolism by a newly re-constructed brain-specific metabolic network. *FEBS Open Bio*, 4:542–553, 2014.
 - [59] João V. Sá, Susanne Kleiderman, Catarina Brito, Ursula Sonnewald, Marcel Leist, Ana P. Teixeira, and Paula M. Alves. Quantification of Metabolic Rearrangements During Neural Stem Cells Differentiation into Astrocytes by Metabolic Flux Analysis. *Neurochemical Research*, 2016.
 - [60] Arabinda Das, Naren L. Banik, and Swapam K. Ray. Flavonoids activated caspases for apoptosis in human glioblastoma T98G and U87MG cells but not in human normal astrocytes. *Cancer*, 116(1):164–176, 2010.

- [61] Rupa Bhowmick, Abhishek Subramanian, and Ram Rup Sarkar. Exploring the differences in metabolic behavior of astrocyte and glioblastoma: a flux balance analysis approach. *Systems and Synthetic Biology*, 2015.
- [62] Christelle Le Foll and Barry E Levin. Fatty acid-induced astrocyte ketone production and the control of food intake. *American journal of physiology. Regulatory, integrative and comparative physiology*, page ajpregu.00113.2016, 2016.
- [63] Li Liu, Rebecca Martin, and Christina Chan. Palmitate-activated astrocytes via serine palmitoyltransferase increase BACE1 in primary neurons by sphingomyelinases. *Neurobiology of Aging*, 34(2):540–550, 2013.
- [64] Rafael Rangel-Aldao. The unfolded protein response, inflammation, oscillators, and disease: a systems biology approach. *Endoplasmic Reticulum Stress in Diseases*, 2(1):30–52, 2015.
- [65] Rachel Williams, Cassandra L. Buchheit, Nancy E J Berman, and Steven M. Levine. Pathogenic implications of iron accumulation in multiple sclerosis. *Journal of Neurochemistry*, 120(1):7–25, 2012.
- [66] V Parpura and P G Haydon. Physiological astrocytic calcium levels stimulate glutamate release to modulate adjacent neurons. *Proc.Natl.Acad.Sci.U.S.A*, 97(0027-8424):8629–8634, 2000.
- [67] Leif Hertz, Ralf Dringen, Arne Schousboe, and Stephen R. Robinson. Astrocytes: Glutamate producers for neurons. *Journal of Neuroscience Research*, 57(4):417–428, 1999.
- [68] Yu-Cun Niu, Ren-Nan Feng, Yan Hou, Kang Li, Zhen Kang, Jian Wang, Chang-Hao Sun, and Ying Li. Histidine and arginine are associated with inflammation and oxidative stress in obese women. *British Journal of Nutrition*, 108(01):57–61, 2012.
- [69] Yuan Ti Lee, Cheng Chin Hsu, Meng Hsiao Lin, Keh Sen Liu, and Mei Chin Yin. Histidine and carnosine delay diabetic deterioration in mice and protect human low density lipoprotein against oxidation and glycation. *European Journal of Pharmacology*, 513(1-2):145–150, 2005.
- [70] Dong Ok Son, Hideo Satsu, and Makoto Shimizu. Histidine inhibits oxidative stress- and TNF- α -induced interleukin-8 secretion in intestinal epithelial cells. *FEBS Letters*, 579(21):4671–4677, 2005.
- [71] Morris H Baslow. N -Acetylaspartate in the Vertebrate Brain : Metabolism and Function. 28(6):941–953, 2003.

- [72] Leonard T. Rael, Gregory W. Thomas, Raphael Bar-Or, Michael L. Craun, and David Bar-Or. An anti-inflammatory role for N-acetyl aspartate in stimulated human astroglial cells. *Biochemical and Biophysical Research Communications*, 319(3):847–853, 2004.
- [73] F a Chaudhry, R J Reimer, D Krizaj, D Barber, J Storm-Mathisen, D R Copenhagen, and R H Edwards. Molecular analysis of system N suggests novel physiological roles in nitrogen metabolism and synaptic transmission. *Cell*, 99(7):769–80, 1999.
- [74] Michael Doengi, Daniela Hirnet, Philippe Coulon, Hans-Christian Pape, Joachim W Deitmer, and Christian Lohr. GABA uptake-dependent Ca(2+) signaling in developing olfactory bulb astrocytes. *Proceedings of the National Academy of Sciences of the United States of America*, 106:17570–17575, 2009.
- [75] D. R. Green, L. Galluzzi, and G. Kroemer. Metabolic control of cell death. *Science*, 345(6203):1250256–1250256, 2014.
- [76] Sean Murphy, Brian Pearce, James Jeremy, and Paresh Dandona. Astrocytes as eicosanoid-producing cells. *Glia*, 1(4):241–245, 1988.
- [77] Harshica Fernando, John E. Wiktorowicz, Kizhake V. Soman, Bhupendra S. Kaphalia, M. Firoze Khan, and G. A. Shakeel Ansari. Liver proteomics in progressive alcoholic steatosis. *Toxicology and Applied Pharmacology*, 266(3):470–480, 2013.
- [78] Leif Våremo, Camilla Scheele, Christa Broholm, Adil Mardinoglu, Caroline Kampf, Anna Asplund, Intawat Nookaew, Mathias Uhlén, BenteKlarlund Pedersen, and Jens Nielsen. Proteome- and Transcriptome-Driven Reconstruction of the Human Myocyte Metabolic Network and Its Use for Identification of Markers for Diabetes. *Cell Reports*, 11(6):921–933, 2015.
- [79] Sapar M. Saparov, Kun Liu, Peter Agre, and Peter Pohl. Fast and selective ammonia transport by aquaporin-8. *Journal of Biological Chemistry*, 282(8):5296–5301, 2007.
- [80] Anje a Te Velde, Inge Pronk, Floor de Kort, and Pieter C F Stokkers. Glutathione peroxidase 2 and aquaporin 8 as new markers for colonic inflammation in experimental colitis and inflammatory bowel diseases: an important role for H2O2? *European journal of gastroenterology & hepatology*, 20:555–560, 2008.
- [81] Clemente Landriscina, Gabriele V Gnani, and Ernesto Quaqliariello. Fatty -Acid Biosynthesis Present in Microsomes and Mitochondria of Rat Liver. 196:188–196, 1972.
- [82] Kenji Tamura, Asami Makino, Françoise Hullin-Matsuda, Toshihide Kobayashi, Mutsuo Furihata, Suyoun Chung, Shingo Ashida, Tsuneharu Miki, Tomoaki Fujioka, Taro Shuin, Yusuke Nakamura, and Hidewaki Nakagawa. Novel lipogenic enzyme ELOVL7 is involved in prostate cancer growth through saturated long-chain fatty acid metabolism. *Cancer Research*, 69(20):8133–8140, 2009.

-
- [83] Barbara Ahlemeyer, Stefan Kölker, Yuan Zhu, Georg F. Hoffmann, and Josef Kriegstein. Increase in glutamate-induced neurotoxicity by activated astrocytes involves stimulation of protein kinase C. *Journal of Neurochemistry*, 82(3):504–515, jul 2002.
- [84] Georgia B. Schuller-Levis and Eunkyue Park. Taurine: new implications for an old amino acid. *FEMS Microbiology Letters*, 226(2):195–202, sep 2003.
- [85] D W Russell and K D Setchell. Bile acid biosynthesis. *Biochemistry*, 31(20):4737–49, 1992.
- [86] Nün Amen-Ra. Humans are evolutionarily adapted to caloric restriction resulting from ecologically dictated dietary deprivation imposed during the Plio–Pleistocene period. *Medical Hypotheses*, 66(5):978–984, jan 2006.
- [87] Adam M. Feist and Bernhard O. Palsson. The biomass objective function. *Current Opinion in Microbiology*, 13(3):344–349, 2010.
- [88] Graham A. Colditz, Kathleen M. Egan, and Meir J. Stampfer. Hormone replacement therapy and risk of breast cancer: Results from epidemiologic studies. *American Journal of Obstetrics and Gynecology*, 168(5):1473–1480, may 1993.
- [89] Graham A. Colditz, Susan E. Hankinson, David J. Hunter, Walter C. Willett, JoAnn E. Manson, Meir J. Stampfer, Charles Hennekens, Bernard Rosner, and Frank E. Speizer. The Use of Estrogens and Progestins and the Risk of Breast Cancer in Postmenopausal Women. *New England Journal of Medicine*, 332(24):1589–1593, jun 1995.
- [90] Dominique Pessayre, Alain Berson, Bernard Fromenty, and Abdellah Mansouri. Mitochondria in Steatohepatitis. *Seminars in Liver Disease*, 21(01):057–070, 2001.
- [91] F. Sun, M. L. Xie, L. J. Zhu, J. Xue, and Z. L. Gu. Inhibitory effect of osthole on alcohol-induced fatty liver in mice. *Digestive and Liver Disease*, 41(2):127–133, 2009.
- [92] Marco Avila-Rodriguez, Luis Miguel Garcia-Segura, Oscar Hidalgo-lanussa, Eliana Baez, Janneth Gonzalez, and George E. Barreto. Tibolone protects astrocytic cells from glucose deprivation through a mechanism involving estrogen receptor beta and the upregulation of neuroglobin expression. *Molecular and Cellular Endocrinology*, 433:35–46, 2016.