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Spreading depolarizations : the missing link between migraine and stroke

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LIST OF PUBLICATIONS

Ayata C. Migraine: Treasure hunt in a minefield - exploring migraine with GWAS. *Nat Rev Neurol*. 2016;12(9):496-8.

Chen SP, Ay I, de Moraes AL, Qin T, Zheng Y, Sadeghian H, Oka F, Simon B, Eikermann-Haerter K, Ayata C. Vagus nerve stimulation inhibits cortical spreading depression. *Pain*. 2016;157(4):797-805.

Singhal AB, Maas MB, Goldstein JN, Mills BB, Chen DW, Ayata C, Kacmarek RM, Topcuoglu MA. High-flow oxygen therapy for treatment of acute migraine: A randomized crossover trial. *Cephalalgia*. 2016 May 20. [Epub ahead of print]

Chen SP, Ayata C. Spreading Depression in Primary and Secondary Headache Disorders. *Curr Pain Headache Rep*. 2016;20(7):44.

Seidel JL, Escartin C, Ayata C, Bonvento G, Shuttleworth CW. Multifaceted roles for astrocytes in spreading depolarization: A target for limiting spreading depolarization in acute brain injury? *Glia*. 2016;64(1):5-20.

Chung DY, Oka F, Ayata C. Spreading Depolarizations: A Therapeutic Target Against Delayed Cerebral Ischemia After Subarachnoid Hemorrhage. *J Clin Neurophysiol*. 2016;33(3):196-202.

Boltze J, Wagner DC, Henninger N, Plesnila N, Ayata C. Phase III Preclinical Trials in Translational Stroke Research: Community Response on Framework and Guidelines. *Transl Stroke Res*. 2016;7(4):241-7.

Dreier JP, Fabricius M, Ayata C, Sakowitz OW, William Shuttleworth C, Dohmen C, Graf R, Vajkoczy P, Helbok R, Suzuki M, Schiefecker AJ, Major S, Winkler MK, Kang EJ, Milakara D, Oliveira-Ferreira AI, Reiffurth C, Revankar GS, Sugimoto K, Dengler NF, Hecht N, Foreman B, Feyen B, Kondziella D, Friberg CK, Piilgaard H, Rosenthal ES, Westover MB, Maslarova A, Santos E, Hertle D, Sánchez-Porras R, Jewell SL, Balanço B, Platz J, Hinzman JM, Lückl J, Schoknecht K, Schöll M, Drenckhahn C, Feuerstein D, Eriksen N, Horst V, Bretz JS, Jahnke P, Scheel M, Böhner G, Rostrup E, Pakkenberg B, Heinemann U, Claassen J, Carlson AP, Kowoll CM, Lublinsky S, Chassidim Y, Shelef I, Friedman A, Brinker G, Reiner M, Kirov SA, Andrew RD, Farkas E, Güresir E, Vatter H, Chung LS, Brennan KC, Lieutaud T, Marinesco S, Maas AI, Sahuquillo J, Dahlem MA, Richter F, Herreras O, Boutelle MG, Okonkwo DO, Bullock MR, Witte OW, Martus P, van den Maagdenberg AM, Ferrari MD, Dijkhuizen RM, Shutter LA, Andaluz N, Schulte AP, MacVicar B, Watanabe T, Woitzik J, Lauritzen M, Strong AJ, Hartings JA. Recording, analysis, and interpretation of spreading depolarizations in neurointensive care: Review and recommendations of the COSBID research group. *J Cereb Blood Flow Metab*. 2016 Jun 17 [Epub ahead of print]

Hartings JA, Shuttleworth CW, Kirov SA, Ayata C, Hinzman JM, Foreman B, Andrew RD, Boutelle MG, Brennan KC, Carlson AP, Dahlem MA, Drenckhahn C, Dohmen C, Fabricius M, Farkas E, Feuerstein D, Graf R, Helbok R, Lauritzen M, Major S, Oliveira-Ferreira AI, Richter F, Rosenthal ES, Sakowitz OW, Sánchez-Porrás R, Santos E, Schöll M, Strong AJ, Urbach A, Westover MB, Winkler MK, Witte OW, Woitzik J, Dreier JP. The continuum of spreading depolarizations in acute cortical lesion development: Examining Leão's legacy. *J Cereb Blood Flow Metab.* 2016 Jun 21. [Epub ahead of print]

Oka F, Hoffmann U, Lee JH, Shin HK, Chung DY, Yuzawa I, Chen SP, Atalay YB, Nozari A, Hopson KP, Qin T, Ayata C. Requisite ischemia for spreading depolarization occurrence after subarachnoid hemorrhage in rodents. *J Cereb Blood Flow Metab.* 2016 Jul 18. [Epub ahead of print]

Hoffmann U, Sheng H, Ayata C, Warner DS. Anesthesia in Experimental Stroke Research. *Transl Stroke Res.* 2016;7(5):358-67.

Mawet J, Eikermann-Haerter K, Park KY, Helenius J, Daneshmand A, Pearlman L, Avery R, Negro A, Velioglu M, Arsava EM, Ay H, Ayata C. Sensitivity to acute cerebral ischemic injury in migraineurs: A retrospective case-control study. *Neurology.* 2015;85(22):1945-9.

Eikermann-Haerter K, Lee JH, Yalcin N, Yu ES, Daneshmand A, Wei Y, Zheng Y, Can A, Sengul B, Ferrari MD, van den Maagdenberg AM, Ayata C. Migraine prophylaxis, ischemic depolarizations, and stroke outcomes in mice. *Stroke.* 2015;46(1):229-36.

Shyti R, Eikermann-Haerter K, van Heiningen SH, Meijer OC, Ayata C, Joëls M, Ferrari MD, van den Maagdenberg AM, Tolner EA. Stress hormone corticosterone enhances susceptibility to cortical spreading depression in familial hemiplegic migraine type 1 mutant mice. *Exp Neurol.* 2015;263:214-20.

Haerter F, Simons JC, Foerster U, Moreno Duarte I, Diaz-Gil D, Ganapati S, Eikermann-Haerter K, Ayata C, Zhang B, Blobner M, Isaacs L, Eikermann M. Comparative Effectiveness of Calabadiol and Sugammadex to Reverse Non-depolarizing Neuromuscular-blocking Agents. *Anesthesiology.* 2015 Dec;123(6):1337-49.

Sakadžić S, Mandeville ET, Gagnon L, Musacchia JJ, Yaseen MA, Yucel MA, Lefebvre J, Lesage F, Dale AM, Eikermann-Haerter K, Ayata C, Srinivasan VJ, Lo EH, Devor A, Boas DA. Large arteriolar component of oxygen delivery implies a safe margin of oxygen supply to cerebral tissue. *Nat Commun.* 2014;5:5734.

Ferrari MD, Klever RR, Terwindt GM, Ayata C, van den Maagdenberg AM. Migraine pathophysiology: lessons from mouse models and human genetics. *Lancet Neurol.* 2015;14(1):65-80.

Chen X, Wales P, Quinti L, Zuo F, Moniot S, Herisson F, Rauf NA, Wang H, Silverman RB, Ayata C, Maxwell MM, Steegborn C, Schwarzschild MA, Outeiro TF, Kazantsev AG. The sirtuin-2 inhibitor AK7 is neuroprotective in models of Parkinson's disease but not amyotrophic lateral sclerosis and cerebral ischemia. *PLoS One*. 2015;10(1):e0116919.

Blasi F, Whalen MJ, Ayata C. Lasting pure-motor deficits after focal posterior internal capsule white-matter infarcts in rats. *J Cereb Blood Flow Metab*. 2015;35(6):977-84.

Chaparro RE, Izutsu M, Sasaki T, Sheng H, Zheng Y, Sadeghian H, Qin T, von Bornstadt D, Herisson F, Duan B, Li JS, Jiang K, Pearlstein M, Pearlstein RD, Smith DE, Goldberg ID, Ayata C, Warner DS. Sustained functional improvement by hepatocyte growth factor-like small molecule BB3 after focal cerebral ischemia in rats and mice. *J Cereb Blood Flow Metab*. 2015;35(6):1044-53.

Dilekoz E, Houben T, Eikermann-Haerter K, Balkaya M, Lenselink AM, Whalen MJ, Spijker S, Ferrari MD, van den Maagdenberg AM, Ayata C. Migraine mutations impair hippocampal learning despite enhanced long-term potentiation. *J Neurosci*. 2015;35(8):3397-402.

von Bornstädt D, Houben T, Seidel JL, Zheng Y, Dilekoz E, Qin T, Sandow N, Kura S, Eikermann-Haerter K, Endres M, Boas DA, Moskowitz MA, Lo EH, Dreier JP, Woitzik J, Sakadžić S, Ayata C. Supply-Demand Mismatch Transients in Susceptible Peri-infarct Hot Zones Explain the Origins of Spreading Injury Depolarizations. *Neuron*. 2015;85(5):1117-31.

Blasi F, Herisson F, Wang S, Mao J, Ayata C. Late-onset thermal hypersensitivity after focal ischemic thalamic infarcts as a model for central post-stroke pain in rats. *J Cereb Blood Flow Metab*. 2015;35(7):1100-3.

Sakadžić S, Lee J, Boas DA, Ayata C. High-resolution in vivo optical imaging of stroke injury and repair. *Brain Res*. 2015;1623:174-92.

Wilks MQ, Normandin MD, Yuan H, Cho H, Guo Y, Herisson F, Ayata C, Wooten DW, El Fakhri G, Josephson L. Imaging PEG-like nanoprobes in tumor, transient ischemia, and inflammatory disease models. *Bioconjug Chem*. 2015;26(6):1061-9.

Eikermann-Haerter K, Arbel-Ornath M, Yalcin N, Yu ES, Kuchibhotla KV, Yuzawa I, Hudry E, Willard CR, Klimov M, Keles F, Belcher AM, Sengul B, Negro A, Rosen IA, Arreguin A, Ferrari MD, van den Maagdenberg AM, Bacskaí BJ, Ayata C. Abnormal synaptic Ca(2+) homeostasis and morphology in cortical neurons of familial hemiplegic migraine type 1 mutant mice. *Ann Neurol*. 2015;78(2):193-210.

Ayata C, Lauritzen M. Spreading Depression, Spreading Depolarizations, and the Cerebral Vasculature. *Physiol Rev*. 2015;95(3):953-93.

Buckley EM, Miller BF, Golinski JM, Sadeghian H, McAllister LM, Vangel M, Ayata C, Meehan WP 3rd, Franceschini MA, Whalen MJ. Decreased microvascular cerebral blood flow assessed by diffuse correlation spectroscopy after repetitive concussions in mice. *J Cereb Blood Flow Metab.* 2015;35(12):1995-2000.

Srinivasan VJ, Yu E, Radhakrishnan H, Can A, Klimov M, Leahy C, Ayata C, Eikermann-Haerter K. Micro-heterogeneity of flow in a mouse model of chronic cerebral hypoperfusion revealed by longitudinal Doppler optical coherence tomography and angiography. *J Cereb Blood Flow Metab.* 2015;35(10):1552-60.

Mawet J, Kurth T, Ayata C, Migraine and stroke: In search of shared mechanisms. *Cephalalgia.* 2015; 35(2):165-81.

Lee JH, Zheng Y, von Bornstadt D, Wei Y, Balcioglu A, Daneshmand A, Yalcin N, Yu E, Herisson F, Atalay YB, Kim MH, Ahn YJ, Balkaya M, Sweetnam P, Schueller O, Poyurovsky MV, Kim HH, Lo EH, Furie KL, Ayata C. Selective ROCK2 Inhibition In Focal Cerebral Ischemia. *Ann Clin Transl Neurol.* 2014;1(1):2-14.

Diaz-Gil D, Mueller N, Moreno-Duarte I, Lin H, Ayata C, Cusin C, Cotten JF, Eikermann M. Etomidate and Ketamine: Residual Motor and Adrenal Dysfunction that Persist beyond Recovery from Loss of Righting Reflex in Rats. *Pharmaceuticals (Basel).* 2014 Dec 29;8(1):21-37.

Lu L, Barfejani AH, Qin T, Dong Q, Ayata C, Waeber C. Fingolimod exerts neuroprotective effects in a mouse model of intracerebral hemorrhage. *Brain Res.* 2014;1555:89-96.

Shin HK, Oka F, Kim JH, Atochin D, Huang PL, Ayata C, Endothelial dysfunction abrogates the efficacy of normobaric hyperoxia in stroke. *J Neurosci.* 2014;34(46):15200-7.

Ebrahimkhani MR, Daneshmand A, Mazumder A, Allocca M, Calvo JA, Abolhassani N, Jhun I, Muthupalani S, Ayata C, Samson LD. Aag-initiated base excision repair promotes ischemia reperfusion injury in liver, brain, and kidney. *Proc Natl Acad Sci USA.* 2014;111(45):E4878-86.

Blasi F, Wei Y, Balkaya M, Tikka S, Mandeville JB, Waeber C, Ayata C, Moskowitz MA. Recognition memory impairments after subcortical white matter stroke in mice. *Stroke.* 2014;45(5):1468-73.

Boltze J, Ayata C, Wagner DC, Plesnila N. Preclinical phase III trials in translational stroke research: call for collective design of framework and guidelines. *Stroke.* 2014;45(2):357.

Shin HK, Huang PL, Ayata C. Rho-kinase inhibition improves ischemic perfusion deficit in hyperlipidemic mice. *J Cereb Blood Flow Metab.* 2014;34(2):284-7.

Hoffmann U, Sukhotinsky I, Eikermann-Haerter K, Ayata C. Glucose modulation of spreading depression susceptibility. *J Cereb Blood Flow Metab.* 2013;33(2):191-5.

Seo JH, Miyamoto N, Hayakawa K, Pham LD, Maki T, Ayata C, Kim KW, Lo EH, Arai K. Oligodendrocyte precursors induce early blood-brain barrier opening after white matter injury. *J Clin Invest*. 2013;123(2):782-6.

Lee J, Radhakrishnan H, Wu W, Daneshmand A, Climov M, Ayata C, Boas DA. Quantitative imaging of cerebral blood flow velocity and intracellular motility using dynamic light scattering-optical coherence tomography. *J Cereb Blood Flow Metab*. 2013;33(6):819-25.

Ayata C, Shin HK, Dileköz E, Atochin DN, Kashiwagi S, Eikermann-Haerter K, Huang PL. Hyperlipidemia disrupts cerebrovascular reflexes and worsens ischemic perfusion defect. *J Cereb Blood Flow Metab*. 2013;33(6):954-62.

Hoffmann U, Grosse-Sundrup M, Eikermann-Haerter K, Zaremba S, Ayata C, Zhang B, Ma D, Isaacs L, Eikermann M. Calabadiol: A New Agent to Reverse the Effects of Benzylisoquinoline and Steroidal Neuromuscular-blocking Agents. *Anesthesiology*. 2013;119(2):317-25.

Srinivasan VJ, Mandeville ET, Can A, Blasi F, Climov M, Daneshmand A, Lee JH, Yu E, Radhakrishnan H, Lo EH, Sakadžić S, Eikermann-Haerter K, Ayata C. Multiparametric, longitudinal optical coherence tomography imaging reveals acute injury and chronic recovery in experimental ischemic stroke. *PLoS One*. 2013;8(8):e71478.

Miyamoto N, Pham LD, Hayakawa K, Matsuzaki T, Seo JH, Magnain C, Ayata C, Kim KW, Boas D, Lo EH, Arai K. Age-Related Decline in Oligodendrogenesis Retards White Matter Repair in Mice. *Stroke*. 2013;44(9):2573-2578.

Hoffmann U, Ayata C. Neurovascular coupling during spreading depolarizations. *Acta Neurochir Suppl*. 2013;115:161-5.

Dapul H, Park J, Zhang J, Lee C, Daneshmand A, Lok J, Ayata C, Gray T, Scalzo A, Qiu J, Lo EH, Ph D, Whalen M. Concussive injury before or after controlled cortical impact exacerbates histopathology and functional outcome in a mixed traumatic brain injury model in mice. *J Neurotrauma*. 2013;30(5):382-91.

Koide M, Sukhotinsky I, Ayata C, Wellman GC. Subarachnoid hemorrhage, spreading depolarizations and impaired neurovascular coupling. *Stroke Res Treat*. 2013;2013:819340.

Eikermann-Haerter K, Negro A, Ayata C. Spreading depression and the clinical correlates of migraine. *Rev Neurosci*. 2013;24(4):353-63

Costa C, Tozzi A, Rainero I, Cupini LM, Calabresi P, Ayata C, Sarchielli P. Cortical spreading depression as a target for anti-migraine agents. *J Headache Pain*. 2013;14(1):62.

Ayata C. Spreading depression and neurovascular coupling. *Stroke*. 2013;44(6 Suppl 1):S87-9.

Ayata C. Pearls and pitfalls in experimental models of spreading depression. *Cephalalgia*. 2013;33(8):604-13.

Koide M, Sukhotinsky I, Ayata C, Wellman GC. Subarachnoid hemorrhage, spreading depolarizations and impaired neurovascular coupling. *Stroke Res Treat*. 2013;2013:819340

Yuzawa I, Sakadžić S, Srinivasan VJ, Shin HK, Eikermann-Haerter K, Boas DA, Ayata C. Cortical spreading depression impairs oxygen delivery and metabolism in mice. *J Cereb Blood Flow Metab*. 2012;32(2):376-86.

Eikermann-Haerter K, Can A, Ayata C. Pharmacological targeting of spreading depression in migraine. *Expert Rev Neurother*. 2012;12(3):297-306.

Eikermann-Haerter K, Lee JH, Yuzawa I, Liu CH, Zhou Z, Shin HK, Zheng Y, Qin T, Kurth T, Waeber C, Ferrari MD, van den Maagdenberg AM, Moskowitz MA, Ayata C. Migraine Mutations Increase Stroke Vulnerability by Facilitating Ischemic Depolarizations. *Circulation*. 2012;125(2):335-45.

Hoffmann U, Sukhotinsky I, Atalay YB, Eikermann-Haerter K, Ayata C. Increased glucose availability does not restore prolonged spreading depression durations in hypotensive rats without brain injury. *Exp Neurol*. 2012;238(2):130-2.

Hoffmann U, Dileköz E, Kudo C, Ayata C. Oxcarbazepine Does Not Suppress Cortical Spreading Depression. *Cephalalgia* 2011;31(5):537-42.

Eikermann-Haerter K, Yuzawa I, Dilekoz E, Joutel A, Moskowitz MA, Ayata C. CADASIL mutations increase susceptibility to spreading depression. *Ann Neurol* 2011;69(2):413-8.

Srinivasan VJ, Atochin DN, Radhakrishnan H, Jiang JY, Ruvinskaya S, Wu W, Barry S, Cable AE, Ayata C, Huang PL, Boas DA. Optical coherence tomography for the quantitative study of cerebrovascular physiology. *J Cereb Blood Flow Metab* 2011;31(6):1339-45.

Eikermann-Haerter K, Yuzawa I, Qin T, Wang Y, Baek K, Kim YR, Hoffmann U, Dilekoz E, Waeber C, Ferrari MD, van den Maagdenberg AMJM, Moskowitz MA, Ayata C. Enhanced subcortical spreading depression in familial hemiplegic migraine type 1 mutant mice. *J Neurosci* 2011;31(15):5755-63.

Arboleda-Velasquez JF, Manent J, Lee JH, Tikka S, Ospina C, Vanderburg CR, Frosch MP, Rodríguez-Falcón M, Villen J, Gygi S, Lopera F, Kalimo H, Moskowitz MA, Ayata C, Louvi A, Artavanis-Tsakonas S. Hypomorphic Notch 3 alleles link Notch signaling to ischemic cerebral small-vessel disease. *Proc Natl Acad Sci U S A*. 2011;108(21):E128-35.

Hoffmann U, Lee JH, Qin T, Eikermann-Haerter K, Ayata C. Gabapentin reduces infarct volume but does not suppress peri-infarct depolarizations. *J Cereb Blood Flow Metab* 2011 Jul;31(7):1578-82.

Baraghis E, Devor A, Fang Q, Srinivasan VJ, Wu W, Lesage F, Ayata C, Kasischke KA, Boas DA, Sakadžić S. Two-photon microscopy of cortical NADH fluorescence intensity changes: correcting contamination from the hemodynamic response. *J Biomed Opt.* 2011;16(10):106003.

Sukhotinsky I, Dilekoz E, Wang Y, Qin T, Eikermann-Haerter K, Waeber C, Ayata C. Chronic daily cortical spreading depressions suppress spreading depression susceptibility. *Cephalalgia.* 2011; 31(16):1601-8.

Garcia-Alloza M, Gregory J, Kuchibhotla KV, Fine S, Wei Y, Ayata C, Frosch MP, Greenberg SM, Bacskai BJ. Cerebrovascular lesions induce transient β -amyloid deposition. *Brain.* 2011;134(Pt 12):3697-707.

Lee JH, Bacskai BJ, Ayata C. Genetic Animal Models of Cerebral Vasculopathies. *Progress in Molecular Biology and Translational Science* 2011;105:25-55.

Nozari A, Dilekoz E, Sukhotinsky I, Stein T, Eikermann-Haerter K, Liu C, Wang Y, Frosch MP, Waeber C, Ayata C, Moskowitz MA. Microemboli May Link Spreading Depression, Migraine Aura and Patent Foramen Ovale. *Ann Neurol* 2010;67(2):221-9.

Sukhotinsky I, Yaseen MA, Sakadžić S, Ruvinskaya S, Sims JR, Boas DA, Moskowitz MA, Ayata C. Perfusion pressure-dependent recovery of cortical spreading depression is independent of tissue oxygenation over a wide physiological range. *J Cereb Blood Flow Metab* 2010;30(6):1168-77.

Gohil VM, Sheth SA, Nilsson R, Wojtovich AP, Lee JH, Perocchi F, Chen W, Clish CB, Ayata C, Brookes PS, Mootha VK. Nutrient-sensitized screening for drugs that shift energy metabolism from mitochondrial respiration to glycolysis. *Nat Biotechnol* 2010;28(3):249-55.

Hoffmann U, Dilekoz E, Kudo C, Ayata C. Gabapentin suppresses cortical spreading depression susceptibility. *J Cereb Blood Flow Metab* 2010;30(9):1588-92.

Atochin DN, Yuzawa I, Li Q, Rauwerdink KM, Malhotra R, Chang J, Brouckaert P, Ayata C, Moskowitz MA, Bloch KD, Huang PL, Buys ES. Soluble guanylate cyclase $\alpha 1\beta 1$ limits stroke size and attenuates neurological injury. *Stroke* 2010;41(8):1815-9.

Eikermann-Haerter K, Ayata C. Cortical spreading depression and migraine. *Curr Neurol Neurosci Rep* 2010;10(3):167-73.

Ayata C. Cortical spreading depression triggers migraine attack: Pro. *Headache* 2010;50(4):725-30.

Ayata C. CADASIL: Experimental insights from animal models. *Stroke* 2010;41(10 Suppl):S129-34.

Ayata C. Spreading depression: from serendipity to targeted therapy in migraine prophylaxis. *Cephalalgia* 2009;29(10):1095-114.

Eikermann-Haerter K, Dileköz E, Kudo C, Savitz SI, Waeber C, Baum MJ, Ferrari MD, van den Maagdenberg AM, Moskowitz MA, Ayata C. Genetic and hormonal factors modulate spreading depression and transient hemiparesis in mouse models of familial hemiplegic migraine type 1. *J Clin Invest* 2009;119(1):99-109.

Eikermann-Haerter K, Yuzawa I, Baum MJ, Ferrari MD, van den Maagdenberg AM, Moskowitz MA, Ayata C. Androgenic suppression of spreading depression in familial hemiplegic migraine type 1 mutant mice. *Ann Neurol* 2009;66(4):564-8.

Sakadžić S, Yuan S, Dilekoz E, Ruvinskaya S, Vinogradov SA, Ayata C, Boas DA. Simultaneous imaging of cerebral partial pressure of oxygen and blood flow during functional activation and cortical spreading depression. *Appl Opt* 2009;48(10):D169-77.

Shin HK, Nishimura M, Jones PB, Ay H, Boas DA, Moskowitz MA, Ayata C. Mild Induced Hypertension Improves Blood Flow and Oxygen Metabolism in Transient Focal Cerebral Ischemia. *Stroke* 2008;39(5):1548-55.

Jones PB, Shin HK, Boas DA, Hyman BT, Moskowitz MA, Ayata C, Dunn AK. Simultaneous multispectral reflectance imaging and laser speckle flowmetry of cerebral blood flow and oxygen metabolism in focal cerebral ischemia. *J Biomed Opt* 2008;3(4):044007-1-11.

Arboleda-Velasquez JF, Zhou Z, Shin HK, Louvi A, Kim HH, Savitz SI, Liao JK, Salomone S, Ayata C, Moskowitz MA, Artavanis-Tsakonas S. Linking notch signaling to ischemic stroke. *Proc Natl Acad Sci USA* 2008;105(12):4856-61.

Sukhotinsky I, Dilekoz E, Moskowitz MA, Ayata C. Hypoxia and hypotension transform the blood flow response to cortical spreading depression from hyperemia into hypoperfusion in the rat. *J Cereb Blood Flow Metab* 2008;28(7):1369-76.

Kudo C, Nozari A, Moskowitz MA, Ayata C. The impact of anesthetics and hyperoxia on cortical spreading depression. *Exp Neurol* 2008;212(1):201-6.

Chou SH, Smith EE, Badjatia N, Nogueira RG, Sims JR, Ogilvy CS, Rordorf GA, Ayata C. A randomized, double-blind, placebo-controlled pilot study of simvastatin in aneurismal subarachnoid hemorrhage. *Stroke*. 2008;39(10):2891-3.

Shin HK, Salomone S, Ayata C. Targeting cerebrovascular Rho-kinase in stroke. *Expert Opin Ther Targets*. 2008;12(12):1547-64.

Atocin DN, Wang A, Liu VW, Critchlow JD, Dantas AP, Looft-Wilson R, Murata T, Salomone S, Shin HK, Ayata C, Moskowitz MA, Michel T, Sessa WC, Huang PL. The phosphorylation state of eNOS modulates vascular reactivity and outcome of cerebral ischemia in vivo. *J Clin Invest* 2007;117(7):1961-1967.

Shin HK, Jones PB, Garcia-Alloza M, Borrelli L, Greenberg SM, Bacskai BJ, Frosch MP, Hyman BT, Moskowitz MA, Ayata C. Age-dependent cerebrovascular dysfunction in a transgenic mouse model of cerebral amyloid angiopathy. *Brain* 2007;130(Pt 9):2310-9.

Lee SR, Lok J, Rosell A, Kim HY, Murata Y, Atocin D, Huang PL, Wang X, Ayata C, Moskowitz MA, Lo EH. Reduction of hippocampal cell death and proteolytic responses in tissue plasminogen activator knockout mice after transient global cerebral ischemia. *Neuroscience* 2007;150(1):50-7.

Ay H, Benner T, Arsava EM, Furie KL, Singhal AB, Jensen MB, Ayata C, Towfighi A, Smith EE, Chong JY, Koroshetz WJ, Sorensen AG. A computerized algorithm for etiologic classification of ischemic stroke: The Causative Classification of Stroke System. *Stroke* 2007;38(11):2979-84.

Shin HK, Salomone S, Potts EM, Lee SW, Millican E, Noma K, Huang PL, Boas DA, Liao JK, Moskowitz MA, Ayata C. Rho-kinase inhibition acutely augments blood flow in focal cerebral ischemia via endothelial mechanisms. *J Cereb Blood Flow Metab* 2007;27(5):998-1009.

Shin HK, Dunn AK, Jones PB, Boas DA, Lo EH, Moskowitz MA, Ayata C. Normobaric hyperoxia improves cerebral blood flow and oxygenation, and inhibits peri-infarct depolarizations in experimental focal ischemia. *Brain* 2007;130(Pt 6):1631-42.

Shin HK, Dunn AK, Jones PB, Boas DA, Moskowitz MA, Ayata C. Vasoconstrictive Neurovascular Coupling during Focal Ischemic Depolarizations. *J Cereb Blood Flow Metab* 2006; 26(8):1018-30.

Ayata C, Moskowitz MA. Cortical spreading depression confounds concentration-dependent pial arteriolar dilation during N-methyl-D-aspartate superfusion. *Am J Physiol Heart Circ Physiol* 2006;290(5):H1837-41.

Ay H, Koroshetz WJ, Benner T, Vangel MG, Melinosky C, Arsava EM, Ayata C, Zhu M, Schwamm LH, Sorensen AG. Neuroanatomic correlates of stroke-related myocardial injury. *Neurology* 2006; 66(9):1325-9.

Ayata C, Jin H, Kudo C, Dalkara T, Moskowitz MA. Suppression of cortical spreading depression in migraine prophylaxis. *Ann Neurol* 2006;59(4):652-61.

Haerter K, Ayata C, Moskowitz MA. Cortical spreading depression: a model for understanding migraine biology and future drug targets. *Headache Currents* 2005;1-7.

Ayata C, Dunn AK, Gursoy-Özdemir Y, Huang Z, Boas DA, Moskowitz MA. Laser speckle flowmetry for the study of cerebrovascular physiology in normal and ischemic mouse cortex. *J Cereb Blood Flow Metab* 2004;24(7):744-55.

Ayata C, Shin HK, Salomone S, Ozdemir-Gursoy Y, Boas DA, Dunn AK, Moskowitz MA. Pronounced hypoperfusion during spreading depression in mouse cortex. *J Cereb Blood Flow Metab* 2004;24(10):1172-82.

Atochin DN, Murciano JC, Gursoy-Ozdemir Y, Krasik T, Noda F, Ayata C, Dunn AK, Moskowitz MA, Huang PL, Muzykantov VR. Mouse model of microembolic stroke and reperfusion. *Stroke* 2004;35(9):2177-82.

Badjatia N, O'Donnell J, Baker J, Huang D, Ayata C, Greer D, Carter BS, Ogilvy C, McDonald CT. Achieving Normothermia in Patients With Febrile Subarachnoid Hemorrhage: Feasibility and Safety of a Novel Intravascular Cooling Catheter. *Neurocritical Care* 2004;1(2):145-156.

Ayata C, Rordorf G. Craniocervical Endovascular Stenting and Angioplasty. In Karen L. Furie, Peter J. Kelley, eds. *Handbook of Stroke Prevention in Clinical Practice*, Humana Press, 2004, pp167-186.

Ayata C, Ropper AH. Intensive care management of specific stroke treatment. In Henry J. Barnett, J. Bogousslavsky, B. Meldrum, eds. *Ischemic Stroke*, Adv Neurol, LWW 2003, pp361-378.

Qureshi AI, Suarez JJ, Yahia AM, Mohammad Y, Uzun G, Suri MF, Zaidat OO, Ayata C, Ali Z, Wityk RJ. Timing of neurologic deterioration in massive middle cerebral artery infarction: a multicenter review. *Crit Care Med* 2003;31:272-7.

Ropper AH, Ayata C, Adelman L. Vasculitis of the spinal cord. *Arch Neurol* 2003; 60:1791-4.

Ayata C, Ropper AH. Ischaemic brain oedema. *J Clin Neurosci* 2002;9:113-24.

Ayata C, Shimizu-Sasamata M, Lo EH, Noebels JL, Moskowitz MA. Impaired neurotransmitter release and elevated threshold for cortical spreading depression in mice with mutations in the $\alpha 1A$ subunit of P/Q type calcium channels. *Neurosci* 2000;95:639-45.

Marota JJ, Ayata C, Moskowitz MA, Weiskoff RM, Rosen BR, Mandeville JB. Investigation of the early response to rat forepaw stimulation. *Magn Reson Med* 1999;41:247-52.

Dalkara T, Ayata C, and Moskowitz MA. Constitutive nitric oxide synthase and ischemic/excitotoxic brain injury. In: Ruffolo RR Jr., Feuerstein G, Hunter AJ, Poste G, BW Metcalf BW, eds. *Inflammatory Cells and Mediators in CNS Diseases*, Amsterdam: Harwood Academic Publishers, 1999, pp 85-96.

Browne SE, Ayata C, Huang PL, Moskowitz MA, Beal MF. The cerebral metabolic consequences of nitric oxide synthase (NOS) deficiency: glucose utilization in endothelial and neuronal NOS null mice. *J Cereb Blood Flow Metab* 1999;19:144-8.

Mandeville JB, Marota JJ, Ayata C, Zaharchuk G, Moskowitz, Rosen BR, Weiskoff RM. Evidence of a cerebrovascular post-arteriole windkessel with delayed compliance. *J Cereb Blood Flow Metab* 1999;19:679-89.

Mandeville JB, Marota JJ, Ayata C, Moskowitz MA, Weiskoff RM, Rosen BR. MRI measurement of the temporal evolution of relative CMRO(2) during rat forepaw stimulation. *Magn Reson Med* 1999;42:944-51.

Meng W, Ayata C, Waeber C, Huang PL, Moskowitz MA. Neuronal NOS-cGMP-dependent Ach-induced relaxation in pial arterioles of endothelial NOS knockout mice. *Am J Physiol* 1998;274:H411-5.

Moskowitz MA, Ayata C. A neurological double-header: Spontaneous mouse mutations provide novel insights and new implications for migraine and epilepsy. *Neurology Network Commentary* 1997;1:265-268.

Hara H, Friedlander RM, Gagliardini V, Ayata C, Huang Z, Sasamata M, Yuan J, Moskowitz MA. Inhibition of interleukin 1 β converting enzyme family proteases reduces ischemic and excitotoxic neuronal damage. *Proc Natl Acad Sci* 1997;94:2007-12.

Okamoto H, Meng W, Ma J, Ayata C, Roman RJ, Bosnjak ZJ, Kampine JP, Huang PL, Hudetz AG, Moskowitz MA. Isoflurane-induced cerebral hyperemia in neuronal nitric oxide synthase gene deficient mice. *Anesthesiology* 1997;86:875-84.

Ayata C, Ayata C, Hara H, Matthews RT, Beal MF, Ferrante RJ, Endres M, Kim A, Christie RH, Waeber C, Huang PL, Hyman BT, Moskowitz MA. Mechanisms of reduced striatal NMDA excitotoxicity in type I nitric oxide synthase knockout mice. *J Neurosci* 1997;17:6908-17.

Hara H, Ayata C, Huang PL, Waeber C, Ayata G, Fujii M, Moskowitz MA. [3H] L-NG-Nitro-arginine binding after transient focal ischemia and NMDA-induced excitotoxicity in type I and type III nitric oxide synthase null mice. *J Cereb Blood Flow Metab* 1997;17:515-26.

Demirci M, Ayata C, Dalkara T, Erdemli G, Onur R. Monitoring cellular edema at single-neuron level by electrical resistance measurements. *J Neurosci Methods* 1997;72:175-81.

Dalkara T, Ayata C, Demirci M, Erdemli G, Onur R. Effects of cerebral ischemia on N-methyl-D-aspartate and dihydropyridine-sensitive calcium currents. An electrophysiological study in the rat hippocampus in situ. *Stroke* 1996;27:127-33.

Ma J, Ayata C, Huang PL, Fishman MC, Moskowitz MA. Regional cerebral blood flow response to vibrissal stimulation in mice lacking type I nitric oxide synthase gene expression. *Am J Physiol* 1996;270:H1085-90.

Ayata C, Ma J, Meng W, Huang PL, Moskowitz MA. L-NA-sensitive rCBF augmentation during vibrissal stimulation in type III nitric oxide synthase mutant mice. *J Cereb Blood Flow Metab* 1996;16:539-41.

Meng W, Ma J, Ayata C, Hara H, Huang PL, Fishman MC, Moskowitz MA. ACh dilates pial arterioles in endothelial and neuronal NOS knockout mice by NO-dependent mechanisms. *Am J Physiol* 1996;271:H1145-50.

Huang Z, Huang PL, Ma J, Meng W, Ayata C, Fishman MC, Moskowitz MA. Enlarged infarcts in endothelial nitric oxide synthase gene knockout mice are attenuated by nitro-L-arginine. *J Cereb Blood Flow Metab* 1996;16:981-7.

Ma J, Meng W, Ayata C, Huang PL, Fishman MC, Moskowitz MA. L-NNA-sensitive regional cerebral blood flow augmentation during hypercapnia in type III NOS mutant mice. *Am J Physiol* 1996;271:H1717-19.

Ayata C, Moskowitz MA. Ketamine antagonizes NO release from cerebral cortex after middle cerebral artery ligation. *Stroke* 1996;27:752.

Moskowitz MA, Ayata C. Potentiation of oxygen-glucose deprivation-induced neuronal death after induction of iNOS. Editorial. *Stroke* 1996;27:1591.

Lee WS, Limmroth V, Ayata C, Cutrer FM, Waeber C, Yu X, Moskowitz MA. Peripheral GABA-A receptor-mediated effects of sodium valproate on dural plasma protein extravasation to substance P and trigeminal stimulation. *Br J Pharm* 1995;116:1661-7.

Onur R, Bozdagi O, Ayata C. Effects of aconitine on neurotransmitter release in the rat neuromuscular junction. *Neuropharm* 1995;34:1139-45.

CURRICULUM VITAE

Cenk Ayata was born in 1968 in Ankara, Turkey. He started his medical training at the Hacettepe University Faculty of Medicine, the top medical school in Turkey, in 1985 by successfully passing a national university entrance and ranking examination. After obtaining his MD degree in 1991, he enrolled as a graduate student in the Department of Pharmacology of the same university. In 1994, he was offered a research fellowship position at the Massachusetts General Hospital, Harvard Medical School, under the mentorship of Professor Michael A. Moskowitz. After three years of research fellowship, he decided to return to his medical training, successfully passed the board examinations and started his specialty training in 1997 as a Resident in Neurology at the Tufts University program under the mentorship of Professor Alan H. Ropper. After completing his residency in 2001, he was accepted to a Clinical Fellowship in Vascular and Critical Care Neurology, at the Massachusetts General Hospital, Harvard Medical School, and by this way returned to his previous institution. As part of his fellowship, he spent part of his time in the research laboratory of Dr. Moskowitz. After completing his fellowship in 2003, he launched two new lines of investigation, focusing of optical imaging of cerebral blood flow and metabolism, and physiology and pharmacology of spreading depression. Since 2009 he has worked together with Professor Michel D. Ferrari and Professor Arn M.J.M. van den Maagdenberg to examine their transgenic knockin mouse models with human pathogenic gene mutations in order to dissect neurobiological mechanisms related to the susceptibility to spreading depression and ischemic injury relevant to the pathophysiology of migraine and stroke, and their interrelation. The work performed on these transgenic mouse models of migraine was the basis of this thesis. He was appointed as an Instructor at the Massachusetts General Hospital, Harvard Medical School in 2001, promoted to Assistant Professor in 2006, and then Associate Professor in 2010.

