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Age-related impairment of metabo-vascular coupling during cortical spreading depolarizations

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Running headline: Cortical spreading depolarizations in aging

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Abstract

Cortical spreading depolarizations (SDs) may lead to long-lasting alterations in cerebral blood flow (CBF), which contribute to neuronal dysfunction and hypoxic tissue injury. There is growing evidence to suggest that age-related structural and functional alterations of the neurovascular unit significantly increase both the incidence of SDs and aggravate their functional consequences. Recent studies suggest that metabolic signaling plays a major role in modulating cerebral blood flow responses evoked by SDs and provide critical evidence that aging considerably weakens metabovascular coupling with SD. As a consequence, the aged brain becomes increasingly more vulnerable to the deleterious effects of SDs.

Clinical relevance of cortical spreading depolarizations

Spreading depolarizations (SDs) are waves of massive cellular depolarization travelling within the brain at a speed of 2-4 mm/min, characterized by sustained near-complete depolarization of neuronal cells, a massive depolarization of glial cells, and a negative deflection of the extracellular DC potential. In addition to temporarily shutting down neuronal function and information processing within neuronal networks SDs represent an important metabolic challenge for the brain parenchyma due to the large energy demand for repolarizing neuronal and glial cells. Importantly, SDs that propagate in the cortex also trigger rapid vasoconstriction, followed by a significant hyperemic response and then a long-lasting oligemic phase(2, 3, 7, 8, 11, 21, 28, 36, 57). Clinical observations and strong experimental evidence suggest that SDs occur after a diverse range of injury types, including intracerebral hemorrhages, ischemic strokes, migraine, subarachnoid hemorrhages, as well as traumatic brain injuries and correlate with poor outcome (2, 3, 5, 14-16, 25, 27, 29, 31, 34, 41, 43, 44, 58-60). Injury-induced SDs (e.g. in stroke) can propagate along ischemic, but viable areas adjacent to the damaged brain regions, and repetitive occurrence and especially long lasting SD episodes exacerbate neuronal lesions and thereby worsen the clinical outcome (19, 26). Importantly, there is increasing evidence that age-related structural and functional alterations of the cerebral circulation (18, 20, 42, 51) significantly increase both the incidence of SDs and aggravate their functional consequences (11, 21, 28, 36). Despite their importance, the mechanistic effects of aging on SDs and the cellular and molecular mechanisms by which SDs can exacerbate brain injury are still largely unknown.

Age-related impairment of metabo-vascular coupling during SDs

pH is often a neglected aspect of brain metabolism. Brain energy state is most often studied by measuring glucose, lactate and/or pyruvate levels, but pH also offers useful insights into cell metabolism. Increased carbohydrate metabolism results in CO_2 and/or lactate production that contribute to interstitial fluid acidification. In addition, exocytosis of highly acidic synaptic vesicles can induce acidosis in response to increased neuronal activity. These acidic shifts can be mitigated by the buffering capacity of the interstitial fluid and especially, the activity of the enzyme carbonic anhydrase that accelerates CO_2 hydration into carbonic acid, as well as a number of proton pumps that help equilibrate intra- and extracellular pH (10). Despite this high buffering capacity, brain pH is known to change transiently in response

to sustained neuronal activity or pathological states like ischemia. Such pH changes can have profound effects on neuronal excitability by modulating a variety of ion channels, or even lead to cell death when pH deviates too much and/or too long from its physiological value (45).

In this article, published as part of the special collection of papers “Advances in Cardiovascular Geroscience”(4, 12, 13, 17, 22, 23, 35, 39, 46, 47, 52, 54, 56, 61), and in a previous study from the same authors, Menyhárt et al. have monitored pH changes evoked by SDs in control animals, as well as in aged or ischemic rats(37, 38). While SD induced transient acidic shifts in the order of 0.1-0.2 pH units in young healthy animals, pH shifts were considerably larger (about 0.4 pH units) after ischemia or in aged animals. In addition, the correlation between pH shifts, hyperemia and the amplitude of depolarization typically observed in young healthy animals was absent after ischemia or aged animals. These observations were made possible by small pH microelectrodes that could monitor the pH of the interstitial fluid with minimal perturbation of the brain parenchyma. Such pH electrodes were initially developed in the 1980s(1, 30, 40), but remain extremely difficult to handle reliably. The present work by Menyhárt et al. illustrates the power of this brain monitoring technique. The discrepancy between the pH signature of an SD in a healthy brain and that in an ischemic or aged brain could provide a basis for understanding why such events are usually harmless in young animals or patients, but aggravate neuronal lesions in an already injured or aged brain.

The results of Menyhárt et al.(37), corroborate the notion that metabolic signaling plays a major role in the mediation of hyperemia in response to SD. They provide convincing evidence that hyperemic element of the cortical blood flow response to SDs is effectively modulated by tissue pH. The authors put forward the hypothesis that on a hyperemia spectrum with functional and reactive hyperemia as its two end points, the nature of the SD-coupled hyperemic response falls closer to reactive than to functional hyperemia (Figure 1). This would be especially relevant for SD events, which produce a sudden, transient drop of perfusion prior to the evolution of hyperemia. Importantly, Menyhárt et al., also provide critical evidence that aging considerably weakens metabovascular coupling with SD and that tissue acidosis lasts disproportionally longer in the aged cortex, making the tissue increasingly more vulnerable. This important observation can have far-reaching consequences. The results of Menyhárt et al.(37) open exciting new perspectives for improved neuroprotective strategies based on improving the buffering capacity of the brain extracellular fluid by targeting, for example, lactic acid production and clearance. This study illustrates how chemical monitoring

of brain molecules using minimally invasive real-time sensors and/or imaging techniques can reveal physiological or pathological mechanisms, improve our understanding of cellular and molecular brain processes, and guide the development of new therapeutic strategies.

Growing evidence from epidemiological, clinical and experimental studies indicate that aging-induced cerebromicrovascular dysfunction plays a critical role in the pathogenesis of various types of dementia and brain damage in the elderly(9, 24, 32, 33, 48, 54-56). Importantly, there is strong evidence demonstrating that functional hyperemia/neurovascular coupling is impaired in aging both in humans and laboratory animals (6, 42, 53, 62), which likely contributes to the development of vascular cognitive impairment(49, 50). The study of Menyhárt et al. has important relevance for cerebrovascular geroscience, as it also highlights a novel age-related mechanism by which cerebromicrovascular reactivity and thereby normal neurovascular coupling responses may be altered in the elderly.

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References cited

1. **Ammann D, Lanter F, Steiner RA, Schulthess P, Shijo Y, and Simon W.** Neutral carrier based hydrogen ion selective microelectrode for extra- and intracellular studies. *Anal Chem* 53: 2267-2269, 1981.
2. **Ayata C.** Spreading depression and neurovascular coupling. *Stroke* 44: S87-89, 2013.
3. **Ayata C and Lauritzen M.** Spreading Depression, Spreading Depolarizations, and the Cerebral Vasculature. *Physiol Rev* 95: 953-993, 2015.
4. **Badrov MB, Lalande S, Olver TD, Suskin N, and Shoemaker JK.** Effects of aging and coronary artery disease on sympathetic neural recruitment strategies during end-inspiratory and end-expiratory apnea. *Am J Physiol Heart Circ Physiol* 311: H1040-H1050, 2016.
5. **Balanca B, Meiller A, Bezin L, Dreier JP, Marinesco S, and Lieutaud T.** Altered hypermetabolic response to cortical spreading depolarizations after traumatic brain injury in rats. *J Cereb Blood Flow Metab*, 2016.
6. **Balbi M, Ghosh M, Longden TA, Jativa Vega M, Gesierich B, Hellal F, Lourbopoulos A, Nelson MT, and Plesnila N.** Dysfunction of mouse cerebral arteries during early aging. *J Cereb Blood Flow Metab* 35: 1445-1453, 2015.
7. **Bere Z, Obrenovitch TP, Bari F, and Farkas E.** Ischemia-induced depolarizations and associated hemodynamic responses in incomplete global forebrain ischemia in rats. *Neuroscience* 260: 217-226, 2014.
8. **Bere Z, Obrenovitch TP, Kozak G, Bari F, and Farkas E.** Imaging reveals the focal area of spreading depolarizations and a variety of hemodynamic responses in a rat microembolic stroke model. *J Cereb Blood Flow Metab* 34: 1695-1705, 2014.
9. **Castillo-Carranza DL, Nilson AN, Van Skike CE, Jahrling JB, Patel K, Garach P, Gerson JE, Sengupta U, Abisambra J, Nelson P, Troncoso J, Ungvari Z, Galvan V, and Kayed R.** Cerebral Microvascular Accumulation of Tau Oligomers in Alzheimer's Disease and Related Tauopathies. *Aging Dis* 8: 257-266, 2017.
10. **Chesler M.** Regulation and modulation of pH in the brain. *Physiol Rev* 83: 1183-1221, 2003.
11. **Clark D, Institoris A, Kozak G, Bere Z, Tuor U, Farkas E, and Bari F.** Impact of aging on spreading depolarizations induced by focal brain ischemia in rats. *Neurobiol Aging* 35: 2803-2811, 2014.
12. **Cogger VC, Mohamad M, Solon-Biet SM, Senior AM, Warren A, O'Reilly JN, Tung BT, Svistounov D, McMahon AC, Fraser R, Raubenheimer D, Holmes AJ, Simpson SJ, and Le Couteur DG.** Dietary macronutrients and the aging liver sinusoidal endothelial cell. *Am J Physiol Heart Circ Physiol* 310: H1064-1070, 2016.
13. **Diaz-Otero JM, Garver H, Fink GD, Jackson WF, and Dorrance AM.** Aging is associated with changes to the biomechanical properties of the posterior cerebral artery and parenchymal arterioles. *Am J Physiol Heart Circ Physiol* 310: H365-375, 2016.
14. **Dreier JP.** The role of spreading depression, spreading depolarization and spreading ischemia in neurological disease. *Nat Med* 17: 439-447, 2011.
15. **Dreier JP, Drenckhahn C, Woitzik J, Major S, Offenhauser N, Weber-Carstens S, Wolf S, Strong AJ, Vajkoczy P, and Hartings JA.** Spreading ischemia after aneurysmal subarachnoid hemorrhage. *Acta Neurochir Suppl* 115: 125-129, 2013.
16. **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, Sanchez-Porras R, Jewell SL, Balanca B, Platz J, Hinzman JM, Luckl J, Schoknecht K, Scholl M, Drenckhahn C, Feuerstein D, Eriksen N, Horst V, Bretz JS, Jahnke P, Scheel M, Bohner 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, Guresir 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, and 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.

17. **Evin M, Redheuil A, Soulat G, Perdrix L, Ashrafpoor G, Giron A, Lamy J, Defrance C, Roux C, Hatem SN, Diebold B, Mousseaux E, and Kachenoura N.** Left atrial aging: a cardiac magnetic resonance feature-tracking study. *Am J Physiol Heart Circ Physiol* 310: H542-549, 2016.

18. **Faber JE, Zhang H, Lassance-Soares RM, Prabhakar P, Najafi AH, Burnett MS, and Epstein SE.** Aging causes collateral rarefaction and increased severity of ischemic injury in multiple tissues. *Arterioscler Thromb Vasc Biol* 31: 1748-1756, 2011.

19. **Farkas E and Bari F.** Spreading depolarization in the ischemic brain: does aging have an impact? *J Gerontol A Biol Sci Med Sci* 69: 1363-1370, 2014.

20. **Farkas E and Luiten PG.** Cerebral microvascular pathology in aging and Alzheimer's disease. *Prog Neurobiol* 64: 575-611, 2001.

21. **Farkas E, Obrenovitch TP, Institoris A, and Bari F.** Effects of early aging and cerebral hypoperfusion on spreading depression in rats. *Neurobiol Aging* 32: 1707-1715, 2011.

22. **Flavahan S, Chang F, and Flavahan NA.** Local renin-angiotensin system mediates endothelial dilator dysfunction in aging arteries. *Am J Physiol Heart Circ Physiol* 311: H849-854, 2016.

23. **Froogh G, Pinto JT, Le Y, Kandhi S, Aleligne Y, Huang A, and Sun D.** Chymase-dependent production of angiotensin II: an old enzyme in old hearts. *Am J Physiol Heart Circ Physiol* 312: H223-H231, 2017.

24. **Galvan V and Hart MJ.** Vascular mTOR-dependent mechanisms linking the control of aging to Alzheimer's disease. *Biochim Biophys Acta* 1862: 992-1007, 2016.

25. **Hartings JA, Bullock MR, Okonkwo DO, Murray LS, Murray GD, Fabricius M, Maas AI, Woitzik J, Sakowitz O, Mathern B, Roozenbeek B, Lingsma H, Dreier JP, Puccio AM, Shutter LA, Pahl C, and Strong AJ.** Spreading depolarisations and outcome after traumatic brain injury: a prospective observational study. *Lancet Neurol* 10: 1058-1064, 2011.

26. **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, Sanchez-Porras R, Santos E, Scholl M, Strong AJ, Urbach A, Westover MB, Winkler MK, Witte OW, Woitzik J, and Dreier JP.** The continuum of spreading depolarizations in acute cortical lesion development: Examining Leao's legacy. *J Cereb Blood Flow Metab*, 2016.

27. **Hartings JA, Wilson JA, Hinzman JM, Pollandt S, Dreier JP, DiNapoli V, Ficker DM, Shutter LA, and Andaluz N.** Spreading depression in continuous electroencephalography of brain trauma. *Ann Neurol* 76: 681-694, 2014.

28. **Hertelendy P, Menyhart A, Makra P, Sule Z, Kiss T, Toth G, Ivankovits-Kiss O, Bari F, and Farkas E.** Advancing age and ischemia elevate the electric threshold to elicit spreading depolarization in the cerebral cortex of young adult rats. *J Cereb Blood Flow Metab*, 2016.

29. **Hinzman JM, Andaluz N, Shutter LA, Okonkwo DO, Pahl C, Strong AJ, Dreier JP, and Hartings JA.** Inverse neurovascular coupling to cortical spreading depolarizations in severe brain trauma. *Brain* 137: 2960-2972, 2014.

30. **Kraig RP, Ferreira-Filho CR, and Nicholson C.** Alkaline and acid transients in cerebellar microenvironment. *J Neurophysiol* 49: 831-850, 1983.

31. **Lauritzen M, Dreier JP, Fabricius M, Hartings JA, Graf R, and Strong AJ.** Clinical relevance of cortical spreading depression in neurological disorders: migraine, malignant stroke, subarachnoid and intracranial hemorrhage, and traumatic brain injury. *J Cereb Blood Flow Metab* 31: 17-35, 2011.

32. **Lin AL, Jahrling JB, Zhang W, DeRosa N, Bakshi V, Romero P, Galvan V, and Richardson A.** Rapamycin rescues vascular, metabolic and learning deficits in apolipoprotein E4 transgenic mice with pre-symptomatic Alzheimer's disease. *J Cereb Blood Flow Metab* 37: 217-226, 2017.

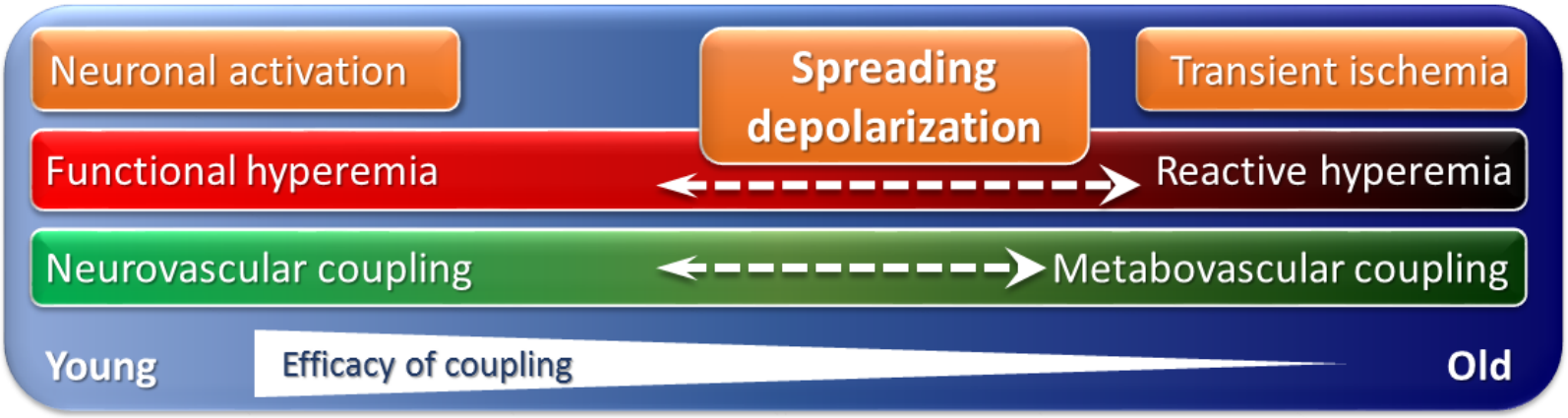
33. **Lin AL, Zheng W, Halloran JJ, Burbank RR, Hussong SA, Hart MJ, Javors M, Shih YY, Muir E, Solano Fonseca R, Strong R, Richardson AG, Lechleiter JD, Fox PT, and Galvan V.** Chronic rapamycin restores brain vascular integrity and function through NO synthase activation and improves memory in symptomatic mice modeling Alzheimer's disease. *J Cereb Blood Flow Metab* 33: 1412-1421, 2013.
34. **Luckl J, Dreier JP, Szabados T, Wiesenthal D, Bari F, and Greenberg JH.** Peri-infarct flow transients predict outcome in rat focal brain ischemia. *Neuroscience* 226: 197-207, 2012.
35. **McGinn R, Poirier MP, and Kenny GP.** Using heat as a therapeutic tool for the aging vascular tree. *Am J Physiol Heart Circ Physiol* 312: H806-H807, 2017.
36. **Menyhart A, Makra P, Szepes BE, Toth OM, Hertelendy P, Bari F, and Farkas E.** High incidence of adverse cerebral blood flow responses to spreading depolarization in the aged ischemic rat brain. *Neurobiol Aging* 36: 3269-3277, 2015.
37. **Menyhart A, Zolei-Szenasi D, Puskas T, Makra P, Bari F, and Farkas E.** Age or ischemia uncouples the blood flow response, tissue acidosis, and the direct current potential signature of spreading depolarization in the rat brain. *Am J Physiol Heart Circ Physiol*: ajpheart 00222 02017, 2017.
38. **Menyhart A, Zolei-Szenasi D, Puskas T, Makra P, Orsolya MT, Szepes BE, Toth R, Ivankovits-Kiss O, Obrenovitch TP, Bari F, and Farkas E.** Spreading depolarization remarkably exacerbates ischemia-induced tissue acidosis in the young and aged rat brain. *Sci Rep* 7: 1154, 2017.
39. **Merlini M, Shi Y, Keller S, Savarese G, Akhmedov A, Derungs R, Spescha RD, Kulic L, Nitsch RM, Luscher TF, and Camici GG.** Reduced nitric oxide bioavailability mediates cerebroarterial dysfunction independent of cerebral amyloid angiopathy in a mouse model of Alzheimer's disease. *Am J Physiol Heart Circ Physiol* 312: H232-H238, 2017.
40. **Mutch WA and Hansen AJ.** Extracellular pH changes during spreading depression and cerebral ischemia: mechanisms of brain pH regulation. *J Cereb Blood Flow Metab* 4: 17-27, 1984.
41. **Ostergaard L, Dreier JP, Hadjikhani N, Jespersen SN, Dirnagl U, and Dalkara T.** Neurovascular coupling during cortical spreading depolarization and -depression. *Stroke* 46: 1392-1401, 2015.
42. **Park L, Anrather J, Girouard H, Zhou P, and Iadecola C.** Nox2-derived reactive oxygen species mediate neurovascular dysregulation in the aging mouse brain. *J Cereb Blood Flow Metab* 27: 1908-1918, 2007.
43. **Sakowitz OW, Santos E, Nagel A, Krajewski KL, Hertle DN, Vajkoczy P, Dreier JP, Unterberg AW, and Sarrafzadeh AS.** Clusters of spreading depolarizations are associated with disturbed cerebral metabolism in patients with aneurysmal subarachnoid hemorrhage. *Stroke* 44: 220-223, 2013.
44. **Sarrafzadeh A, Santos E, Wiesenthal D, Martus P, Vajkoczy P, Oehmchen M, Unterberg A, Dreier JP, and Sakowitz O.** Cerebral glucose and spreading depolarization in patients with aneurysmal subarachnoid hemorrhage. *Acta Neurochir Suppl* 115: 143-147, 2013.
45. **Siesjo BK, Katsura K, and Kristian T.** Acidosis-related damage. *Advances in neurology* 71: 209-233; discussion 234-206, 1996.
46. **Sorrentino A, Signore S, Qanud K, Borghetti G, Meo M, Cannata A, Zhou Y, Wybieralska E, Luciani M, Kannappan R, Zhang E, Matsuda A, Webster A, Cimini M, Kertowidjojo E, D'Alessandro DA, Wunimenghe O, Michler RE, Royer C, Goichberg P, Leri A, Barrett EG, Anversa P, Hintze TH, and Rota M.** Myocyte repolarization modulates myocardial function in aging dogs. *Am J Physiol Heart Circ Physiol* 310: H873-890, 2016.
47. **Sweat RS, Sloas DC, Stewart SA, Czarny-Ratajczak M, Baddoo M, Eastwood JR, Suarez-Martinez AD, Azimi MS, Burks HE, Chedister LO, Myers L, and Murfee WL.** Aging is associated with impaired angiogenesis, but normal microvascular network structure, in the rat mesentery. *Am J Physiol Heart Circ Physiol* 312: H275-H284, 2017.
48. **Tarantini S, Fulop GA, Kiss T, Farkas E, Zolei-Szenasi D, Galvan V, Toth P, Csiszar A, Ungvari Z, and Yabluchanskiy A.** Demonstration of impaired neurovascular coupling responses in TG2576 mouse model of Alzheimer's disease using functional laser speckle contrast imaging. *Geroscience*, 2017.

49. **Tarantini S, Hertelendy P, Tucsek Z, Valcarcel-Ares MN, Smith N, Menyhart A, Farkas E, Hodges EL, Towner R, Deak F, Sonntag WE, Csiszar A, Ungvari Z, and Toth P.** Pharmacologically-induced neurovascular uncoupling is associated with cognitive impairment in mice. *J Cereb Blood Flow Metab* 35: 1871-1881, 2015.
50. **Tarantini S, Tran CH, Gordon GR, Ungvari Z, and Csiszar A.** Impaired neurovascular coupling in aging and Alzheimer's disease: Contribution of astrocyte dysfunction and endothelial impairment to cognitive decline. *Exp Gerontol*: DOI: 10.1016/j.exger.2016.1011.1004, 2016.
51. **Tarantini S, Tucsek Z, Valcarcel-Ares M, Toth P, Gautam T, Giles C, Ballabh P, Wei Y, Wren J, Ashpole N, Sonntag W, Ungvari Z, and Csiszar A.** Circulating IGF-1 deficiency exacerbates hypertension-induced microvascular rarefaction in the mouse hippocampus and retrosplenial cortex: implications for cerebromicrovascular and brain aging. *Age (Dordr)* 38: 273-289, 2016.
52. **Toba H, Cannon PL, Yabluchanskiy A, Iyer RP, D'Armiento J, and Lindsey ML.** Transgenic overexpression of macrophage matrix metalloproteinase-9 exacerbates age-related cardiac hypertrophy, vessel rarefaction, inflammation, and fibrosis. *Am J Physiol Heart Circ Physiol* 312: H375-H383, 2017.
53. **Topcuoglu MA, Aydin H, and Saka E.** Occipital cortex activation studied with simultaneous recordings of functional transcranial Doppler ultrasound (fTCD) and visual evoked potential (VEP) in cognitively normal human subjects: effect of healthy aging. *Neurosci Lett* 452: 17-22, 2009.
54. **Toth P, Tarantini S, Csiszar A, and Ungvari Z.** Functional vascular contributions to cognitive impairment and dementia: mechanisms and consequences of cerebral autoregulatory dysfunction, endothelial impairment, and neurovascular uncoupling in aging. *Am J Physiol Heart Circ Physiol* 312: H1-H20, 2017.
55. **Ungvari Z, Tarantini S, Hertelendy P, Valcarcel-Ares MN, Fülöp GÁ, Logan S, Kiss T, Farkas E, Csiszar A, and Yabluchanskiy A.** Cerebromicrovascular dysfunction predicts cognitive decline and gait abnormalities in a mouse model of whole brain irradiation-induced accelerated brain senescence. *GeroScience*: in press, 2017.
56. **Ungvari Z, Tarantini S, Kirkpatrick AC, Csiszar A, and Prodan CI.** Cerebral microhemorrhages: mechanisms, consequences, and prevention. *Am J Physiol Heart Circ Physiol* 312: H1128-H1143, 2017.
57. **Varga DP, Puskas T, Menyhart A, Hertelendy P, Zolei-Szenasi D, Toth R, Ivankovits-Kiss O, Bari F, and Farkas E.** Contribution of prostanoid signaling to the evolution of spreading depolarization and the associated cerebral blood flow response. *Sci Rep* 6: 31402, 2016.
58. **von Bornstadt 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, Sakadzic S, and Ayata C.** Supply-demand mismatch transients in susceptible peri-infarct hot zones explain the origins of spreading injury depolarizations. *Neuron* 85: 1117-1131, 2015.
59. **Winkler MK, Dengler N, Hecht N, Hartings JA, Kang EJ, Major S, Martus P, Vajkoczy P, Woitzik J, and Dreier JP.** Oxygen availability and spreading depolarizations provide complementary prognostic information in neuromonitoring of aneurysmal subarachnoid hemorrhage patients. *J Cereb Blood Flow Metab*, 2016.
60. **Woitzik J, Hecht N, Pinczolits A, Sandow N, Major S, Winkler MK, Weber-Carstens S, Dohmen C, Graf R, Strong AJ, Dreier JP, and Vajkoczy P.** Propagation of cortical spreading depolarization in the human cortex after malignant stroke. *Neurology* 80: 1095-1102, 2013.
61. **Wong J, Chabiniok R, deVecchi A, Dedieu N, Sammut E, Schaeffter T, and Razavi R.** Age-related changes in intraventricular kinetic energy: a physiological or pathological adaptation? *Am J Physiol Heart Circ Physiol* 310: H747-755, 2016.
62. **Zaletel M, Strucl M, Pretnar-Oblak J, and Zvan B.** Age-related changes in the relationship between visual evoked potentials and visually evoked cerebral blood flow velocity response. *Funct Neurol* 20: 115-120, 2005.

345

Figures

Figure 1. Conceptual overview of the type of coupling between spreading depolarization (SD) and the associated hyperemia in the context of aging (see text for details).


Neuronal activation
Spreading depolarization
Transient ischemia
Functional hyperemia
Reactive hyperemia
Neurovascular coupling
Metabovascular coupling
Young
Efficacy of coupling
Old