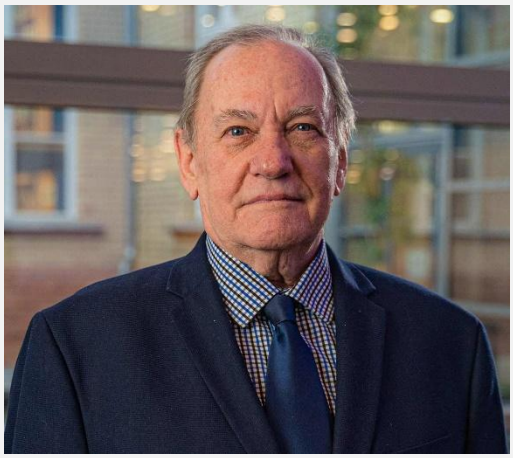
Lecture JCET 149, 07.03.2025

Autoregulation of cerebral blood flow: the return of prostanoids



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SHORT SUMMARY:

Regulation of cerebral blood flow is a complex function of resistance arterial vessels, that are sensitive to mechanical forces, such arises during increases in pressure and flow. Pressure-induced myogenic response of cerebral arteries has been well described. Flow-induced response, however is less known, but it seems that they are mediated - region dependently - by multiple molecules, including arachidonic acid (AA) metabolites (such as 20-HETE, PGI2 and PGE2) and nitric oxide (NO). In extracranial basilar artery (BA) an increase in flow elicits primarily dilation, whereas it results in constriction in the intracranial middle cerebral artery (MCA). This is likely because BA is outside, whereas MCA is inside the cranium, which limits volume changes. We hypothesized that genes and enzymes of flow-activated vascular

mediators are differentially expressed in extracranial (ExCA, such as BA) and intracranial (InCA, such as MCA) cerebral arteries.

Methods: BA and MCA were isolated from rats (3 months old), and protein expressions of key enzymes of the AA pathway, such as vasoconstrictor cyclooxygenases (COX1/COX2), cytochrome P450 hydroxylases (Cyp450), thromboxane synthase (TXAS), thromboxane A2 receptor (TP receptor), vasodilator prostacyclin synthase (PGIS), prostacyclin receptor (IP receptor), neuronal and endothelial NO synthases (nNOS/eNOS) were determined by western blotting. Transcriptome analysis in ExCA and InCA were also assessed by RNA sequencing.

Results: In BA compared to MCA, the protein expression of 1) COX 1/2, and Cyp450 were lower, 2) PGIS was higher, 3) TXAS, and nNOS/eNOS enzymes were similar, 4) TP receptor was lower, 5) IP receptor was higher. Gene expression of COX1/2 was lower in ExCA, but other enzymes and receptors of the AA pathway, and NOS enzymes were similar in ExCA and InCA, respectively. In addition, nearly 1000 genes were differentially expressed in ExCA and InCA. Among them, many genes (636) were associated with 22 canonical pathways regulating vasomotor, including flow-mediated response. ExCA had higher expression of genes involved in canonical pathways of vasodilation, whereas InCA showed higher expression of genes involved in canonical pathways of vasoconstriction.

Conclusions: Hemodynamic forces elicit the release of prostanoids and nitric oxide from the vascular wall and their ratio seems to depend on the specific region of cerebral arteries. The protein and gene expression of enzymes of mediators (AA metabolites and NO, and others) mediating flow dependent vasomotor responses largely correspond to the dilator responses of extra - and constrictor responses intracranial cerebral arteries.

PROFESSIONAL INTERESTS:

Microcirculation: brain, heart and skeletal muscle. The role of hemodynamic forces, especially shear stress and endothelial vasomotor function. Hypertension, physical activity, diabetes, gender differences. He was one of the first to discover the vasomotor role of shear stress in arterioles, veins and lymphatic microvessels. Also, he investigated the function of the endothelium, its modification by age, sex, hypertension, exercise/sport and various diseases. He and his colleagues discovered that an increase in flow in the small arteries of the brain causes a constriction, thus contributing to the better understanding of the autoregulation of cerebral blood flow and its role in hypertension and traumatic brain injury.

During his career, he has trained several young researchers (PhD, Student Researchers), with whom he continues to conduct joint research after obtaining their degrees.

Through his international research activities, he has played an important role in connecting the microcirculation research communities of Hungary, Europe, the United States, and Asia.

RELEVANT PUBLICATIONS:

1: Koller A, Járai Z, Takács J. Development of the European Society of Hypertension guidelines for the management of arterial hypertension: comparison of the helpfulness of ESH 2013, 2018, and 2023 guidelines. J Hypertens. 2025 Feb 14. doi: 10.1097/HJH.0000000000003985. Epub ahead of print. PMID: 39976190.

2: Decker S, Horváth T, Takács J, Koller A. Body Positions and Physical Activity Levels Modulate the Ratio of Abdominal to Thoracic Breathing and Respiratory Rate in Young Individuals. J Clin Med. 2024 Dec 21;13(24):7825. doi: 10.3390/jcm13247825. PMID: 39768748; PMCID: PMC11727880.

3: Nemcsik J, Takács J, Pásztor D, Farsang C, Simon A, Páll D, Torzsa P, Dolgos S, Koller A, Habony N, Járai Z. Frequency of office blood pressure measurements and the seasonal variability of blood pressure: results of the Hungarian Hypertension Registry. Blood Press. 2024 Dec;33(1):2337170. doi: 10.1080/08037051.2024.2337170. Epub 2024 Apr 5. PMID: 38581160.

4: Ezer E, Schrick D, Tőkés-Füzesi M, Papp I, Réger B, Molnár A, Ábrahám H, Koller A, Hársfalvi J, Kellermayer M, Molnár T. Gravity sedimentation reveals functionally and

morphologically different platelets in human blood. Platelets. 2024 Dec;35(1):2298341. doi: 10.1080/09537104.2023.2298341. Epub 2024 Jan 8. PMID: 38186228.

5: Jarai D, Koller A. Walnut Consumption May Contribute to Healthy Cardiovascular/Endothelial Function by Maintaining Membrane Integrity. Life (Basel). 2024 Nov 5;14(11):1426. doi: 10.3390/life14111426. PMID: 39598224; PMCID: PMC11595550.

6: Nemcsik J, Takács J, Kekk Z, Farsang C, Simon A, Páll D, Torzsa P, Dolgos S, Habony N, Koller Á, Pásztor D, Járai Z. White-coat effect and masked hypertension in patients with high-normal office blood pressure: results of the Hungarian ABPM Registry. J Hypertens. 2024 Nov 1;42(11):1976-1984. doi: 10.1097/HJH.0000000000003825. Epub 2024 Jul 29. PMID: 39222067.

7: Ishiko S, Koller A, Deng W, Huang A, Sun D. Liposomal nanocarriers of preassembled glycocalyx restore normal venular permeability and shear stress sensitivity in sepsis: assessed quantitatively with a novel microchamber system. Am J Physiol Heart Circ Physiol. 2024 Aug 1;327(2):H390-H398. doi: 10.1152/ajpheart.00138.2024. Epub 2024 Jun 14. PMID: 38874615; PMCID: PMC11427114.

8: Koller A, Takács J. A Guideline for Guidelines: A Novel Method to Assess the Helpfulness of Medical Guidelines. J Clin Med. 2024 Jun 27;13(13):3783. doi: 10.3390/jcm13133783. PMID: 38999349; PMCID: PMC11242354.

9: Takács J, Deák D, Koller A. Higher level of physical activity reduces mental and neurological symptoms during and two years after COVID-19 infection in young women. Sci Rep. 2024 Mar 22;14(1):6927. doi: 10.1038/s41598-024-57646-2. PMID: 38519586; PMCID: PMC10960016.

10: Koller A, Szebeni J. Covid-19 vaccines elicit effective IgG responses in an elderly thymus cancer patient with chemotherapy. Hum Vaccin Immunother. 2023 Dec 31;19(1):2188035. doi: 10.1080/21645515.2023.2188035. Epub 2023 Apr 16. PMID: 37062957; PMCID: PMC10114996.

11: Magyar-Stang R, Pál H, Csányi B, Gaál A, Mihály Z, Czinege Z, Csipo T, Ungvari Z, Sótonyi P, Varga A, Horváth T, Bereczki D, Koller A, Debreczeni R. Assessment of cerebral autoregulatory function and inter-hemispheric blood flow in older adults with internal

carotid artery stenosis using transcranial Doppler sonography-based measurement of transient hyperemic response after carotid artery compression. Geroscience. 2023 Dec;45(6):3333-3357. doi: 10.1007/s11357-023-00896-1. Epub 2023 Aug 21. PMID: 37599343; PMCID: PMC10643517.

12: Magyar-Stang R, István L, Pál H, Csányi B, Gaál A, Mihály Z, Czinege Z, Sótonyi P, Tamás H, Koller A, Bereczki D, Kovács I, Debreczeni R. Impaired cerebrovascular reactivity correlates with reduced retinal vessel density in patients with carotid artery stenosis: Cross-sectional, single center study. PLoS One. 2023 Sep 14;18(9):e0291521. doi: 10.1371/journal.pone.0291521. PMID: 37708176; PMCID: PMC10501613.

13: Cziraki A, Nemeth Z, Szabados S, Nagy T, Szántó M, Nyakas C, Koller A. Morphological and Functional Remodeling of the Ischemic Heart Correlates with Homocysteine Levels. J Cardiovasc Dev Dis. 2023 Mar 14;10(3):122. doi: 10.3390/jcdd10030122. PMID: 36975886; PMCID: PMC10056082.

14: Alasztics B, Kovács ÁF, Pállinger É, Szabó-Taylor KÉ, Szabó G, Molvarec A, Koller A, Rigó J Jr. Upregulation of exofacial peroxiredoxin-thioredoxin system of lymphocytes and monocytes in preeclampsia. Pregnancy Hypertens. 2023 Mar;31:54-59. doi: 10.1016/j.preghy.2022.12.002. Epub 2022 Dec 12. PMID: 36587441.

15: Csonka D, Kalmár Nagy K, Szakály P, Szukits S, Bogner P, Koller A, Kun S, Wittmann I, Háber IE, Horváth IG. Optimal Renal Artery-Aorta Angulation Revealed by Flow Simulation. Kidney Blood Press Res. 2023;48(1):249-259. doi: 10.1159/000530169. Epub 2023 Mar 20. PMID: 36940678; PMCID: PMC10173746.