

Hypertension and Dementia: a Bench to Bedside Approach



Costantino Iadecola, M.D.
Anne Parrish Titzell Professor of Neurology
Director (Chair) Feil Family Brain and Mind Research Institute
Weill Cornell Medical College, New York, USA

The brain is uniquely dependent on a well-regulated delivery of oxygen and glucose through the blood supply. If the delivery of cerebral blood flow is not adequate to match the dynamic energetic requirements imposed by neural activity, brain dysfunction and damage ensues. Although the mechanisms of the cognitive dysfunction caused by vascular factors (vascular cognitive impairment and dementia) or neurodegeneration (Alzheimer's disease, AD) have traditionally been considered distinct, there is increasing evidence that alterations in cerebral blood flow play a role not only in vascular causes of cognitive impairment, but also in AD. Vascular risk factors and AD impair the structure and function of cerebral blood vessels and associated cells (neurovascular unit), effects mediated by vascular oxidative stress and inflammation. Injury to the neurovascular unit alters cerebral blood flow regulation, depletes vascular reserves, disrupts the blood-brain barrier and reduces the brain's repair potential, effects that amplify the brain dysfunction and damage exerted by incident ischemia and coexisting neurodegeneration. Clinical-pathological studies support the notion that vascular lesions aggravate the deleterious effects of AD pathology by reducing the threshold for cognitive impairment and accelerating the pace of the dementia. In addition, disturbances of cerebral perfusion and/or energy metabolism have also been observed early in the course of AD or even in non-demented subjects at genetic risk for AD. These observations, collectively, indicate that vascular alterations are important both in vascular and neurodegenerative dementias. In the absence of mechanism-based approaches to counteract dementia, targeting vascular risk factors and improving cerebrovascular function offers the opportunity to mitigate the impact of one of the most disabling human afflictions.

CURRICULUM VITAE

Education

1977: MD, University of Rome Medical School, Rome, Italy

Positions and Employment

1980-82: Post-Doctoral Fellow, Lab. of Neurobiology, Cornell University Med. Coll., New York, NY.

1982-83: Instructor in Neurology, Cornell University Med. Coll., New York, NY.

1984-86: Assistant Professor of Neurology, Cornell University Med. Coll, New York, NY.

1986-87: Medical Intern, Columbia University-Harlem Hospital Center, New York, NY.

1987-1990: Neurology Resident, Dept. of Neurology, New York Hospital-Cornell Univ. Med. Ctr., New York

1990-93: Assistant Professor of Neurology, Dept. of Neurology, Univ. of Minnesota School of Medicine, Minneapolis, MN.

1993-97: Associate Professor, Dept. of Neurology, Univ. of Minnesota School of Med., Minneapolis, MN.

1997-2001: Professor, Dept. of Neurology, Univ. of Minnesota School of Medicine, Minneapolis, MN.

2001-2012: G. C. Cotzias Distinguished Professor of Neurology and Neuroscience, Dept. of Neurology and Neuroscience; Chief, Division of Neurobiology, Weill Cornell Medical College, New York, NY.

2012-present: Director (Chair), Brain and Mind Research Institute, The Anne Parrish Titzell Professor of Neurology, Weill Cornell Medical College, New York, NY.

Peer Review Groups and Committees: Study Sections: Chair, NIH ZNS1 SRB Review Committee (2010, 2011, 2012); Member, NSD-A/NINDS Study Section (2002-2006; Chair: 2005-2007); Member BINP study section (2013-); American Heart Association, Brain Study Group (Chair: 2001-2003); Alzheimer Association; MRC; Wellcome Trust; NSF; Scientific Advisory Committees: Hotchkiss Brain Institute, Univ. of Calgary; European Stroke Network; Fondation Leducq; Cluster for Systems Neurology (SyNergy); TargetBrain European Union Consortium; DHU NeuroVasc Sorbonne Paris-Cite; Munich Institute of Stroke and Dementia Research; Stroke Section Strategic Plan, American Academy of Neurology.

Editor: *Journal of Neuroscience* (Reviewing Editor: 2007-2013); *Stroke* (Consulting Editor); *Clinical Science* (Associate Editor); *Circulation* (Guest Editor); *Hypertension* (Guest Editor); *Proceeding of the National Academy of Sciences* (Guest Editor);

Editorial Boards: *Circulation Research*, *Annals of Neurology*; *Cerebrovascular Diseases*; *Journal of Cerebral Blood Flow and Metabolism*; *Cellular and Molecular Neurobiology*.

Selected Publications (from over 270 peer-reviewed publications)

1. Kawano T, Anrather J, Zhou P, Park L, Wang G, Frys KA, Kunz A, Cho S, Orio M and **Iadecola C**: Prostaglandin E₂ EP1 receptors: Downstream effectors of COX-2 neurotoxicity. *Nat Med.* 12:225-229, 2006
2. Kazama K, Anrather J, Zhou P, Girouard H, Frys K, Milner T and **Iadecola C**: Angiotensin II impairs neurovascular coupling in neocortex through NADPH-derived radicals. *Circ. Res.*, 95:1019-1026, 2004
3. Girouard H, Park L, Anrather J, Zhou P and **Iadecola C**: Cerebrovascular nitrosative stress mediates neurovascular and endothelial dysfunction induced by angiotensin II. *Arterioscler. Thromb. Vasc. Biol.*, 27:303-309, 2007
4. Kim Y, Zhou P, Qian L, Chuang J-Z, Lee J, Li C, **Iadecola C**, Nathan C and Ding A: MyD88-5 links mitochondria, microtubules, and JNK3 in neurons and regulates neuronal survival. *J Exp Med.* 204:2063-2074, 2007. PMID: PMC2118693.
5. Moskowitz MA, Lo EH and **Iadecola C**: The science of stroke: mechanisms in search of treatments. *Neuron* 67(2):181-98, 2010. PMID: PMC2957363
6. **Iadecola C**, and Anrather J: The immunology of stroke: From mechanisms to translation. *Nature Medicine*, 17: 796-808, 2011. PMID: PMC3137275
7. Capone C, Faraco G, Coleman C, Young CN, Anrather J, Pickel V, Davisson RL and **Iadecola C**: Endothelin-1-dependent neurovascular dysfunction in chronic intermittent hypoxia. *Hypertension*, 60:106-113, 2012
8. Young C, Cao X, Guraju M, Pierce J, Morgan D, Wang G, **Iadecola C**, Mark AL and Davisson RL: Endoplasmic Reticulum Stress in the Brain Subfornical Organ Mediates Angiotensin-Dependent Hypertension. *J. Clin Invest.*, 122: 3960-4, 2012
9. Kamel H, Johnston SC, Kirkham JC, Turner CG, Kizer JR, Devereux RB and **Iadecola C**: Association Between Major Perioperative Hemorrhage and Stroke or Q-Wave Myocardial Infarction. *Circulation*, 126:207-212, 2012
10. Jackman K, Kahles T, Lane D, Garcia-Bonilla L, Abe T, Capone C, Hochrainer K, Voss H, Zhou P, Ding A, Anrather J and **Iadecola C**: Progranulin deficiency promotes post-ischemic blood-brain barrier disruption. *J. Neurosci.*, 33:19579-19589, 2013
11. **Iadecola C**: The pathobiology and vascular dementia. *Neuron* 80:844-866, 2013.
12. Garcia-Bonilla L, Moore JM, Racchumi G, Butler J, **Iadecola C** and Anrather J: Inducible nitric oxide synthase in neutrophils and endothelium contributes to ischemic brain injury in mice. *J Immunol*, 193:2531-2537, 2014
13. Park L, Wang G, Moore J, Girouard H, Zhou P, Anrather J and **Iadecola C**: Key role of transient receptor potential melastatin-2 channels in amyloid- β -induced neurovascular dysfunction. *Nature Communications*, 5:5318, 2014
14. Park L, Koizumi K, Jamal El S, Zhou P, Previti ML, Van Nostrand WE, Carlson G, **Iadecola C**. Age-Dependent Neurovascular Dysfunction and Damage in a Mouse Model of Cerebral Amyloid Angiopathy. *Stroke*, 45:1815-1821, 2014
15. Gialdini G, Nearing K, Bhave PD, Bonuccelli U, **Iadecola C**, Healey JS and Kamel H: Postoperative atrial fibrillation and the long-term risk of ischemic stroke. *JAMA*, 312:616-622, 2014
16. Yin F, Banerjee R, Thomas B, Zhou P, Qian L, Jia T, Ma X, Ma Y, **Iadecola C**, Beal MF, Nathan C and Ding A: Exaggerated Inflammation and Brain Dysfunction in Progranulin-Deficient Mice. *J. Exp. Med.*, 207:117-128, 2010. PMID: PMC2812536

17. Park L, Zhou J, Zhou P, Pistick R, El Jamal S, Younkin L, Pierce J, Arreguin A, Anrather J, Younkin SG, Carlson GC, McEwen B and Iadecola C: Innate immunity receptor CD36 promotes cerebral amyloid angiopathy. *Proc. Natl. Acad. Sci. USA*, 110:3089, 2013
18. Faraco G, Moraga A, Moore J, Anrather J, Pickel VM and Iadecola C: Circulating Endothelin-1 Alters Critical Mechanisms Regulating Cerebral Microcirculation. *Hypertension*, 62:759-766, 2013
19. Coleman C, Wang G, Faraco G, Lopes JM, Waters E, Milner TA, Iadecola C and Pickel VM: Membrane trafficking of NADPH oxidase p47phox in paraventricular hypothalamic neurons parallels local free radical production in angiotensin II slow-pressor hypertension. *J. Neurosci.* 33:4308-4316, 2013
20. Meschia JF, Bushnell C, Boden-Albala B, Braun LT, Bravata DM, Chaturvedi S, Creager MA, Eckel RH, Elkind MSV, Fornage M, Goldstein LB, Greenberg SM, Horvath SE, Iadecola C, Jauch EC, Moore WS and Wilson JA: Guidelines for the primary prevention of stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*, 45:3754-3832, 2014