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Homoarginine Levels Are Regulated by L-Arginine:Glycine Amidinotransferase and Affect Stroke Outcome - Results From Human and Murine Studies

Chi-un Choe*; Dorothee Atzler*; Philipp S. Wild; Angela M. Carter; Rainer H. Böger; Francisco Ojeda; Olga Simova; Malte Stockebrand; Karl Lackner; Christine Nabuurs; Bart Marescaur; Thomas Streichert; Christian Müller; Nicole Lüneburg; Peter P. De Deyn; Ralf A. Benndorf; Stephan Baldus; Christian Gerloff; Stefan Blankenberg; Arend Heerschap; Peter J. Grant; Tim Magnus; Tanja Zeller; Dirk Isbrand and Edzard Schwedhelm
**contributed equally*

ABSTRACT:
BACKGROUND: Endogenous arginine homologues, including homoarginine, have been identified as novel biomarkers for cardiovascular disease and outcomes. Our studies of human cohorts and a confirmatory murine model associated the arginine homologue homoarginine and its metabolism with stroke pathology and outcome.
METHODS AND RESULTS: Increasing homoarginine levels were independently associated with a reduction in all-cause mortality in patients with ischemic stroke (7.4 years of follow-up; hazard ratio for 1-SD homoarginine, 0.79 [95% confidence interval, 0.64-0.96]; P=0.019; n=389). Homoarginine was also independently associated with the National Institutes of Health Stroke Scale+age score and 30-day mortality after ischemic stroke (P<0.05; n=137). A genome-wide association study revealed that plasma homoarginine was strongly associated with single nucleotide polymorphisms in the l-arginine:glycine amidinotransferase (AGAT) gene (P<2.1×10-8; n=2806), and increased AGAT expression in a cell model was associated with increased homoarginine. Next, we used two genetic murine models to investigate the link between plasma homoarginine and outcome after experimental ischemic stroke: (1) an AGAT deletion (AGAT-/-) and (2) a guanidinoacetate N-methyltransferase deletion (GAMT-/-) causing AGAT upregulation. As suggested by the genome-wide association study, homoarginine was absent in AGAT-/- mice and increased in GAMT-/- mice. Cerebral damage and neurological deficits in experimental stroke were increased in AGAT-/- mice and attenuated by homoarginine supplementation, whereas infarct size in GAMT-/- mice was decreased compared with controls.
CONCLUSIONS: Low homoarginine appears to be related to poor outcome after ischemic stroke. Further validation in future trials may lead to therapeutic adjustments of homoarginine metabolism that alleviate stroke and other vascular disorders.

STATEMENT: *We identified homoarginine as a novel biomarker for short- and long-term outcome after acute ischemic stroke. In multivariable models, adjusted for previously identified risk factors, a 21% to 31% reduction in risk for secondary events was observed by increasing plasma homoarginine. Furthermore, homoarginine was significantly correlated with neurological impairment quantified by National Institutes of Health Stroke Scale score and age. Using genome-wide association studies and genetically modified mice, we showed that homoarginine is regulated by the enzyme L-arginine:glycine-amidinotransferase (AGAT) in humans and mice and demonstrated that this pathway is the major source for homoarginine synthesis in mice. Applying an experimental model of ischemic stroke in AGAT-deficient mice, we confirmed a causal link between homoarginine and stroke. These findings suggest that homoarginine is a novel biomarker and potential therapeutic target in the management of stroke in humans.*

BACKGROUND: This work was performed at the Departments of Neurology, Clinical Pharmacology and Toxicology, and the DFG-Heisenberg-Group Experimental Neuropediatrics. In total, five departments and 17 scientists from the UKE were involved in this translational project combining human and murine studies. This work was supported by the Deutsche Forschungsgemeinschaft, an Else Kröner Memorial Stipendium, Stiftung Rheinland-Pfalz Wissen-schafft-Zukunft, Integrierte Verbünde der Medizinischen Genomforschung–NGFN-Plus, Stiftung Pathobiochemie and Werner-Otto-Stiftung.