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Potential therapeutic targets for stroke and truamatic brain injury.

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Abstract

Traumatic brain injury (TBI) often causes disturbances in cerebral blood flow (CBF) through cerebral or/ and Subarachnoid hemorrhage (SAH) leading to ischemic damage. Despite our knowledge of the etiology and consequences of TBI/SAH, therapeutic management of this devastating condition continues to elude healthcare professionals. We have studied series of molecular strategies involving tyrosine kinase, the gaso-transmitters (H_2S and CO), HO-1, and PPAR in an attempt to evaluate their neurovascular protection capabilities. Urethane-anesthetized rats grouped into three study groups were subjected to SAH (0.3 mL of blood, i.c) before or after treatment with vehicle, tyrphostin or Calphostin C (inhibitor of PTK or PKC); clofibrate a PPAR activator, HO-1 activator $CoCl_2$ or inhibitor SnMPP; H_2S precursor L-Cysteine, CBS/CSE inhibitor propargylyglycine (PPG). Laser Doppler Scanner/flowmetry (Moor LDI 5152/PERIMED) was used to determine changes in CBF. Basal CBF was increased by PTK and PKC inhibition and SAH reduced CBRF by 47$\pm$6%. Inhibition of PTK but not PKC before SAH attenuated fall in CBF. Post SAH administration of inhibitors resulted in full reversal of SAH-induced fall in CBF for PTK but not for PKC inhibition. Clofibrate and $CoCl_2$ increased CBF while SnMPP reduced CBF by 30%. Clofibrate and $CoCl_2$ pretreatments prevented and SnMPP potentiated SAH-induced fall in CBF. SnMPP obliterated clofibrate-induced attenuation of SAH-induced fall in CBF. NaHS or L-Cysteine increased and PPG reduced basal CBF. L-Cysteine had no effect on PPG-induced reduction of CBF but NaHS elicited a short-lived reversal. H_2S-induced regulation of CBF was influenced by age as L-Cysteine as well as NaHS increased CBF in the young compared to a sustained reduction in the adult rat. Pretreatment with L-Cysteine prevented SAH-induced fall in CBF. **Conclusions**: PTK but not PKC, precursor of H_2S as well as activation of HO-1 and PPAR increased CBF, prevented, and reversed SAH-induced fall in CBF indicating a possible crucial role for PTK, H S, HO-1 and PPAR pathways in the clinical manifestation and complications of Stroke and TBI.These pathways could serve as therapeutic targets for the prevention and management of early ischemic brain damage following stroke/TBI. Further studies elucidating the molecular mechanisms of these pathways in cerebral neurovascular function and regulations are needed.

Biography: *MOMOH A. YAKUBU, PhD* obtained his PhD in Materia Medica from the University of Glasgow Scotland and postdoctoral studies in Michigan State University, Lansing, MI and was at the UTHSc, Memphis TN. He joined the Center for Cardiovascular Disease in 2001 as Senior Scientist & Head, Vascular Biology Unit Texas Southern University, Houston, Tx. He is currently Associate Professor, Environmental & Interdisciplinary Sciences, a member of Mission Connect-The Institute for Rehabilitation and Research (TiRR) dedicated to pioneering medical treatments to help people who have sustained a neurological injury -spinal cord or traumatic brain injury.