Mark S Kindy, Brain Disord Ther 2015, 4:5
http://dx.doi.org/10.4172/2168-975X.S1.005

OMICS International
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International Conference on
Brain Disorders & Therapeutics
August 24-26, 2015 London, UK

The cysteine protease cathepsin B is a key drug target and cysteine protease inhibitors are potential therapeutics for traumatic brain injury

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There are currently no effective therapeutic agents for traumatic brain injury (TBI) but drug treatments for TBI can be developed by validation of new drug targets and demonstration that compounds directed to such targets are efficacious in TBI animal models using a clinically relevant route of drug administration. The cysteine protease, cathepsin B has been implicated in mediating TBI but it has not been validated by gene knockout (KO) studies. Therefore, this investigation evaluated mice with deletion of the cathepsin B gene receiving controlled cortical impact TBI trauma. Results indicated that KO of the cathepsin B gene resulted in amelioration of TBI shown by significant improvement in motor dysfunction, reduced brain lesion volume, greater neuronal density in brain and lack of increased proapoptotic Bax levels. Notably, oral administration of the small-molecule cysteine protease inhibitor, E64d immediately after TBI resulted in recovery of TBI-mediated motor dysfunction and reduced the increase in cathepsin B activity induced by TBI. E64d outcomes were as effective as cathepsin B gene deletion for improving TBI. E64d treatment was effective even when administered 8 hours after injury indicating a clinically plausible time period for acute therapeutic intervention. These data demonstrate that a cysteine protease inhibitor can be orally efficacious in a TBI animal model when administered at a clinically relevant time point post-trauma and that E64d-mediated improvement of TBI is primarily the result of inhibition of cathepsin B activity. These results validate cathepsin B as a new TBI therapeutic target.

Biography

Mark S Kindy is a Professor/Associate Chair for Research in the Department of Regenerative Medicine and Cell Biology at MUSC and Senior Research Career Scientist/Deputy ACOS for Research at the VA Medical Center in Charleston, SC. He received his BS from the University of Massachusetts in Zoology and PhD from Boston University School of Medicine in Biochemistry. He was a Post-doctoral fellow at the Salk Institute. He was at University of Kentucky in the Department of Biochemistry and the Center on Aging. His area of expertise is neurodegenerative disorders, animal modeling, mechanisms associated with diseases and regeneration of the brain.

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