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Compound 21 is pro-angiogenic in the brain and results in sustained recovery after ischemic stroke

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Introduction: Angiotensin II type 2 receptor (AT2R) stimulation is neuroprotective after experimental stroke. However, the therapeutic utility of AT2R stimulation has been hampered by the lack of a specific agonist with favorable bioavailability. Compound 21 (C21) - the first non-peptide AT2R agonist - offers a potential option to enhance stroke recovery. This study aimed to investigate the effect of C21 administration on early and late stroke outcomes, and the molecular mediators involved.

Methods: Rats were subjected to 3 h or 90min of middle cerebral artery occlusion (MCAO) and randomized to intraperitoneal C21 (0.03 mg/kg) or saline at reperfusion. Animals were sacrificed at 24h or 7 days and brains were collected for molecular analysis and immunostaining, respectively. Functional outcome at days 1, 4 and 7 was assessed blindly. C21 angiogenic potential was assessed *in vitro*.

Results: After 3h of MCAO, C21 treatment reduced infarct size and improved behavioral outcome at 24h without affecting blood pressure. Co-administration of the AT2R antagonist (PD123319) blocked these effects. On the molecular level, C21 decreased brain hemoglobin content, down-regulated apoptotic and oxidative markers, and increased pro-survival molecules in the brain. After 90min of MCAO, C21 treatment resulted in sustained functional improvement at 7 days, together with increased vascular density in the ischemic penumbra. *In vitro*, C21 showed a pro-angiogenic effect that was blocked with brain-derived neurotrophic factor neutralization.

Conclusion: These findings demonstrate that a single dose of C21 is neurovascular-protective and improves stroke outcome possibly through increasing neurotrophin activity, mitigating brain inflammation and promoting antioxidant and pro-angiogenic effects.

Biography

Ahmed Alhusban graduated from Jordan University of Science and Technology (JUST) in 2008 with a Doctor of Pharmacy (PharmD) degree. He had his PhD in Experimental Therapeutics from University of Georgia, USA. His PhD research was under the supervision of Dr. Susan C. Fagan to study the mechanisms of recovery after cerebral ischemia and how to manipulate them to improve stroke outcome. His PhD thesis focused on interventions to up-regulate brain derived neurotrophic factor (BDNF) mediated signaling after stroke. His research interests are focused on brain angiogenesis. Currently he is an Assistant Professor at the Faculty of Pharmacy, JUST.

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