A-1866

ADAM17 mediated activation of microglia leads to neuronal excitation and neuroinflammation in Ang-II induced hypertension.

Laiba Iqbal[1], Uma Priya Mohan[2,3], Eric Lazartigues[3,4]

[1]Cardiovascular Center of Excellence, Louisiana State University Health Sciences Center - School of Medicine, [2]Cardiovascular Center of Excellence, Louisiana State University Health Sciences Center New Orleans, [3]Southeast Louisiana Veterans Health Care System, [4]Cardiovascular Center of Excellence, Cardiovascular Center of Excellence, Louisiana State University Health Sciences Center - School of Medicine

Text:
ADAM17 sheds several cytokines and receptors (e.g. TNFα, CX3CL1 and IL-6R) which act on surrounding cells, including neurons and microglia, to modulate synaptic function. We recently observed that CX3CL1 is significantly elevated in neuronal cultures exposed to Ang-II and that ADAM17 on microglia is involved in the local reduction of ACE2 levels. Accordingly, we hypothesize that ADAM17 – mediated shedding of CX3CL1 from neurons will promote CX3CR1 activation in microglia leading to TNF-α and IL-1β secretion. Mature neurons (N2A) and microglia (BV2) cell lines were grown to 80% confluency. Neurons were pre-treated with siRNA for iRhom1, a protein involved in ADAM17 maturation, or scrambled siRNA (10 nM) and after 48 h, the neurons were exposed to Ang-II (300 nM). After 24 h, the conditioned medium was collected and divided for ACE2 activity and measurement of cytokine levels. Microglia cultures were exposed for 24 h to conditioned medium before the medium was assessed for cytokine levels. In addition, proteins were also extracted from the cells for analyzing the expression of ADAM17 and ACE2. Neurons treated with iRhom1 siRNA + Ang-II showed a reduced level of proinflammatory cytokines, including IL-6 (Scramble siRNA + Ang-II: 759±65 pg/mL, iRhom1 siRNA + Ang-II: 523±38 pg/mL, $P<0.05$), and increased TNFα receptor 1 (Scramble siRNA + Ang-II: 0.43±0.1 pg/mL vs iRhom1 siRNA + Ang-II: 1.4±0.1 pg/mL vs Control: 1±0.1 pg/mL and scramble siRNA: 0.9±0.2 pg/mL), respectively ($P<0.05$ n=6). Microglia activation was assessed by the expression of TMEM119 using capillary western. (Scramble siRNA + Ang-II: 0.38±0.1, iRhom1 siRNA + Ang-II: 1.0±0.2 vs. Control: 1.1±0.2 and scramble siRNA: 0.9±0.2, $P<0.05$). Taken together our data suggests that neuronal ADAM17 maturation is required for microglial activation in Ang-II induced hypertension.

Support or Funding Information:
This work was supported in part by a research grant from the National Institutes of Health (HL163588).

Print Close