Modulation of endoplasmic reticulum stress response in gut-origin encephalopathy: Impact of vascular endothelial growth factor receptor-2 manipulation

Hanan Salah ,Doaa A Zaky, Walaa Wadie, Wagdy M Eldehna, Ahmed M El Kerdawy, Dalaal M Abdallah

Abstract

Background: Septic encephalopathy, the most frequent complication of sepsis, is orchestrated by a complex interplay of signals that leads to high mortality rates among intensive care unit patients. However, the role of the vascular endothelial growth factor receptor-2 (VEGFR2) in endoplasmic reticulum stress response (ERSR), during septic encephalopathy, is still elusive.
Aim: This study was aimed to examine the effect of an in-house designed/synthesized VEGFR2 antagonist, named WAG4S, on septic encephalopathy using cecal ligation and perforation (CLP).
Main methods: Rats were intraperitoneally injected with WAG-4S (1 mg/kg/d) for 7 days post-CLP.
Key findings: In septic animals, VEGFR2 antagonism declined the expression of cortical p-VEGFR2 and p-mammalian target of rapamycin complex-1 (p-mTORC1). It also worsened the behavioral and histopathological alterations beyond CLP. However, and contrary to CLP, WAG-4S decreased the p-protein kinase R-like ER kinase (p-PERK) and eukaryotic initiation factor-2Ŭ (p-eIF2Ŭ) expression. Moreover, VEGFR2 blockade upregulated the mRNA expression of activating transcription factor-4 (ATF4), binding immunoglobulin protein/glucose-regulated protein-78 (Bip/GRP78), growth arrest and DNA damage-34 (GADD34) and spliced X-box binding protein-1 (XBP1s) above CLP. Similarly, it boosted inositol requiring enzyme-1Ŭ (IRE1Ŭ) activation and redox imbalance. In the same context, WAG-4S augmented the protein levels of CLP-induced ERSR apoptotic markers, namely C/EBP homologous protein (CHOP/GADD153), c-jun N-terminal kinase (JNK) and caspase-3.
Significance: In conclusion, the PERK/eIF2Ŭ axis inhibition, during septic encephalopathy, is VEGFR2-independent, whereas the activated IRE1Ŭ/XBP1s/CHOP/JNK/caspase-3 cue promotes the ERSR execution module through VEGFR2 inhibition. This has turned VEGFR2 into a potential therapeutic target for ameliorating such an ailment.

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