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Targeting specific gene splicing with Calcium channel inhibitors against the inflammatory effect of bacterial lipopolysaccharide in vivo

Bahram Alamdary Badlou

Utrecht University, The Netherlands

Abstract

Trauma patients, who are exposed to bacterial infections i.e. traumatic accidents are at risk to be exposed to so-called "LUCOHAS" (mortal LPS-UPR- Calcium Overload Hyper- Activation System). The essential components of LUCOHAS signaling pathway are consist of 4 main key players. The aim of this study is to evaluate induction of inflammatory processes and assess the administration effects at molecular and tissue cytokine changes, in an innovative prepared model system, in vivo.

Methods: The LPS was extracted from patients' burned wounds after Pseudomonas aeruginosa isolation (hLPS), with informed consent. The male c57/BL6 mice divided into 6 groups: 1. Two controls, one received nothing another sterile pyrogen-free normal saline, 3. hLPS (3 mg/kg/ intraperitoneal), 4. hLPS+ Dantrolene sodium (Dan)-calcium release inhibitor (CCI1) (40 mg/kg), 5. 2-aminomethyl phenyl borinate (2APB)-CCI2 (1 mg/kg) and 6. hLPS+CCI1/CCI2. Subsequently, mice livers were extracted for evaluating the X-box Binding Protein 1 gene (XBP-1) Splicing as a marker of the adaptive UPR activation and cytokine assay after 2, 8 and 24 hrs.

Results: Compared to the controls, the IL-1β levels in hLPS group significantly increased after 8 and 24 h injection ($P<0.05$). Treatment with CCIs decrease dramaticallythis level ($P < 0.05$). TNF-α level 2, 8 and 24 h after hLPS injection remarkably increase in comparison to the control group ($P < 0.01$), treatment with CCIs decreases this level ($P <0.05$). Compared to control groups, treatments with the hLPS injections showed a significant increase in the XBP-1 splicing. Compared to all attempts to inhibit calcium release, hLPS with combined CCI1/ CCI2 showed significant increase in the XBP-1 splicing after 2, 8 and 24 h ($P < 0.05$). Our results clearly showed that combination of both CCIs had better effectiveness to inhibit (pro-) inflammatory processes and could be considered as a new strategy to manage and prevent the LUCOHAS, appropriately.

Biography

Bahram Alamdary Badlou is working as CEO and Medical Advisor at BBAdvies and Research, Zeist, The Netherlands. He got his PhD on Hematology with specialty over Platelets metabolism in Health and Diseases from Medicine Faculty UMCU, Utrecht The Netherlands. He got his Drs in Medical Biology with specialty over Cardiology.

Publications

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