Carbon monoxide and nitric oxide as antimicrobial agents

– focus on ESBL-producing uropathogenic E. coli

av

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Akademisk avhandling

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Abstract
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Urinary tract infections (UTI) are common in humans and most often caused by uropathogenic Escherichia coli (E. coli). Extended-spectrum beta-lactamase (ESBL)-producing E. coli are increasing worldwide and they are frequently multidrug-resistant with limited treatment options. The overall aim of this thesis was to study the role of the host-derived factors nitric oxide (NO) and carbon monoxide (CO) as antimicrobial agents against ESBL-producing uropathogenic strains of E. coli (UPEC).

The NO-donor DETA/NO caused a temporary growth inhibition in ESBL-producing UPEC. The antibacterial effect of DETA/NO was improved when DETA/NO was combined with miconazole, a pharmacological inhibitor of NO-protective mechanisms. Combination treatment with DETA/NO, miconazole and polymyxin B nonapeptid prolonged the bacteriostatic effect in the majority of examined isolates. The CO-donor CORM-2 showed a pronounced antibacterial effect in ESBL-producing UPEC with a fast bactericidal effect. Moreover, CORM-2 was shown to reduce the bacterial viability of ESBL-producing UPEC grown under biofilm-like conditions and to decrease the bacterial colonization of human bladder epithelial cells. A microarray analysis was performed to define transcriptomic targets of CORM-2 after a single exposure and after repeated exposure to CORM-2. Many processes were affected by CORM-2, including a downregulation in energy metabolism and biosynthesis pathways and upregulation of the SOS response and DNA repair. Repeated exposure to CORM-2 did not change the gene expression patterns or fold changes and the growth inhibitory response to CORM-2 was not altered after repeated exposure.

In conclusion, NO- and CO-donors have antibacterial effects against ESBL-producing UPEC and may be interesting candidates for development of new antibiotics to treat UTI caused by multidrug-resistant uropathogens.

Keywords: biofilm, carbon monoxide, CORM-2, DETA/NO, extended-spectrum beta-lactamases, nitric oxide, urinary tract infection, uropathogenic Escherichia coli.

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