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Inhibition of human neutrophil elastase by mean of enriched polysulfone membrane by synthetic elastase inhibitor

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Chronic kidney disease patients undergoing haemodialysis (HD) treatment suffer from chronic inflammation caused by the disease associated conditions and by the long-term contact of blood with artificial material of HD membrane. As consequence of inflammation, the patients have elevated risk of cardiovascular diseases, and therefore markedly higher mortality rate, compared to healthy population.[1]

One of the promising approach to diminish inflammation is to inhibit human neutrophil elastase (HNE), which is excessively released from overstimulated neutrophils during the HD treatment. Synthetic inhibitors with structure derived from 4-oxo-β-lactams showed to be highly potent and selective in inhibition of free circulating HNE. The inhibitors react with an active site of HNE and cause irreversible enzyme inhibition.[2]

The enrichment of HD membrane with inhibitor could provide direct HNE inhibition during the treatment procedure. For this purpose, in-house prepared polysulfone membrane was enriched with newly synthetized inhibitor containing 4-oxo-β-lactam structure. The ability of modified membrane to diminish elastase activity was evaluated *in vitro*, using kinetic fluorometric assay. Membrane with identical composition, without inhibitor, was used as a blank membrane.

Two enrichment approaches were evaluated: direct incorporation of the inhibitor into membrane structure during the preparation process; and adsorption on membrane surface after immersion in inhibitor solution.

Using the adsorption technique, we reached the inhibition of HNE activity up to 30 %, while the direct incorporation didn't show such as satisfactory result. Different inhibitor concentrations (100; 50; 20; 10 nM) were used for superficial adsorption to reach the maximal inhibition, however the adsorption capacity of the membrane has to be further studied, in order to obtain the best initial inhibitor concentration. The inhibitor in all tested concentrations was evaluated for haemolytic activity in order to screen the hemocompatibility of the tested compound. None of the evaluated concentration did cause lysis of erythrocytes.

These preliminary results show, that adsorption of the newly synthetized HNE inhibitor on the polysulfone membrane used directly for HD procedure could represent new promising therapeutic strategy to diminish negative impact of elevated HNE levels, presented by the chronic kidney disease patients.

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