NCX 4016 (NO-ASPIRIN) INHIBITS LPS-INDUCED TISSUE FACTOR EXPRESSION IN VIVO: ROLE OF NITRIC OXIDE

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Background: NCX-4016 is an acetylsalicylic acid (ASA) derivative containing a nitric oxide-releasing moiety. Compared to ASA, NCX-4016 has a broader spectrum of antithrombotic and antiinflammatory activities. We hypothesized that NCX-4016 might inhibit *in vivo* LPS-induced expression of tissue factor (TF).
Methods and Results: Rats were administered 90 mg/kg NCX-4016 orally for 5 days. Placebo, 50 mg/kg acetylsalicylic acid (ASA), and 80 mg/kg isosorbide-5-mononitrate (ISMN) were used in control groups. On day 5, rats were injected intraperitoneally with 100 μg/kg LPS and sacrificed 6 hours later. The expression of TF in monocytes was measured by flow-cytometry and Western blot analysis. RT-PCR was performed to assess expression of TF and cyclooxygenase-2 (COX-2) genes. Plasma concentrations of interleukin-1β and tumor necrosis factor-α were measured. Urine samples were collected to evaluate the excretion of the thromboxane metabolite 11-dehydro-TXB_2. Gastric mucosa was inspected. LPS injection was followed by synthesis TF and COX-2 mRNAs in circulating monocytes, that were blunted by NCX-4016 but not by ASA or ISMN. Both NCX-4016 and ISMN reduced TF expression on surface of circulating monocyte. LPS increased the excretion 11-dehydro-TXB_2, and this was prevented by NCX-4016 and ASA. Unlike ASA, NCX-4016 reduced plasma interleukin-1 and tumor necrosis factor- . In addition, NCX-4016 almost completely prevented mucosal damage, while ASA increased the extension of gastric lesions in LPS-injected rats.

Conclusions: NCX-4016 prevents monocyte TF expression; this is accompanied by inhibition of TX and cytokine biosynthesis. These additive effects of nitric oxide release and COX inhibition, may help explain efficacy and tolerability of NCX-4016.