NCX 4040, A NITRIC OXIDE-DONATING ASPIRIN DERIVATIVE WITH IMPROVED ANTI-INFLAMMATORY PROPERTIES

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Aspirin has been modified by incorporating into the chemical structure a nitric oxide (NO)-donating moiety. Among the different compounds synthesized, here we describe the profile of NCX 4040, a NO-donating aspirin derivative, in studies conducted in human whole blood and isolated monocytes. Its property to release NO may translate into lesser gastrointestinal and renal side effects as compared to NSAIDs. In this study, we tested the inhibitory effects of NCX 4040 *versus* aspirin on COX-isozyme activity and cytokine production [interleukin (IL)-1β, tumor necrosis factor (TNF)-α and IL-10] in human whole blood in response to lipopolysaccharide (LPS). In isolated human monocytes, we explored whether inhibition of NF-κB activation contributes to the antiinflammatory effects of NCX 4040. In whole blood, aspirin was a potent inhibitor of platelet COX-1, while not significantly affecting inducible COX-2. NCX 4040 only partially inhibited platelet COX-1 (<50% at 100 μM), while caused a concentration-dependent inhibition of LPS-induced COX-2 activity with an IC_{50} value of 0.27 μM (95% CI: 0.049-1.5). Differently from aspirin, NCX 4040 inhibited the release of IL-10, IL-1β and TNF-α with IC_{50} values of: 0.16 μM (95% CI, 0.08-0.32), 1.8 μM (95% CI, 0.8-4.2) and 1.2μM (95% CI, 0.7-1.9), respectively. In isolated monocytes, NCX 4040, but not aspirin, down-regulated COX-2 protein expression and cytokine production. These effects were associated with increased levels of IκBα. In conclusion, NCX 4040 is a novel compound with improved antiinflammatory properties *versus* the parent drug due to an inhibitory effect on NF-κB activation. The compound is of interest to assess the role of inflammation in different pathological conditions.