EFFECT OF NITRIC OXIDE (NO)-DONATING AGENTS ON MONOCYTE COX-2

M. Leone, T. Corazzi, P. Del Soldato *, P. Gresele.
*Department of Internal Medicine, Section of Internal and Cardiovascular Medicine, University of Perugia, Italy; * NicOx Research Institute, Milan, Italy.*

Two COX isoforms exist : COX-1 (constitutive) and COX-2 (inducible). COX-2 is involved in inflammation but has been implicated in ischemic cardiovascular disease too. Aspirin is only a weak COX-2 inhibitor. As NO regulates COX activity in various cell system, we have investigated the effect of the novel NO-donating aspirin NCX 4016, and other NO-donors, on monocyte COX-2.

Heparinized human whole blood was incubated with LPS for 24 hours at 37°C and PGE_2 was measured in the supernatant plasma as an index of monocyte COX-2 activity. Serum TxB_2 was also assessed as an index of platelet COX-1 activity. The selective COX-2 inhibitor DUP697 (0.05-0.25 micromolar) reduced dose-dependently PGE_2 production (85% maximal inhibition) and dexamethasone (10 micromolar) totally suppressed it, whereas aspirin (10-300 micromolar) was almost ineffective, producing only 15% inhibition at 300 micromolar. NCX 4016 (50-300 micromolar) inhibited dose-dependently, though only partially, PGE_2 production (50 micromolar = 19% inhibition, $p=0.01$; 300 micromolar= 36% inhibition, $p<0.001$). Among the NO-donors, SNP (0.1-1 mM) inhibited PGE_2 dose-dependently (80% maximal inhibition, $p< 0.05$) and DetaNONOate (10 mM) completely suppressed it, whereas GSNO (0.1-1 mM) and SNAP (0.1 mM) were ineffective. NCX 4016 and aspirin inhibited platelet COX-1 with comparable activity (IC_{50} 0.02 and 0.01 micromolar, respectively) while DUP697 and SNP were ineffective.

Under the same experimental conditions COX-2 expression, measured by western blot, was completely suppressed by Dexamethasone while it was unaffected by aspirin, DUP697, NCX 4016, and SNP.

Finally, the role of NO-stimulated guanylyl-cyclase in the inhibitory effect of the drugs tested was assessed by the guanylyl-cyclase inhibitor ODQ (1 mM).

A significant reduction of PGE_2 inhibition by ODQ was observed for NCX4016 (-28%, $p<0.05$) and SNP(-38%, $p<0.05$), suggesting a partly GC-dependent mechanism.

In conclusion, Nitroaspirin, as well as other, but not all, NO-donors, inhibits monocyte COX-2 activity. This might represent an advantage over aspirin, given the possible detrimental role of COX-2 in cardiovascular disease.