NITRIC OXIDE ACTIVATES PHOSPHOLIPASE A2 IN THE VASCULAR SMOOTH MUSCLE, THROUGH A cGMP-INDEPENDENT PATHWAY

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Endothelial nitric oxide (NO) is a fundamental factor, involved in the control of vascular tone[1]. The NO-induced activation of the soluble Guanylyl Cyclase (sGC) into the vascular smooth muscle cell determines the production of cGMP, causing vasorelaxation via multiple mechanisms, like decreased entry/release and increased extrusion of Ca^{++}, inhibition of the sensitivity of myofilaments for Ca^{++} and activation of hyperpolarising K^+ channels[2]. Altough the sGC-cGMP pathway is the major mechanism, accounting for the effects of NO, recent experimental results suggest that NO may also act independently of cGMP, by activation of G proteins, stimulation of Na^+/K^+-ATPase and membrane hyperpolarisation, through the opening of Ca^{++}-dependent K^+ channels[3]. This work aimed to detect a possible cGMP-independent NO-induced activation of phospholipase A2 (PLA2) and production of vasorelaxing Arachidonic Acid derivatives.
In endothelium-denuded rings of rat thoracic aorta, contracted by a "low" level of membrane depolarisation (KCl 20 mM), sodium nitroprusside (SNP, a nitric oxide donor) determined a full vasorelaxation (100, as a % of the contractile tone). The pre-incubation of the PLA2 inhibitor Aristolochic Acid (AA, 100 µM) did not influence the effects of SNP. In aortic rings contracted by a "high" level of membrane depolarisation (KCl 60 mM), abolishing the vasorelaxing effects due to hyperpolarising mechanisms, SNP determined a reduced vasorelaxation (61 ± 2). The pre-incubation of AA inhibited the effects of SNP (47 ± 3). The vasorelaxing effects of 8-Br cGMP (a stable analogue of cGMP) in KCl 20 and 60 mM-contracted rings (respectively 96 ± 3 and 45 ± 4) were not inhibited by AA. Finally, in KCl 20 mM-contracted rings, SNP showed ODQ (10 µM, a sGC inhibitor)-resistant vasorelaxing effects (85 ± 2), which were strongly inhibited by both AA (25 ± 4) and Palmitoyl-trifluoromethylketone (10µM), another inhibitor of PLA2 (35 ± 9). This evidence of a low-sensitivity and cGMP-independent NO-PLA2 pathway, unmasked only when sGC or cGMP-mediated hyperpolarising mechanisms are inhibited, could contribute to a deeper comprehension of therapeutic and/or side effects of NO-donors.

References

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