

Sympathoadrenergic modulation of human polymorphonuclear leukocyte function and its possible relevance in cardiovascular disease

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Background: The catecholamines (CA) noradrenaline (NA) and adrenaline (A) are neurotransmitters and neurohormones in the central nervous system and in the sympathetic branch of the autonomic nervous system (1) and are among the key mediators of the neuroendocrine responses to stressful stimuli. Available evidence supports a detrimental role of chronic stress on the cardiovascular system (2).

Since polymorphonuclear leukocytes (PMNs) contribute to cardiovascular disease (CVD) (3) and respond to CA through adrenoceptors (AR) expressed on their membranes, we investigated catecholaminergic pathways in human PMNs and whether CA influence PMN functions. In particular, we assessed the ability of A, NA and of the β -AR agonist isoprenaline (ISO) to modulate migration, reactive oxygen species (ROS) generation, interleukin (IL)-8 production and β_2 -integrin expression, all key steps involved in vascular damage and atherosclerotic plaque development.

Methods: PMNs were obtained from venous blood of healthy subjects and tyrosine hydroxylase (TH, the rate limiting enzyme for catecholamine synthesis) and AR expression was assayed by real-time PCR. ROS were detected by spectrofluorimeter and β_2 -integrin expression by flow cytometry. Migration was evaluated by Boyden chamber and CA assayed by HPLC. IL-8 production was measured by ELISA.

Results: PMNs expressed mRNA for TH as well as for several subtypes of α - and β -ARs. Stimulation with fMLP 0.1 μ M significantly increased α_{1A} - ([ratio fMLP/resting, mean \pm SD] 2.3 \pm 1.3), α_{2A} - (3.3 \pm 2.9), β_1 - (3.3 \pm 1.6), β_2 - (8.1 \pm 4.8) and β_3 -ARs (13.9 \pm 10.8), but not TH.

A did not affect spontaneous migration but concentration-dependently (10 nM–1 μ M) significantly reduced fMLP-induced chemotaxis. Incubation with the α_1 -AR antagonist prazosin (PRA), the α_2 -AR antagonist yohimbine (YOH) or the β -AR antagonist propranolol (PRO), all at 10 μ M, did not affect spontaneous migration. The inhibitory effect of A on fMLP-induced chemotaxis was reverted by PRO but not by YOH or PRA.

Spontaneous ROS production was unaffected by A (0.01 μ M–1 μ M) or NA (1 μ M) while it was significantly reduced by 1 μ M ISO (P <0.005 vs resting conditions). Pretreatment with A (0.0001 μ M–1 μ M) significantly reduced fMLP-induced ROS production and the same effects was observed with NA and ISO. YOH, but not PRA or PRO, significantly increased spontaneous ROS production, while fMLP-induced ROS generation was not affected by any antagonists. YOH and PRO, but not PRA, however reverted the inhibitory effects of A on fMLP-induced ROS generation.

A was unable to affect either resting or fMLP-stimulated IL-8 production. A, NA, or ISO did not modify resting β_2 -integrin expression but reverted fMLP-induced expression.

Conclusions: CA affect several PMN functional responses involved in vascular damage and atherosclerosis development. In vivo studies are now warranted to assess PMN responses to AR-activating stimuli in CVD, also in regard to stressful stimuli. PMNs could represent a target for adrenergic agents aimed at decreasing inflammation and vascular damage in CVD.

References

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