PHARMACOMETRIC ANALYSIS OF $\alpha_1$-ADRENOCEPTOR FUNCTION IN RAT TAIL ARTERY PRETREATED WITH LIPOPOLYSACCHARIDES

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The inhibitory effect of lipopolysaccharides (LPS) on contraction evoked by $\alpha$-adrenergic stimulation is quite well-known, but molecular mechanism of this inhibition is unclear. In the present study, an interaction between $\alpha$-adrenoceptor response and LPS in rat tail artery was investigated using chemical stimulation. In the presence of LPS noradrenaline and phenylephrine, concentration-response curves were shifted to the right with a change in maximal responses. The $K_A$ and $K_B$ values calculated in the presence and absence of LPS did not differ significantly. The results strongly suggest that LPS did not change the affinity of $\alpha_1$-adrenoceptors. Changes in the plot showing relationship between agonist-evoked responses and receptor occupancy in the presence of LPS and reduction of $K_A/ED_{50}$ value suggest reduction of $\alpha$-adrenoceptor reserve. In the experiments performed on arteries without endothelium, the inhibitory effect of LPS was still present. In the presence of atropine, antazoline and indomethacin, the reduction of $\alpha$-adrenoceptor reserve was noted, but in the presence of N$^\omega$-nitro-L-arginine methyl ester (L-NAME), the inhibitory effect of LPS was not significant. Moreover, in LPS-pretreated arteries, in the presence of L-NAME, the increase in the receptor reserve was observed. It suggests that inhibitory effect of LPS is partially reversible. The results strongly indicate that in early endotoxemia, main inhibitory effect of LPS is connected with releasing nitric oxide and decreasing coupling between $\alpha_1$-adrenoceptor and signal induction.

Key words: $\alpha$-adrenoceptors, receptor reserve, septicemia, lipopolysaccharides, nitric oxide, rat tail artery

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