Physiological antagonism of angiotensin II and lipopolysaccharides in early endotoxemia: pharmacometric analysis

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The inhibitory effect of lipopolysaccharides (LPS) on α-adrenergic contraction is quite well known, but molecular mechanism of this inhibition is unclear. In the present study, the interaction between α-adrenoceptor and vasopressin receptor response, and LPS in rat tail artery was investigated using chemical stimulation. In the presence of LPS, noradrenaline, phenylephrine and arginine-vasopressin, concentration-response curves (CRCs) were shifted to the right with the 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 receptors affinity. The changes in the relationship between receptor occupancy and response to an agonist in the presence of LPS and reduction of $K_A/ED_{50}$ value suggest reduction of receptor reserve. In the presence of angiotensin II (Ang II), CRCs were shifted to the right with significant increase in receptor reserve. Moreover, this effect was still present in LPS-pretreated arteries. The receptor reserve reduced by LPS significantly increased in the presence of Ang II.

It suggests that inhibitory effect of LPS is partially reversible. The results strongly suggest that in early endotoxemia, inhibitory effect of LPS may be partially reverted by an increase in activity of renin-angiotensin-aldosterone system.

Key words: receptor reserve, septicemia, lipopolysaccharides, angiotensin II, nitric oxide, rat tail artery

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