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LPS induction of endothelium-dependent constriction of large arteries in endotoxemic hypotensive shock

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Effective managements of refractory hypotension to vasoconstrictors in severe sepsis are limited. A new strategy to ameliorate endotoxemic hypotension by inducing endothelium-dependent constriction of endotoxemic large arteries was examined. In lipopolysaccharide (LPS)-induced endotoxemic rats, oroxylin-A (OroA, 15 mg/kg, iv) administered 6 hours after LPS-challenge promptly reversed/normalized diminished mean arterial pressure and heart rate. OroA (1-10 mM), which did not constrict isolated normal arteries, repeatedly induced exclusive endothelium-dependent sustained-constriction without tachyphylaxis of isolated endotoxemic aortic, and tail arteries. OroA-induced constriction of mesenteric arteries with intact-endothelium (EC+) was blocked by endothelin-1 (ET-1)-receptor antagonists which, did not affect that of tail or aortic arteries, suggesting ET-1-mediated and non-ET-1-substance(s)-mediated vasoconstrictions, respectively. Meanwhile, OroA enhanced LPS-induced expression of ET-1 in mesenteric, but decreased that in tail and aortic arteries. OroA-induced ET-1-mediated and non-ET-1-substance(s)-mediated constrictions of all isolated arteries (EC+) were blocked exclusively by ROCK inhibitors. OroA reversed LPS-induced suppression of RhoA-activities and enhanced ROCK-phosphorylation only in arteries with endothelium. Activated muscle ROCK-activities in mesenteric arteries (EC+) but not those in tail or aortic arteries (EC+) were blocked by ET-1-receptor antagonists. Moreover, OroA-post-treatment suppressed, via inhibiting NF- κ B, inducible-NOS expression and circulating NO. LPS induces region-dependent expression of endothelial ET-1- and/or non-ET-1-vasoconstrictors. Both released specifically by OroA activate muscle RhoA/ROCK-pathway, causing prompt-and-sustained vasoconstriction that partly is due to OroA-induced decrease of circulating NO. Simultaneous preservation of endothelial functions, induction of endothelium-dependent constriction of large arteries, and suppression of systemic inflammation, as shown by OroA, offer new strategies for acute management of endotoxemic-hypotensive shock.

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