

Role of nitric oxide in lipopolysaccharide-induced mortality from spontaneously hypertensive rats.

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Abstract

To investigate whether nitric oxide (NO) contributed to a higher mortality induced by lipopolysaccharide (LPS) in spontaneously hypertensive rats (SHR), NO synthase inhibitors were used to examine the mortality from LPS in SHR and normotensive Wistar-Kyoto (WKY) rats. We evaluated the mortality from LPS in a series of doses (5, 10, or 20 mg/kg, i.v.) in the anesthetized rat. Plasma nitrite was measured before and at 1, 2, and 3 h after treated rats with LPS (5 mg/kg, i.v.). Pressure responses to N omega-nitro-L-arginine methyl ester (L-NAME) and aminoguanidine (AG) were performed in rats treated with or without LPS for 3 h. Thoracic aortic cyclic guanosine 3',5'-monophosphate (cGMP) levels were also assessed. Our results demonstrated that injection of LPS caused a dose-dependent mortality in both strains, having a more marked effect in SHR. The survival time of rats after injection of LPS (5 mg/kg, i.v.) was much shorter in SHR. A higher basal level of plasma nitrite was observed in SHR and this difference was further augmented by LPS. The administration of L-NAME (3 mg/kg, i.v.) and AG (15 mg/kg, i.v.) 3 h after LPS had no significant effects on the survival time of WKY rats, but significantly prolonged that of SHR to a similar time of WKY rats. The injection of L-NAME prior to LPS increased blood pressure of WKY rats by 28 ± 5 mmHg and increased that of SHR by 38 ± 4 mmHg. At 3 h after LPS, L-NAME had a greater pressor effect in SHR than in WKY rats. By contrast, before rats injected with LPS, AG slightly increased blood pressure of SHR by 7 ± 3 mmHg but not of WKY rats (3 ± 2 mmHg), whereas it also had a greater pressor effect in SHR than in WKY rats after treated rats with LPS for 3 h. In addition, LPS induced a higher level of cGMP in SHR than in WKY rats, which was attenuated by in vitro treatment of aortic rings from LPS-rats with L-NAME or AG to a similar level in SHR and WKY rats. These results suggest that a higher level of NO evoked by LPS is associated with a higher mortality in SHR and we propose that the elevated NO synthesis in SHR may play an important role in the compensatory mechanisms activated to combat the hypertensive state.