



Title	Thymoquinone causes endothelium-dependent augmentation of contraction depending on activation of soluble guanylyl cyclase in isolated arteries
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THYMOQUINONE CAUSES ENDOTHELIUM-DEPENDENT AUGMENTATION OF CONTRACTION DEPENDING ON ACTIVATION OF SOLUBLE GUANYLYL CYCLASE IN ISOLATED ARTERIES

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Introduction: Experiments were designed to determine the effects of thymoquinone, an alkaloid with in vivo vasodilator properties, in isolated arteries.

Methods: Rings, with or without endothelium, of rat mesenteric arteries, rat aorta and porcine coronary arteries were suspended in conventional organ chambers for isometric tension recording. Certain rings were incubated with inhibitors of nitric oxide (NO) synthase inhibitor (L-N^G-nitroarginine methyl ester, L-NAME) or soluble guanylyl cyclase (1H-[1,2,4]oxadiazolo[4,3-a]quinoxalin-1-one, ODQ). They were contracted with phenylephrine (rat arteries) or prostaglandin F_{2α} (porcine coronary arteries) and exposed to increasing concentrations of thymoquinone.

Results: Thymoquinone caused a sustained further increase of tension in rings with endothelium. This augmentation was prevented by endothelium-removal, L-NAME and ODQ. Incubation with the NO-donor detaNONOate in L-NAME-treated rings restored and even increased the contractile response to thymoquinone. By contrast, treatment with 8-bromo cyclic GMP of ODQ-treated preparations did not restore the augmentation by thymoquinone.

Conclusion: These findings demonstrate that thymoquinone causes an endothelium-dependent augmentation similar to that seen in hypoxia (Chan et al., Am J Physiol: H2313, 2011). This facilitation also requires endothelium-derived NO and activation of soluble guanylyl cyclase, but not the presence of cyclic GMP.

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DIFFERENTIAL MECHANISMS OF VASODILATOR EFFECT OF NITRITE IN NORMOTENSIVE AND HYPERTENSIVE RAT AORTAS

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Introduction: A growing body of recent data indicate that dietary inorganic nitrites causes vasodilation leading to lowering of blood pressure in the body; however, the precise mechanisms of nitrite-induced vasodilation remain unclear. Herein, therefore, we studied the mechanisms of nitrite-induced vasodilation *in vitro* in an isolated tissue bath experiment.

Method: Relaxation responses to sodium nitrite (NaNO₂, 10⁻⁹ to 10⁻³ mol/L) were measured in phenylephrine pre-contracted aortic rings isolated from gender- and age-matched normotensive Wistar-Kyoto and spontaneously hypertensive rats in the presence or absence of various pharmacological agents.

Results: Sodium nitrite elicited relaxation in both normotensive and hypertensive tissues, but with a significantly higher potency in the latter tissues. Inhibition of endothelial nitric oxide synthase (NOS) enzyme activity decreased nitrite-induced relaxations in normotensive, but not in hypertensive, tissues. Inhibition of cyclooxygenase (COX) enzyme activity increased relaxation responses to nitrite in both types of tissues. Free radical scavenging with ascorbic acid did not alter responses to nitrite in both types of tissues. Inhibition of NADPH oxidase enzyme activity did not alter responses to nitrite in normotensive tissues but decreased in hypertensive tissues bringing the responses to a level that is seen in untreated control normotensive tissues.

Conclusion: Our findings indicate that 1) nitrite causes varying degree of vasodilation in normotensive and hypertensive tissues with higher response in the latter tissues, 2) COX-derived substances antagonizes relaxations to nitrite, and 3) differential mechanisms (i.e., NOS in normotensive tissues and NADPH in hypertensive tissues) may participate in nitrite-induced relaxations in normal and hypertensive vasculature.