ELSEVIER

European Journal of Pharmacology 307 (1996) R5–R7

ejp

Rapid communication

Elevation in arterial blood pressure following the development of tachyphylaxis to peroxynitrite

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Received 29 April 1996; accepted 3 May 1996

Abstract

The systemic administration of peroxynitrite produces transient reductions in mean arterial pressure and vascular resistances in anesthetized rats. The repeated administration of peroxynitrite results in tachyphylaxis. We now report that anesthetized rats ($n = 8$) treated with peroxynitrite (10 injections of 10 μmol/kg i.v.) subsequently develop increases in mean arterial pressure (20 ± 4%) and hindquarter (153 ± 28%), renal (93 ± 21%), and mesenteric (133 ± 25%) vascular resistances. These findings suggest that the in vivo production of peroxynitrite may contribute to the pathogenesis of hypertension.

Keywords: Peroxynitrite; Tachyphylaxis; Hemodynamics, in vivo

Nitric oxide reacts with superoxide anion to produce the potent oxidant peroxynitrite (Huie and Padmaja, 1993). Peroxynitrite production occurs within the vasculature of humans during inflammatory disease processes (Kooy et al., 1995). Peroxynitrite exhibits similar biological properties to nitric oxide in vitro, including vascular relaxation (Wu et al., 1994) and inhibition of platelet aggregation (Moro et al., 1994). These effects of peroxynitrite may be due to the formation of *S*-nitrosothiols (Moro et al., 1994; Wu et al., 1994). The systemic administration of peroxynitrite produces marked reductions in mean arterial pressure and vascular resistances in anesthetized rats (Kooy et al., 1996). These effects are subject to rapid tachyphylaxis as the repeated administration of peroxynitrite (10 injections of 10 μmol/kg i.v.) produces progressively smaller hemodynamic responses (Kooy et al., 1996). In the present study, we examined the alterations in mean arterial pressure and vascular resistances following tachyphylaxis to systemically administered peroxynitrite. Specifically, we observed a sustained increase in mean arterial pressure which was associated with marked increases in hindquarter, renal and mesenteric vascular resistances over time. These findings raise the intriguing possibility that endogenously produced peroxynitrite may contribute to the pathophysiology of hypertension.

Male Sprague-Dawley rats ($n = 16$) weighing 280–340 g were anesthetized with pentobarbital (50 mg/kg i.p.) and were surgically implanted with femoral arterial and venous catheters for the measurement of mean arterial pressure and the administration of drugs, respectively. A midline laparotomy was then performed and miniature pulse Doppler flow probes were placed around the lower abdominal aorta, renal and superior mesenteric arteries for the measurement of hindquarter, renal and mesenteric blood flow velocities, respectively, and for the determination of hindquarter, renal and mesenteric vascular resistances as previously described (Lacolley et al., 1991). To maintain anesthesia, supplemental doses of pentobarbital (5 mg/kg i.v.) were given as necessary throughout the experiments. Following stabilization of the hemodynamic parameters, one group of rats ($n = 8$) received 10 injections of peroxynitrite (10 μmol/kg i.v.) at approximately 5-min intervals, after which the hemodynamic variables were monitored for 120 min. A second group of rats ($n = 8$) received injections of saline (0.9% w/v NaCl i.v.) and the hemodynamic variables were monitored as in the peroxynitrite-treated group. The data were analyzed by repeated mea-

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PII S0014-2999(96)00343-3

sures analysis of variance followed by Student's modified t-test with the Bonferroni correction for multiple comparisons and are reported as mean ± S.E.M. A value of $P < 0.05$ was taken to denote statistical significance.

The pretreatment values for the two groups of rats receiving either saline ($n = 8$) or peroxynitrite ($n = 8$) were: mean arterial pressure, 106 ± 4 vs. 112 ± 4 mm Hg, respectively ($P > 0.05$); hindquarter resistance, 64 ± 11 vs. 83 ± 12 mm Hg/kHz ($P > 0.05$); renal resistance, 69 ± 12 vs. 73 ± 22 mm Hg/kHz ($P > 0.05$) and mesenteric resistance, 36 ± 7 vs. 44 ± 10 mm Hg/kHz ($P > 0.05$). The initial injection of peroxynitrite (10 μmol/kg i.v.) produced marked reductions in mean arterial pressure (−42 ± 6%, $P < 0.05$), hindquarter resistance (−52 ± 9%, $P < 0.05$) and mesenteric resistance (−54 ± 6%, $P < 0.05$), but no changes in renal resistance (−11 ± 5%, $P > 0.05$). The subsequent injections of peroxynitrite produced progressively smaller responses. The decreases produced by the 10th injection of peroxynitrite were: mean arterial pressure −12 ± 2% ($P < 0.05$ compared to the first injection), hindquarter resistance −17 ± 4% ($P < 0.05$), mesenteric resistance −12 ± 3% ($P < 0.05$) and renal resistance −8 ± 6% ($P > 0.05$). The hemodynamic responses following the 10th injection of peroxynitrite returned to preinjection values within 2–3 min. Similar injections of saline did not affect these hemodynamic parameters (data not shown). The time-course of the increases in mean arterial pressure and vascular resistances which gradually developed following the final injection of peroxynitrite are summarized in Fig. 1. The peroxynitrite-treated rats developed a sustained increase in mean arterial pressure and marked and sustained increases in vascular resistances. These increases were evident within 30–60 min and were most prominent at 120 min. In comparison, the hemodynamic values of the saline-treated rats did not change over time.

The present study confirms that the systemic administration of peroxynitrite produces marked decreases in mean arterial pressure and vascular resistances which are subject to rapid tachyphylaxis (Kooy et al., 1996). The principal finding of the present study is the gradual development of a sustained increase in mean arterial pressure and a marked and sustained vasoconstriction within the renal, hindquarter and mesenteric vascular beds following development of tachyphylaxis to peroxynitrite. These vasoconstrictor effects are unlikely to be due to augmented sympathetic neurogenic vasomotor tone since the catecholamines norepinephrine and epinephrine produce substantially smaller vasoconstrictor responses in peroxynitrite-tolerant rats (Kooy et al., 1996). In vitro evidence suggests that peroxynitrite may produce its vasorelaxant responses through the formation of S-nitrosothiols (Wu et al., 1994). However, peroxynitrite is a potent oxidant capable of thiol oxidation (Radi et al., 1991). Therefore, the repeated administration of peroxynitrite may deplete biological sources of reduced thiols, decreasing S-nitrosothiol formation. Alternatively,

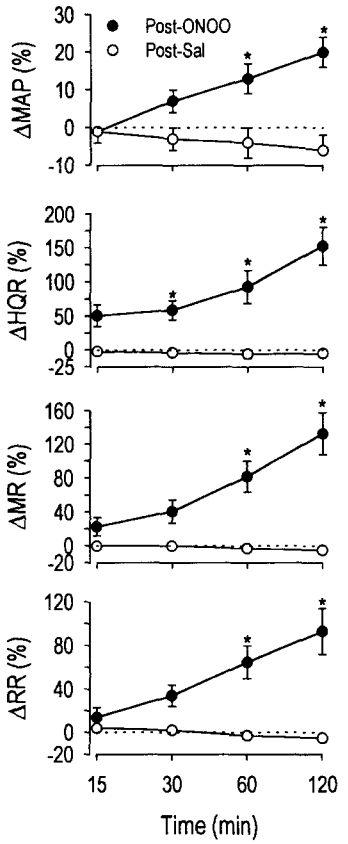

Fig. 1. A summary of the time-dependent changes in mean arterial pressure (MAP) and renal (RR), hindquarter (HQR), and mesenteric (MR) vascular resistances occurring subsequent to the administration of peroxynitrite (10 injections of 10 μmol/kg, $n = 8$; Post-ONOO) or saline ($n = 8$; Post-Sal) in pentobarbital-anesthetized rats. * $P < 0.05$ Post-ONOO vs. Post-sal.

prolonged exposure of vascular tissues to peroxynitrite may affect the cellular processes whereby S-nitrosothiols such as the endothelium-derived relaxing factor S-nitrosocysteine (Myers et al., 1990) relax vascular smooth muscle. Inhibition of the biological activity of S-nitrosothiols may therefore be expected to promote increases in vascular tone. In conclusion, the development of increased mean arterial pressure and vasoconstriction following peroxynitrite administration raises the intriguing possibility that endogenously formed peroxynitrite may contribute to the pathophysiology of hypertension.

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