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Non-endothelial nitric oxide modulates alpha-adrenoceptor and trace amine vasoconstrictor responses of guinea-pig aorta

K. J. Broadley, H. D. Broadley. Pharmacy & Pharmaceutical Sciences, Cardiff University, Cardiff, United Kingdom.

Introduction: Nitric oxide (NO) released from the vascular endothelium produces vasodilatation by acetylcholine. It is also released by vasoconstrictors such as the α-adrenoceptor agonist phenylephrine to cause an opposing vasodilatation (1). Here we compare phenylephrine and β-phenylethylamine, which constricts blood vessels via trace amine-associated receptors (TAARs)(2), in guinea-pig aorta and determine the role of NO in vessels with and without endothelium by use of the NO synthase inhibitor, L-NAME.

Method: Aortic rings (0.5 cm) from male Dunkin-Hartley guinea-pigs were immersed in Kreb's solution gassed with 5% CO_2 in O_2 at 37±0.5°C. 1.5 g resting tension was applied and isometric contraction measured using a computerized Power Lab, Chart 5 data acquisition system (ADInstruments). Cumulative concentration-response curves (CRC) for β-phenylethylamine hydrochloride (PEA) or (-)-phenylephrine HCl were obtained and after washout (x2), a second curve obtained in the presence of L-NAME (100µM). Contractions were measured by subtracting baseline tension from plateau responses and expressed as a percentage of the contraction to KCl (60mM) added at the end. Responses were compared by Student's paired t-test, $P \leq 0.05$ indicating significance.

Results: Phenylephrine contractions of guinea-pig aorta had rapid onset but were not sustained. The response to $3x10^{-6}$M, which was the 55.5±6.6% response, peaked at 3.9±0.4min (n=13). PEA contractions were slow in onset and sustained and the mean peak for the 40.0±6.8% response ($3x10^{-4}$M) occurred at 13.6±1.3min (n=14), which was significantly longer than for phenylephrine. In endothelium-intact aortae, L-NAME significantly potentiated PEA, increasing the maximum from 59.1±3.6 to 87.5±2.8% (n=7). The vasoconstriction to phenylephrine was also potentiated by L-NAME, the maximum significantly increasing from 75.8±2.2 to 94.0±0.8% (n=5). Endothelium removal was tested by adding acetylcholine (100µM) to a sample of tissues contracted with U46619 (1 or 0.5µM). In endothelium-intact aortae (n=6), Ach caused small relaxations of 0.07±0.02g, representing 7.1±3.0% of the U46619 contraction (1.33±0.27g). No relaxations occurred in denuded aortae. In endothelium-denuded aortae, L-NAME potentiated the vasoconstriction to PEA, the maximum significantly increasing from 60.8±6.9 to 86.9±2.3% (n=6). Vasoconstriction of denuded aortae by phenylephrine was also potentiated by L-NAME, the maximum significantly increasing from 70.3±6.8 to 88.9±3.7% (n=5).

Conclusion: phenylephrine and PEA constrictions of guinea-pig aorta were characterized by fast transient and slow sustained contractions, respectively. They release NO from non-endothelial sources causing underlying vasodilatation which opposes the predominant vasoconstriction.

References:

1. Bullock GR *et al*. (1986). *Br J Pharmacol* **89**: 819-830.
2. Broadley KJ *et al*. (2013). *Eur J Pharmacol* **715:** 370-380.