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Comparison of nitric oxide scavengers and synthesis inhibition on β-phenylethylamine- and phenylephrine-induced vasoconstriction of guinea-pig aorta

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Introduction: Although β-phenylethylamine (PEA) is conventionally regarded as an indirectly acting sympathomimetic amine releasing noradrenaline onto α-adrenoceptors (1), vasoconstriction by PEA may also be via trace amine-associated receptors (TAARs), since we showed no α_1-adrenoceptor antagonism by prazosin (2). Here we examine whether TAAR-mediated vasoconstriction of guinea-pig aorta to PEA is accompanied by release of nitric oxide (NO) using the NO synthase inhibitor, L-NAME or NO scavengers, curcumin and astaxanthin.

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^{o}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), curcumin (100µM), astaxanthin (100µM), their vehicles, or nothing (controls). 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≤0.05 indicating significance.

Results: PEA and phenylephrine constricted aortae and in controls, the phenylephrine maximum increased from 70.7±4.1% to 78.9±4.9% (n=6) while L-NAME significantly potentiated from 78.2±3.2% to 93.1±1.2% (n=6). There was no change in the maximum PEA response in controls (65.7±6.0 and 74.8±1.4%, n=7) but L-NAME significantly potentiated the maximum from 45.1±2.8 to 101.3±8.0% (n=4). In endothelium-denuded aortae, the second CRC of PEA controls also showed a small enhanced maximum contraction from 68.4±2.9 to 80.0±2.9% (n=6). L-NAME caused significantly greater potentation from 60.8±6.9 to 86.9±2.3% (n=6). Potentiation of phenylephrine and PEA by L-NAME may arise from a fall in baseline between CRCs. However, when L-NAME was examined in denuded aortae with baseline adjusted back to 1.5g before the second CRC, the maximum was still significantly potentiated from 49.4±6.0 to 83.6±3.9% (n=5). Curcumin did not affect phenylephrine (maxima, 83.1±5.9 and 85.0±1.2%) but significantly depressed the PEA maximum from 135.4±41.5 to 70.0±1.9% (n=5), while astaxanthin potentiated PEA.

Conclusion: PEA releases NO from non-endothelial sources causing underlying vasodilatation opposing the predominant TAAR-mediated vasoconstriction. NO inhibition is mimicked by the NO scavenger, astaxanthin but not by curcumin, which exerts opposing inhibitory actions on the TAAR response.

References:

1. Broadley KJ (2010). Pharmacol Ther **125:** 363-375.
2. Broadley KJ et al (2013). Eur J Pharmacol **715:** 370-380.