B6

TITLE: ATTENUATED VASCULAR RELAXATION BY FENOLDOPAM AND DOPAMINE IN ENDOTOXIN TREATED RATS

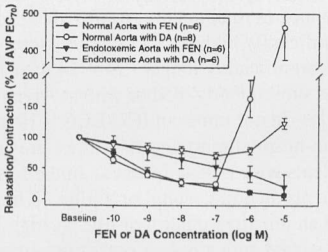
AUTHORS: M.H. Wall, MD, P.R. Roberts, MD, M. Shouse, MS, J.R. Tobin, MD, R.C. Prielipp, MD

AFFILIATION: Dept. of Anesthesiology, Wake Forest University School of Medicine, Winston-Salem, NC 27157

Fenoldopam (FEN), a selective dopamine DA1 receptor agonist, would be predicted to produce progressive relaxation of vascular smooth muscle, in contrast to dopamine (DA), a non-selective DA, beta and alpha agonist. We hypothesized that FEN would cause progressive relaxation in preconstricted isolated aortic (Ao) vascular rings, whereas DA would have a biphasic response. Also, we hypothesized that these responses would be diminished in vascular rings from endotoxemic (ENDO) animals.

The thoracic Ao was removed from euthanized normal (NL) or ENDO 325-350 gm male Sprague-Dawley rats. ENDO was induced by i.p. injection of 6.5 mg/kg E.coli endotoxin 055:B5 20 hours prior to vessel isolation. 3mm rings were prepared and suspended in oxygenated Krebs-Henseleit buffer at 37°C. Tension was recorded with force transducers. Baseline (BL) tension of each ring was determined; intact endothelium was confirmed by relaxing a phenylephrine (10^{-6} M) preconstricted vessel with 10^{-7} M acetylcholine. Cumulative concentration-contraction curves were obtained for vasopressin (AVP) (10^{-10} to 10^{-7} M). The AVP concentration causing 70% of the maximum contraction was determined (EC_{70}). The EC_{70} was used to preconstrict the rings; then a concentration-response curve was obtained for FEN and DA (10^{-10} to 10^{-5} M). Data shown are % of AVP EC_{70} ± SEM. Differences between groups were analyzed by repeated measures ANOVA ($P<0.05$ considered significant).

ENDO and NL AVP concentration-response curves were not different (data not shown). The concentration-response curves between all four ring groups were statistically different (main effect: $P<0.0001$; ring/dose interaction: $P<0.0001$). FEN and DA produced equivalent concentration-related relaxation of NL rings between 10^{-10} M to 10^{-7} M (see fig.). FEN caused relaxation in NL and ENDO rings at 10^{-6} and 10^{-5} M. In contrast, DA caused 163±30 and 463±86% ring constriction at 10^{-6} and 10^{-5} M. In the ENDO rings, the response curves were attenuated for both DA and FEN ($P<0.05$). The vasoconstrictor properties of DA were also attenuated at 10^{-6} and 10^{-5} M DA in the ENDO rings ($P<0.05$ vs. NL rings), causing 78±6 and 123±9% ring constriction.



The selective DA1 agonist, FEN, maintains a consistent vascular relaxation pharmacodynamic profile in the Ao throughout the dose range 10^{-10} to10^{-5} M, in contrast to DA. While rings from ENDO rats were equally responsive to AVP, both FEN and DA showed diminished relaxant efficacy. We conclude only FEN maintains a predictable pharmacodynamic profile in both NL rings and rings from ENDO rats, at all doses.