Young Investigator Presentation

ALPHA2-MEDIATED VASOCONSTRICTION BY FENOLDOPAM IN RAT RENAL ARTERIES IN VITRO

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Introduction. Fenoldopam (FEN), a selective dopamine (DA1) agonist, causes a biphasic response on vascular smooth muscle in renal artery (RA) rings of normal adult rats (1). The mechanism of the secondary progressive contraction at higher doses of FEN has yet to be explained. FEN may illicit α2 activity at high concentrations (2). We hypothesized that FEN’s action on α-receptors is responsible for the biphasic response in RA vascular rings of normal adult male rats.

Methods. RA (n=5) were harvested from euthanized 325-350 g male Sprague-Dawley rats. Vascular rings (3-mm) were prepared and suspended in a bath of oxygenated Krebs-Henseleit buffer (37°C). Tension was recorded with Grass FT03 force transducers. Baseline tension of each ring was determined, and intact endothelium confirmed by relaxing a vasopressin (AVP) preconstricted ring with 10^-5 M acetylcholine. Cumulative concentration-response curves (CRCs) for FEN (10^-10 to 10^-5 M) were obtained after preconstriction with the AVP EC70 dose (3x10^-9 M) as determined from previous studies (1). Next, the effective blocking dose of the α1 antagonist prazosin was determined by near-complete inhibition of phenylephrine (a pure α agonist) contraction. This blocking dose of prazosin (10^-5 M) was added prior to AVP-constriction, and repeat CRCs for FEN were obtained. Finally, in an identical fashion, a blocking dose of the α2 antagonist yohimbine (YOH) was determined (10^-3 M), and added prior to AVP-constriction and new CRCs for FEN obtained. Data shown are % of AVP EC70 response±SEM. Differences between groups were analyzed by repeated measures ANOVA; p<0.05 significant.

Results. The control FEN CRCs exhibited a biphasic response in the RA rings, as noted previously. With prazosin, no statistical difference was noted from the control curve through all the FEN concentrations tested. With the addition of YOH, however, there was impaired relaxation at FEN concentrations of 10^-6 and 10^-5 M. At higher FEN concentrations of 10^-6 and 10^-5 M, contraction was significantly impaired by YOH (fig.).

Conclusions. FEN has a biphasic response in normal RA vascular rings that is inhibited by YOH, a relatively selective α2 antagonist, but not by prazosin, an α1 inhibitor. YOH also blunted FEN relaxation at moderate concentrations. More studies revealed YOH alone causes mild contraction of RA rings, perhaps due to an α1 mechanism (data not shown). We conclude that the mechanism of FEN’s secondary vasoconstriction at increasing concentrations is mediated by α2 effects on vascular smooth muscle contraction. Also, the initial vascular relaxation of FEN attributed to DA1 receptor activation may be attenuated by α2 blockade.

References.