Title: CALCITONIN-GENE RELATED PEPTIDE AS POTENT DILATOR IN ISOLATED HUMAN UTERINE ARTERIES

Authors: S.H. Nelson, Ph.D and M. S. Suresh, M.D.

Affiliation: Department of Anesthesiology, The University of Texas Medical Branch, Galveston, Texas 77550

Introduction. Calcitonin gene-related peptide (CGRP) is a potent vasodilator in humans and animals. It is a 37 residue peptide that is distributed in plexus arteriosus nerves and is found in high concentrations in the urogenital tract and in blood vessels in the uterus of humans. CGRP concentrations in the plasma have been reported to be significantly increased throughout pregnancy with the highest concentrations being found close to term. Because of the possibility that CGRP may play a role in regulating uterine vascular tone, this study was undertaken to characterize the vasoactive properties of CGRP in uterine arteries from pregnant patients (P) and nonpregnant patients (NP) arteries.

Methods. Use of uterine arteries from patients undergoing hysterectomy was approved by the Institutional Review Board. Ring sections (2 mm in length) of uterine arteries (ascending branch) were mounted in 5 ml-volume chambers and perfused at a constant flow rate (4 ml/min) with a polystatic pump. The suffusate was oxygenated Krebs-bicarbonate solution (pH 7.4) maintained at 37°C. Drugs were administered in the flowing suffusate. Changes in isometric tension were measured by a force-displacement transducer and recorded. The arterial rings with 1 g resting tension were allowed to equilibrate for about 1 hour before commencement of the experiment. All drugs were prepared daily from powder forms. In some arterial segments the endothelium was removed mechanically by gently rubbing the inside of the arterial ring.

Results. CGRP (1nM-0.1μM) (n=2) did not affect the resting tension of (P) and (NP) arteries that had no apparent active tone. When the tone of the uterine arteries was increased by norepinephrine (NE) (1μM), a concentration that produced 50-60% of the maximal contraction to NE, CGRP (1nM-0.1μM) produced a concentration-dependent inhibition of the tone. Figure 1 is a record from an experiment that demonstrates this CGRP-induced inhibition. The concentrations of CGRP that produced 50% inhibition of the NE-induced contraction were 0.7±1.1nM (n=4) and 4.7±0.8nM (n=7) in (P) and (NP) arteries, respectively. These values are not significantly different. The CGRP-induced relaxation was not affected by propranolol (1μM) a beta adrenergic antagonist, by indomethacin (5μM), an inhibitor of cyclooxygenase, by methylene blue (10μM), an inhibitor of guanylate cyclase, or by the removal of the endothelium.

Conclusions. The results show that CGRP acts as a very potent dilator of human uterine arteries from both pregnant and nonpregnant patients and that the sensitivity to the vasodilatory effect of CGRP is not altered by pregnancy. Although the results do not reveal a mechanism for the relaxing effect of CGRP, they do show that the vasodilatory action of CGRP is not mediated by beta adrenergic receptors, vasodilator prostanooids, increased levels of cyclic-GMP, or endothelium-derived relaxing factor (EDRF). We conclude that, because of the potent relaxant effect of CGRP in the isolated human uterine arteries and the reported elevated plasma concentrations of CGRP during pregnancy, CGRP conceivably could have a physiological vasodilator role in the uterine vasculature during pregnancy.

References.

Figure 1. CGRP-induced relaxation of a precontracted uterine artery from a nonpregnant patient. NE(1μM) was administered for 20 minutes before the artery was exposed to CGRP. Note that the NE-induced oscillatory contractile activity was not inhibited by CGRP. The amplitude of the rhythmic activity was not included in the measurements.