Effects of the vasopressin V₁a receptor antagonist, VA111913, on vasopressin-induced human uterine artery contractions

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Background: Abnormal contractions of uterine muscle and arteries are thought to be important in the aetiology of dysmenorrhoea (Hauksson et al., 1989; Dmitrovic et al., 2003). Since, vasopressin (AVP), primarily via the V₁a receptor, is able to induce uterine muscle and artery contractions (Bossmar et al., 1995; Hauksson et al., 1988), a vasopressin V₁a antagonist is potentially a novel treatment of dysmenorrhoea. We studied the effect of VA111913, a selective antagonist of the human V₁a receptor, on vasopressin-induced human uterine artery contractions.

Method: Medium (0.6-0.8 mm inner diameters)- and small (<0.4 mm)-sized uterine arteries were isolated from women undergoing hysterectomy. Arteries were mounted in organ baths containing Krebs-Ringer solution (pH 7.4; 37°C; aerated with 95% O₂ and 5% CO₂). In the first study, medium arteries were stimulated with cumulative concentrations of AVP (0.03 - 10 000 nM) in the presence of vehicle (0.0005% dimethyl sulfoxide) or VA111913 (0.5 – 150 nM). In a second study, responses to AVP in the presence of vehicle or VA111913 in paired medium- and small-sized arteries were evaluated. In both studies responses were measured as area under the recording curve (AUC) over 5 minute periods and compared to maximal stimulation with KCl (80 mM).

Results: Study 1: Incubation of medium-sized uterine arteries with increasing concentrations of AVP, in the presence of vehicle, resulted in dose-dependent contractions of the uterine arteries with a mean pEC₅₀ of 8.26 ± 0.44 (mean ± Standard Deviation (SD); n=14). Pre-incubation with VA111913 resulted in a dose-dependent competitive antagonism of AVP-induced contractions (pKB 8.65; Schild-slope 1.08; n=6). Study 2: Both small and medium sized arteries responded to AVP; pEC₅₀ were 8.55 ± 0.19 and 8.13 ± 0.52 (mean ± SD; n=4) and Emax were 92.06% ± 18.83 and 54.47% ± 15.52 (represented as a % of maximal KCl stimulation; mean ± SD; n=4), respectively. VA111913 was an equieffective inhibitor of AVP-induced contractions at medium- and small-sized arteries with a pA2 of 8.52 ± 0.40 and 9.03 ± 0.47 (mean ± SD; n=4).

Conclusion: These results confirm vasopressin to be a powerful vasoconstrictor of both small and medium uterine arteries. The V₁a receptor antagonist, VA111913, effectively and concentration-dependently inhibited the vasopressin induced responses. These results indicate a potential use of the compound in dysmenorrhoea. VA111913 is currently in Phase II clinical development as a novel treatment for dysmenorrhoea.