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Poster presentation

Differential effects of selective PDE5 inhibitors in rat cerebral arteries in vitro and in vivo

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Introduction

Compounds which increase cGMP levels are implicated in migraine pathophysiology as well as stroke recovery. Inhibitors of the cGMP degrading enzyme phosphodiesterase type 5 (PDE5) induce headache and migraine in humans, however surprisingly and unlike other migraine inducing drugs without measurable dilatation of cerebral arteries [1] or changes in hemodynamic response or excitability [2]. We aimed to investigate whether sildenafil and tadalafil induced dilatation of rat middle cerebral and meningeal arteries in vitro and in vivo.

Methods

Dilatory responses of middle cerebral arteries from Sprague-Dawley rats were investigated using pressurised arteriograhy with application of the UK 114–542, sildenafil, tadalafil either intraluminally or extraluminally. Effects of i.v sildenafil and tadalafil on dural arteries in a closed cranial window in vivo rat model were investigated.

Results

Abluminal sildenafil induced dilatation only at concentrations above 0.1 μM with a pEC_{50} of 6.74 ± 0.86 and E_{max} of 36.3 ± 8.3. UK 114542 was slightly more potent with Emax 70.4 ± 14.4% and pEC_{50} of 6.8 ± 0.05 (n = 4). Abluminal application of tadalafil (n = 4) showed no dilatory effect compared to control. When applied luminally all PDE5 inhibitors elicited a slight contraction of approximately 10% at higher doses (n = 4).

Sildenafil dilated dural arteries at high doses in a dose dependent manner (0.5 to 3 mg/kg), with 1 mg/kg producing 60 ± 14% dilatation (n = 6). Tadalafil, however, failed to elicit significant dilatations in vivo.

Discussion

The selective PDE5 inhibitors tadalafil and sildenafil are poor vasodilators of intact cerebral arteries. Only at high concentrations where unspecific effects may prevail did they induce dilatation. In vivo, the rat dural artery may dilate at lower doses of the PDE5 inhibitors, than in vitro however still doses higher than the normal therapeutic level. In pain generation primary vascular effects of PDE5 inhibitors seems unrelated to migraine generation. Further, in intact cerebral arteries PDE5 inhibitor in clinical doses appear to mixed vascular effects at high doses.

References

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