Differential vasoactive effects of sildenafil and tadalafil on cerebral arteries – relevant to migraine?

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Background
Phosphodiesterase 5 (PDE5) is associated with migraine pathophysiology, stroke recovery and vasospasm treatment [1,2]. We have shown previously that vasodilatation was not a prerequisite for migraine induction; sildenafil elicited migraine-like attacks in migraine patients without measurable changes in intra- or extracerebral artery diameter. Further, sildenafil was found to not affect neurovascular response or excitability [3]. However, dural artery responses were not accounted for in the human studies and minor vascular changes of functional importance may not have been detected.

The potential vascular interplay of PDE5 inhibitors sildenafil, tadalafil and UK-114,542 were studied by intravascular and extra-luminal administration in rat middle cerebral arteries (MCA) in vitro and on middle meningeal arteries (MMA) in vivo.

Aim
To examine a possible vascular site of action, if any, of each of sildenafil and tadalafil by investigating 1) the effects of PDE5 inhibitors in vitro dilatation of the middle cerebral artery (MCA) with controlled luminal or extra-luminal application of the drugs and 2) the in vivo effects of intravenous PDE5 inhibitors on the middle meningeal artery (MMA) dilatation in a closed cranial window model in rats.

Methods
Rat MCA diameter was investigated using pressurised arteriography, applying UK-114,542, sildenafil, and tadalafil intra- or extra-luminally. Effects on MMA were studied in the in vivo closed cranial window model.

Results
At high concentrations, abluminal sildenafil and UK-114,542, but not tadalafil, induced dilatation. Luminal application elicited a contraction of 4% (sildenafil, p = 0.03) and 10% (tadalafil, p = 0.02). In vivo, sildenafil, but not tadalafil, dose-dependently dilated MMA concomitant to blood pressure reduction (1-3 mg/kg); 1 mg/kg sildenafil inducing 60 ± 14% (p = 0.04) and vehicle (DMSO) 13 ± 6% dilatation.

Conclusion
PDE5 inhibitors applied luminaly had contractile effect on MCA. Abluminal sildenafil induced MCA dilatation above therapeutic levels. In vivo, sildenafil dilated MMA. Tadalafil had no dilatory effects. PDE5 inhibitors show differential vascular activity in arteries, although clinically the potential for headache induction appears similar. Such findings support clinical studies showing no vasodilatory effects of sildenafil on cerebral arteries in healthy subjects.

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