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Letter to the Editor

Endothelin-1-induced Endothelin-1 Release Causes Cerebral Vasospasm In-vivo

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There is mounting evidence that the release of endothelin-1 may play an important role in subarachnoid haemorrhage-induced cerebral vasospasm (Zuccarello et al 1994). The endothelin-1 release apparently occurs over a relatively long time period following subarachnoid haemorrhage, since the vasospasm present 6 days following the initial subarachnoid haemorrhage was completely reversed by a non-selective endothelin receptor antagonist (Zuccarello et al 1994). Although the initial release of endothelin-1 following subarachnoid haemorrhage may be due to events associated with blood-clot formation, including hypoxia, as well as haemoglobin and 5-HT release (Ohlstein et al 1991; Ohlstein & Storer 1992; Gertler & Ocasio 1993), blood clot removal does not reverse the vasospasm. Thus, subarachnoid haemorrhage may trigger a series of events resulting in the continuous release of endothelin-1, and this release may be responsible for the vasospasm. This study tests the hypothesis that endothelin-1 may serve as a positive modulator of its own release.

A mini-osmotic pump (Alza) containing 10 μM endothelin-1 (1 μL h^{-1}; Peninsula Laboratories) was implanted in the neck of New Zealand White male rabbits (3–4 kg), with the catheter placed into the cisterna magna. After 3 days, a basilar artery cranial window was prepared (Zuccarello et al 1993), the catheter removed, and the basilar artery suffused with artificial cerebrospinal fluid (CSF) in the presence or absence of the endothelin ET_A-receptor antagonist, BQ123 (1 μM; cyclo (D-Trp-D-Asp-L-Pro-D-Val-L-Leu; Peninsula Laboratories).

Endothelin-1-treatment of rabbits decreased basilar artery diameter, measured 5 min following suffusion of the artery in-situ with artificial CSF, from a control value of 966 ± 19 (n = 13; from Zuccarello et al (1994)) to 649 ± 24 (n = 3) μm. After 45-min suffusion with artificial CSF, a steady-state level of vasoconstriction was achieved at 726 ± 6 (n = 8) μm (Table 1). BQ123 relaxed basilar artery from endothelin-1-treated rabbits, but not from controls (Table 1). Following BQ123 washout, the magnitude of vasospasm returned to that observed before BQ123 exposure (740 μm; n = 2).

These results support the hypothesis that endothelin-1 may be responsible for subarachnoid haemorrhage-induced cerebral vasospasm and, furthermore, suggest that the continual release of endothelin-1 following subarachnoid haemorrhage may be due to endothelin-1-induced endothelin-1 release. Endothelin-1-induced endothelin-1 release may be mediated through endothelin ET_B receptors located on the basilar artery endothelial cells, as has been demonstrated in human umbilical vein endothelial cells (Fujitani et al 1992; Saijonmaa et al 1992), although this hypothesis remains to be tested. The inability of BQ123 to completely reverse the endothelin-1 infusion-induced spasm may be due to activation of smooth muscle cell endothelin ET_B receptors, in addition to endothelin ET_A receptors, by endogenously released ET-1. Endothelin-1-induced endothelin-1 release may represent a positive feedback loop that maintains cerebral vasospasm and, thereby, induces the vascular changes associated with chronic cerebral vasospasm.

Table 1. Effects of the endothelin ET_A receptor antagonist, BQ123, in-situ on endothelin-1-induced vasospasm of the rabbit basilar artery.

	Basilar artery diameter (μm ± s.e.)	
	Control	Endothelin-1-treated
−BQ123	966 ± 13* (n = 13)	726 ± 6† (n = 8)
+BQ123	962 ± 11* (n = 3)	805 ± 11 (n = 5)
BQ123, then wash-out	—	740 (n = 2)

*Significantly greater than vessels from endothelin-1-treated rabbits; †significantly less than vessels from control and endothelin-1-treated rabbits in the presence and absence of BQ123.

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