Does Endothelin-1 Play a Role in the Pathogenesis of Cerebral Vasospasm?

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Background
Endothelin-1 is a very powerful endogenous vasoconstrictor substance produced by endothelial cells. Its long-lasting vasoconstrictor and hypertensive action has been well documented in several species, including humans.

Summary of Review
It is generally accepted that endothelin-1 may contribute to the pathogenesis of a number of cardiovascular diseases. In the cerebral vasculature, endothelin-1 has been proposed as a key mediator of cerebral vasospasm following subarachnoid hemorrhage. Availability of endothelin-1 antagonist provided a pharmacologic tool to test the role of endothelin in the development of vasospasm.

Conclusions
This brief review is focused on the controversial results reported by different groups concerning the possible role of endothelin-1 in narrowing of cerebral arteries exposed to autologous blood. (Stroke. 1994;25:904-908.)

Key Words • cerebral vasospasm • endothelin

Endothelial cells play a key role in the local regulation of the vascular smooth muscle tone by producing and releasing relaxing and contracting factors.1-3 Although the physiological role of endothelium-dependent contractions in regulation of the cardiovascular system is unclear, existing evidence supports the concept that vasoconstrictor substances may become important regulators of vascular tone under pathological conditions.4-9 Endothelin-1 (ET-1), one of the most potent endogenous vasoconstrictor substances known, is produced by endothelial cells.3,10,11 Its long-lasting vasoconstrictor and hypertensive action has been well documented,12 and it is generally accepted that increased production of ET-1 may contribute to the pathogenesis of a number of cardiovascular diseases.10,13-18 In the cerebral vasculature, ET-1 has been proposed as a key mediator of cerebral vasospasm following subarachnoid hemorrhage (SAH).10,11,19

Cerebral vasospasm remains one of the major causes of morbidity and mortality in patients with aneurysmal SAH.20-22 Angiographic vasospasm, defined as a focal or diffuse narrowing of the major cerebral arteries, appears most often 4 to 10 days after the onset of SAH. Approximately 60% of patients with SAH exhibit delayed vasoconstriction; however, its pathogenesis is still not well understood. A strong correlation has been found between the presence of a thick clot in the subarachnoid space and the future development of symptomatic vasospasm.24 A very large number of putative spasmogens released from the intracisternal clot have been proposed.25,26 They may be directly spasmogenic24 or induce the release of vasoconstrictors and/or impair endothelium-dependent relaxations.25-28 This brief review focuses on the current knowledge concerning the potential pathophysiological role of ET-1 in cerebral vasospasm after SAH.

Background
There are three structurally and pharmacologically separate endothelin (ET) isopeptides in human and other mammalian species named ET-1, ET-2, and ET-3. The only one produced by endothelial cells is ET-1.10,11 The production of ET-1 is well characterized and involves the final transformation of big ET-1 catalyzed by a putative endothelin-converting enzyme (ECE)29,30 (Figure). ET-1 might be released in response to thrombin, arginine vasopressin, angiotensin II, or transforming growth factor-β.31,32 The relatively slow rate of production of ET-1 suggests that the peptide is more likely to participate in long-term regulation of vascular tone rather than in acute responses.29 Two different ET receptor subtypes have been identified: ET_A and ET_B. The ET_A receptor has a greater affinity for ET-1 and ET-2, whereas the B subtype has about equal affinity for all endothelins.33,34 Cerebral arterial endothelial cells may produce ET-1.35 The contracting effect of the peptide on vascular smooth muscle can be explained not only by a direct activation of ET_A receptor but also by sensitizing blood vessels to other vasoconstrictor substances.36-38 Such responses may favor the occurrence of abnormal vasoconstrictions and therefore be important in cerebral arterial vasospasm after SAH.

Endothelin-1 and Cerebral Vasospasm
To imply a major role for ET-1 in the pathophysiology of cerebral vasospasm after SAH, one would have to determine (1) cerebral vascular reactivity to ET-1, (2) levels of ET-1 after SAH, and (3) whether or not ECE inhibitors or selective ET-1 antagonists may prevent development of cerebral vasospasm.

Can ET-1 Induce Cerebral Vasospasm?
Several studies have confirmed the vasoconstrictor effect of ET-1 in cerebral arteries in vitro and in vivo. In isolated arteries ET-1-induced contractions are concentration dependent, long lasting, and difficult to wash.
Is ET-1 Production Increased During SAH?

One of the consequences of SAH is exposure of brain tissue to direct contact with blood. Production of ET-1 is stimulated by various vasoactive substances present in the blood, including arginine vasopressin, angiotensin II, and thrombin. Excessive local production of these substances is reported after SAH. Furthermore, oxyhemoglobin can directly stimulate endothelin biosynthesis in cultured endothelial cells. Excessive concentrations of oxyhemoglobin may also inactivate endothelium-derived nitric oxide, decrease cyclic guanosine monophosphate levels, with subsequent increased production of ET-1. However, the existence of a correlation between plasma or cerebrospinal fluid (CSF) ET-1 synthesis in cultured endothelial cells. Excessive concentrations of oxyhemoglobin can directly stimulate endothelin bio-

Schematic representation of endothelin-1 (ET-1) biosynthetic pathway. Big ET-1 is converted to ET-1 by a converting enzyme. Once ET-1 is released, it diffuses to the underlying smooth muscle cells where activating the ET receptors leads to contraction. The inhibitory effect of phosphoramidon on endothelin-converting enzyme and the selective receptor antagonism of BQ 123 is outlined. AT II indicates angiotensin II; AVP, arginine vasopressin; TGF/β, transforming growth factor-β; BQ 123, endothelin-1 receptor antagonist; ETα, endothelin-A receptor.

out. In vivo intracisternal injections of ET-1 induce extremely sustained vasoconstriction of the canine basilar artery assessed by angiography. The vasoconstriction lasted for more than 24 hours. One study reported that the effect of ET-1 was still present after 3 days. In cerebral vessels ET-1 causes vasoconstriction only if it is applied from the adventitial side. The existence of blood-brain barrier prevents a vasoconstrictor effect of circulating ET-1. However, ET-1 produced in the endothelium of cerebral arteries may be secreted abluminally, having access to its receptor on the smooth muscle cells.

Considering the slow onset and long duration of the ET-1 vasoconstrictor effect, it has been proposed that this peptide may be the mediator of chronic decrease in arterial diameter after SAH. However, the onset of arteriographic vasospasm in humans is usually between 4 to 10 days after SAH. Thus, the arterial narrowing produced by intracisternal injection of ET-1 occurs in a time course that is not entirely consistent with that of cerebral vasospasm.

Do ECE Inhibitors or ET, Receptor Antagonists Prevent Cerebral Vasospasm?

ET-1 is formed from big ET-1 via a putative ECE. Because big ET-1 is two or three orders of magnitude less potent a vasoconstrictor than ET-1, inhibition of ECE should effectively block the biological effects of ET-1. Although no specific inhibitors are available, a metalloprotease inhibitor, phosphoramidon, has been shown to reduce the conversion of big ET-1 to ET-1 in vitro and its pressor activity in vivo. (Figure).

In dogs intracisternal administration of big ET-1 caused a profound decrease in the diameter of the basilar artery that was inhibited by pretreatment with phosphoramidon. Furthermore, phosphoramidon prevented development of cerebral vasospasm in a "double-hemorrhage" canine model of the disease. In contrast, there are studies that did not detect any preventive effect of phosphoramidon. In particular, the results of our study demonstrated that a daily intracisternal injection of a high dose of phosphoramidon did not significantly affect SAH-induced cerebral vasospasm. Only a few studies have been reported concerning the effects of ETα receptor antagonists in experimental models of SAH so far. The ET-1 receptor antagonists
Summary of the Reports Concerning the Effect of ETA Receptor Antagonists on Cerebral Vasospasm

<table>
<thead>
<tr>
<th>ETA Antagonist</th>
<th>Experimental Model</th>
<th>Administration Regimen</th>
<th>Placebo</th>
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<tr>
<td>BQ123&lt;sup&gt;54&lt;/sup&gt;</td>
<td>Rat (one hemorrhage)</td>
<td>Single IC injection</td>
<td></td>
<td>*</td>
</tr>
<tr>
<td>FR139317&lt;sup&gt;55&lt;/sup&gt;</td>
<td>Dog (double hemorrhage)</td>
<td>IC injections on days 0, 2, 4</td>
<td>62</td>
<td>76†</td>
</tr>
<tr>
<td>BQ123&lt;sup&gt;55&lt;/sup&gt;</td>
<td>Dog (double hemorrhage)</td>
<td>Daily IC injection</td>
<td>56</td>
<td>62</td>
</tr>
<tr>
<td>BO485&lt;sup&gt;56&lt;/sup&gt;</td>
<td>Dog (double hemorrhage)</td>
<td>Continuous systemic infusion</td>
<td>60</td>
<td>75†</td>
</tr>
</tbody>
</table>

Values are expressed as percent diameter of basilar arteries in placebo and ETA antagonist–treated groups compared with 100% control diameter before injections of autologous blood.

ET<sub>A</sub> indicates endothelin-A; IC, intracisternal.

<sup>†</sup>Significantly different from placebo group (P<.01).

Tested were synthetic peptides named BQ123, BQ485, and FR139317. Recent reports on isolated arteries demonstrated selective inhibitory effect of BQ123 on ET-1–mediated contractions in systemic and pulmonary arterial vessels (Figure). In our study, BQ123 (10<sup>-5</sup> mol/L) selectively inhibited contractions caused by ET-1 in canine basilar artery. However, daily intracisternal administration of BQ123 in a concentration 10 times higher than the concentration that in vitro abolished the contractile effect of ET-1 did not prevent experimentally induced cerebral vasospasm. These findings suggest that ET-1 may not be the major mediator responsible for the decrease in cerebral arterial diameter associated with SAH. By contrast, other reports showing that administration of ET<sub>A</sub> receptor antagonists reduces cerebral vasospasm support the hypothesis that ET-1 plays a key role in this condition.
36. Consigny PM. Endothelin-1 increases arterial sensitivity to
34. Godfraind T, Mennig D, Morel N, Wibo M. Effect of endothelin-1
33. Yoshimoto S, Ishizaki Y, Kurihara H, Sasaki T, Yoshizumi M,
32. Sakurai T, Yanagisawa M, Takuwa Y, Miyazaki H, Kimura S, Goto
31. Arai H, Hori S, Aramori I, Ohkabo H, Nakanishi S. Cloning and
28. KatulSic ZS, Milde JH, Cosentino F, Mitrovic BS. Subarachnoid
26. Kim P, Sundt TM Jr, Vanhoutte PM. Alterations in endothelium-
20. Weir B, Rothberg C, Grace M, Davis F. Relative prognostic sig-
17. Cody RJ, Haas GJ, Binkley PF, Capters Q, Kelly R. Plasma endo-
15. Steward DJ, Kubac G, Costello KB, Cernacek P. Increased plasma
14. Nayler W. Endothelin: isoforms, binding sites and possible impli-
5-hydroxytryptamine.
Eur J Pharmacol.
732-735.

Vasoconstrictor response of large cerebral arteries of cats to endo-
thelin, an endothelin-derived vasoactive peptide. Eur J Pharmacol.


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Ikegawa R, Yamazaki M, Tsukahara Y, Takakura M, Morimoto S. Phosphoramidon, a metalloproteinase inhibitor, suppresses the secretion of endothelin-1 from cultured endothelial cells by
64. Clozel M, Watanabe H. BQ-123, a peptidic endothelin ET₄ receptor antagonist, prevents the early cerebral vasospasm following subarachnoid hemorrhage after intracisternal but not intravenous injection. Life Sci. 1992;52:825-834.
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