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

Francesco Cosentino, MD; Zvonimir S. Katusic, MD, PhD

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. Although the physiological role of endothelin-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. Endothelin-1 (ET-1), one of the most potent endogenous vasoconstrictor substances known, is produced by endothelial cells. Its long-lasting vasoconstrictor and hypertensive action has been well documented, and it is generally accepted that increased production of ET-1 may contribute to the pathogenesis of a number of cardiovascular diseases. In the cerebral vasculature, ET-1 has been proposed as a key mediator of cerebral vasospasm.

Cerebral vasospasm remains one of the major causes of morbidity and mortality in patients with aneurysmal subarachnoid hemorrhage (SAH). The ET A receptor has a greater affinity for ET-1 and ET-2, whereas the B subtype has about equal affinity for the three 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. Its long-lasting vasoconstrictor and hypertensive action has been well documented, and it is generally accepted that increased production of ET-1 may contribute to the pathogenesis of cerebral vasospasm after SAH.

Key  • cerebral vasospasm • endothelin

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 the cerebral vascular reactivity to ET-1. 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.

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From the Departments of Anesthesiology and Pharmacology, Mayo Clinic, Rochester, Minn.

Correspondence to Zvonimir S. Katusic, MD, PhD, Department of Anesthesiology, Mayo Clinic and Foundation, Rochester, MN 55905.
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 and the development of vasospasm is controversial. Several studies have demonstrated elevation in immunoreactive ET-1 levels in the CSF and plasma of animals and patients with SAH. Conversely, an equal number of convincing studies failed to uncover augmented levels of the peptide. The problem of determining ET-1 in its very low concentrations is probably an important source of variability. These conflicting findings may be explained by methodological differences, in particular, cross-reactivity of certain antibodies used to measure ET-1 with ET isoforms and/or its precursors as well as with other peptides. Studies reporting elevated levels of ET-1 in plasma and CSF were done in patients subjected to neurosurgical interventions, and ET levels were measured in the perioperative period. A nonsurgical therapeutic approach may lead to different results. It is impossible to rule out that the augmentation of ET-1 levels may be the consequence of surgically induced vascular disturbances.

The existing literature is inconclusive regarding the correlation between circulating levels of ET-1 and development of cerebral vasospasm after SAH. However, it should be stressed that circulating ET levels may not reflect the local modulatory role of the peptide. Indeed, ET-1 most likely acts in a paracrine fashion, regulating vascular smooth muscle cells nearby. Endothelial cells in culture release twice as much ET-1 toward vascular smooth muscle compared with luminal direction. Therefore, circulating levels of the peptide may well be within the normal range even in the presence of an increased concentration in the immediate vicinity of smooth muscle cells. This concept is supported by the findings of a recent study in which immunoreactive ET-1 measured in canine basilar artery wall after SAH was increased only on day 2 and not on day 7, when the presence of vasospasm was confirmed by angiography. The contrasting findings reported in the literature concerning the circulating levels of ET-1 and the availability of ECE inhibitors and ET receptor antagonists prompted new studies to probe the potential link between ET-1 and this pathological condition.

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 ET 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>
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</tr>
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<tr>
<td>BQ123*</td>
<td>Rat (one hemorrhage)</td>
<td>Single IC injection</td>
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<tr>
<td>FR139317†</td>
<td>Dog (double hemorrhage)</td>
<td>IC injections on days 0, 2, 4</td>
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<td>76†</td>
</tr>
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<td>Daily IC injection</td>
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<td>Dog (double hemorrhage)</td>
<td>Continuous systemic infusion</td>
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<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.

*Significant prevention of subarachnoid hemorrhage-induced decrease in cerebral blood flow (P<.01).
†Significantly different from placebo group (P<.01).

ET indicates endothelin-A; IC, intracisternal.

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tested were synthetic peptides named BQ123, BQ485, and FR139317.53,64-68 Recent reports on isolated arteries demonstrated selective inhibitory effect of BQ123 on ET-1-mediated contractions in systemic and pulmonary arterial vessels69-71 (Figure). In our study, BQ123 (10−5 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.52 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 ETA receptor antagonists reduces cerebral vasospasm support the hypothesis that ET-1 plays a key role in this condition.64-68 Differences in the experimental design of these studies may explain these contrasting findings, such as use of different species and models of the disease (rat, rabbit, dog; one hemorrhage versus double hemorrhage), and different concentrations and means and regimens of drug administration (intracisternally versus systemic; single or daily injections versus continuous infusion). After intracisternal administration, diffusion of the active drug to the arterial wall may be prevented by the thick clot surrounding the vessel. Therefore, it is necessary to acknowledge that the local concentration of active compounds may not be high enough to prevent the effect of ET-1.53 On the other hand, the reports of positive findings obtained in the groups treated with ETA receptor antagonist are not definite. Only a slight prevention of subarachnoid hemorrhage-induced decrease in cerebral blood flow (P<.01).52 These studies will certainly resolve the existing controversy surrounding the role of ET-1 in the pathogenesis of cerebral vasospasm.

Acknowledgments

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