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. 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. 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.

Cerebral vasospasm remains one of the major causes of morbidity and mortality in patients with aneurysmal subarachnoid hemorrhage (SAH). 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 vasostenosis; 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. A very large number of putative spasmogens released from the intracerebral clot have been proposed. They may be directly spasmogenic or induce the release of vasoconstrictors and/or impair endothelium-dependent relaxations.

This brief review focuses on the current knowledge concerning the potential pathophysiological role of ET-1 in cerebral vasospasm after SAH.

ET-1 in 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 levels 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 ET<sub>A</sub> Receptor Antagonists on Cerebral Vasospasm

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Values are expressed as percent diameter of basilar arteries in placebo and ET<sub>A</sub> antagonist-treated groups compared with 100% control diameter before injections of autologous blood. ET<sub>A</sub> indicates endothelin-A; IC, intracisternal.

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

ET<sub>A</sub>-mediated effects of ET-1 in cerebral vasospasm. 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.<sup>52</sup> 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 show 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.<sup>64-68</sup> 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 (intracisternal 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.<sup>53</sup> On the other hand, the reports of positive findings obtained in the groups treated with ET<sub>A</sub> receptor antagonist are not definite. Only a slight prevention of subarachnoid hemorrhage-induced decrease in cerebral blood flow (P<.01).<sup>52</sup> These studies will certainly resolve the existing controversy surrounding the role of ET-1 in the pathogenesis of cerebral vasospasm.

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References


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