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COMMENTARY

Bradykinin B_2 receptor antagonism: a new direction for acute stroke therapy?

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Stroke is responsible for 10% of all deaths worldwide, and there remains an urgent need for the development of clinically effective treatments for acute stroke. Stroke is now considered to be a disease characterized by an ongoing inflammatory process rather than simply acute neurodegeneration. Bradykinin has attracted recent interest as a potential mediator of brain injury following stroke, because it activates several mechanisms responsible for the early manifestations of inflammation, including arteriolar dilatation, increased vascular permeability and oedema formation. These actions of bradykinin occur *via* activation of B_2 receptors. New evidence suggests that blocking bradykinin B_2 receptors after experimental cerebral ischaemia reduces brain oedema, infarct volume and neuronal necrosis, and improves neurological outcome. Thus, B_2 receptor antagonists may be a promising new class of compounds for clinical use after the onset of cerebral ischaemia.
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Abbreviations: LF 16-0687 Ms, (1-[[3-[(2,4-dimethylquniolin-8-yl)oxymethyl]-2,4-dichlorophenyl]sulphonyl]-*N*-[3-[[4-aminiminomethyl)phenyl]carbonyl-amino]propyl]-2(*S*)-pyrrolidinecarboxyamide dimesylate salt)

Stroke is the third-leading cause of death in the Western world, and is responsible for 10% of all deaths worldwide (Lo *et al*., 2003). Although valuable prophylactic therapies exist, such as antihypertensive agents, antiplatelet drugs and cholesterol-lowering compounds, with an ageing population there is a very great and urgent need for the development of clinically effective treatments for acute stroke.

Most strokes are ischaemic in nature, due to a thromboembolic occlusion of a major artery supplying the brain. If the clot is not resolved within a short period of time, a core of severely ischaemic brain tissue will develop that cannot be salvaged. Agents that lyse these clots reperfuse the ischaemic brain and form the basis of thrombolytic therapy. Thrombolysis is used for acute stroke in most European countries (Thomassen *et al*., 2003) and the thrombolytic recombinant tissue plasminogen activator is currently the only pharmacological therapy approved for acute stroke in the United States of America (Fisher, 2003; Lo *et al*., 2003). However, the use of thrombolytics is restricted to administration within 3 h after stroke (Barone & Feuerstein, 1999; Fisher, 2003; Thomassen *et al*., 2003), and only 5–8% of patients qualify for treatment within this short time from stroke onset, most commonly due to delayed hospital presentation (Barone & Feuerstein, 1999; Fisher, 2003).

It is now believed that stroke is a disease characterized by an ongoing inflammatory process, rather than simply acute neurodegeneration (Barone & Feuerstein, 1999). In animal models, the central core rapidly proceeds to infarction with irreversible injury after the onset of focal ischaemia, then spreads out circumferentially (Barone & Feuerstein, 1999; Fisher, 2003). The expression of inflammatory mediators and activation of an inflammatory response not only contributes to lipid membrane peroxidation in the brain after focal stroke, but also exacerbates the degree of tissue injury caused by the adherence and infiltration of leucocytes, release of cytotoxic products such as reactive oxygen species and enhanced permeability of brain endothelium.

Importantly, brain inflammation after stroke may be considered as a dual-edged sword, with inflammatory cascades stimulating both detrimental and potentially beneficial pathways (Barone & Feuerstein, 1999). This seems to be because the timing of brain inflammation spans from within a few hours to several days/weeks after the stroke, including early injury and later postinjury repair processes. Although initial inflammation can contribute to the degree of brain damage after injury, broad anti-inflammatory interventions designed to limit the degree of damage have been shown to interfere with nervous regeneration and recovery (Barone & Feuerstein, 1999). Therefore, specific strategies may be required to intervene early in brain inflammation to reduce injury and neurodegeneration, and different interventions may be necessary to facilitate repair and recovery of regeneration processes after central nervous system injury.

Bradykinin is considered an important mediator of the inflammatory response in both the periphery and the central nervous system, and it has attracted recent interest as a potential mediator of brain injury following stroke (Wahl *et al*., 1996; Relton *et al*., 1997; Zausinger *et al*., 2002). This nonapeptide is produced by cleavage from its precursor, kininogen, and it activates several mechanisms responsible for the early manifestations of inflammation, including arteriolar dilatation, increased vascular permeability and resulting oedema formation (Wahl *et al*., 1996; Relton *et al*., 1997;

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Sobey *et al*., 1997; Brian *et al*., 2001). All the components of the kallikrein/kinin system have been identified in the human brain (Raidoo *et al*., 1996a, b), and the tissue kallikrein/kinin system, which influences the permeability of the blood–brain barrier, is activated in humans during stroke (Wagner *et al*., 2002).

The mechanisms by which endogenous bradykinin may mediate ischaemic brain injury seem likely to involve the activation of constitutively expressed B_2 receptors, the release of arachidonic acid and activation of cyclo-oxygenase (COX) enzymes, leading to the production of prostanoids, reactive oxygen species and ultimately lipid peroxidation (Relton *et al*., 1997; Sobey *et al*., 1997; Sarker *et al*., 2000; Brian *et al*., 2001). Bradykinin also stimulates the release of excitatory amino-acid neurotransmitters, and is a potent stimulator of other inflammatory mediators such as cytokines, and it acts as a leucocyte chemoattractant (Relton *et al*., 1997). Stroke results in blood–brain barrier disruption, and sometimes in life-threatening cerebral oedema. Even brief application of bradykinin has been shown to cause marked and prolonged cerebral arteriolar dilatation (Brian *et al*., 2001) and increases in cerebrovascular permeability (Sarker *et al*., 2000). Continuous treatment for 24 h after cerebral ischaemia with a peptide B_2 receptor antagonist, CP-0597, has been reported to reduce brain oedema, infarct volume and neuronal necrosis, and improve neurological outcome in rats (Relton *et al*., 1997). Similarly, administration of the new potent nonpeptide B_2 antagonist, LF 16-0687 Ms, for 3 days commencing before the onset of ischaemia, was recently found to be neuroprotective in rats (Zausinger *et al*., 2002).

In their new study, Ding-Zhou *et al*. (2003) report the impressive findings that administration of LF 16-0687 Ms (3–12 mg kg^{-1} s.c.) to mice in two injections immediately and 6 h *after* 15 min of cerebral ischaemia reduces blood–brain barrier disruption, neutrophil infiltration and neurological impairment by 60–70%, and reduces oedema and infarct volume by ~30% (Ding-Zhou *et al*., 2003). Although cerebral blood flow was not measured, it is likely that identical levels of cerebral ischaemia were experienced in all mice, because LF 16-0687 Ms was administered after the ischaemic insult, and blood pressure was not altered in any of the treatment groups. Hence, these new findings by Ding-Zhou *et al*. further support the concept that B_2 receptor activation participates in postischaemic brain damage, and that treatment during this period with a B_2 receptor antagonist can improve stroke outcome (Relton *et al*., 1997).

The authors did not determine whether the protection by LF 16-0687 Ms in this study was due to actions on vascular or neuronal B_2 receptors, or indeed whether reduced activation of COX enzymes was critical in these outcomes. Since it has now been established that COX-1 is protective in cerebral ischaemia (Iadecola *et al*., 2001b), but COX-2 is harmful (Iadecola *et al*., 2001a), perhaps the protection by LF 16-0687 Ms is due to the inhibition of bradykinin-stimulated COX-2 activity. Thus, it would be interesting in future studies to test whether LF 16-0687 Ms is equally protective as COX-2 inhibition (Iadecola *et al*., 2001a), and perhaps whether even greater cerebral protection might be obtained by LF 16-0687 Ms in combination with a thrombolytic. In summary, by selectively blocking the actions of bradykinin – an early harmful mediator in postischaemic cerebral ischaemia – LF 16-0687 Ms may represent a promising new compound for development as a clinical therapeutic that can be administered after the onset of cerebral ischaemia.

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