Title: Changes in vasoreactivity following experimental subarachnoid hemorrhage or transient middle cerebral artery occlusion

Background: Stroke is a leading cause of mortality and a major cause of disability worldwide. Cerebral ischemia causes damage to the brain within minutes. Prompt restoration of cerebral blood flow may minimize the damage, but ischemia can nevertheless be aggravated by delayed or late cerebral ischemia, post-ischemic hypoperfusion and loss of normal vasomotor responses.

In subarachnoid hemorrhage (SAH), delayed cerebral ischemia is a major contributor to morbidity and mortality, and in occlusive stroke, up-regulation of vasoconstrictive receptors may impair blood flow to ischemic regions even after revascularization.

Over 1000 neuroprotective agents have been tested, but they have all failed in a clinical setting despite promising experimental data. The failure of these agents to protect neurons may warrant the investigation of changes in, and preservation of, the normal function of cerebral blood vessels after stroke.

Aim/Method: The overall aim of the present project is to characterize changes in a limited set of vasoactive receptor systems in two different stroke models. We plan to do so by harvesting cerebral arteries from rats following either occlusive stroke (MCAO) or SAH. Differences in vasomotor responses to VIP- CGRP- and P2Y6 agonists will be measured by a sensitive myography system. The exact location and relative concentration of receptor proteins will be determined either by immunohistochemistry or by flow cytometry.

Preliminary results: Papers I and II demonstrate the localization and distribution of VIP/PACAP and CGRP receptors, respectively. The vasorelaxant effects of VIP and CGRP upon the rat middle cerebral artery (MCA) is clearly shown along with corresponding changes in intracellular calcium levels. Paper III (in progress) demonstrates the changes in vascular responses to VIP following ischemia or SAH. Initial findings include a right-ward shift of the VIP concentration-response curve for SAH while MCAO increased the dilatory response to VIP.

Significance: Better knowledge regarding changes in receptor systems regulating vascular tone after cerebral ischemia and SAH may lead to therapeutic agents counterbalancing vascular dysfunction and delayed ischemia. This may in turn reduce the impact of delayed ischemia and improve clinical outcome after stroke.
Publications:
