Mini-Stroke Does Mega-Damage—Can Memantine Help?

21 December 2012. Cerebrovascular disease is a major risk factor for Alzheimer’s dementia, but how many of the millions of blood vessels in the brain need to be damaged before cognition suffers? In rats, just one, according to a study published December 16 in Nature Neuroscience. Using two-photon microscopy to identify arterioles and venules into the somatosensory cortex, researchers led by David Kleinfeld, University of California, San Diego, induced clots in individual vessels. That was enough to weaken the rats’ decision-making during a behavioral task. A shot of the Alzheimer’s drug memantine alleviated the cognitive defects and associated tissue damage. Though it is not known if single clots would cause similar damage in people, the findings offer hope that the problems may be treatable. In a similar vein, a mouse study in the December 12 Journal of Neuroscience shows that neurons die considerably more slowly after mini-strokes than after larger ones, suggesting there might be time to intervene therapeutically. Maiken Nedergaard of the University of Rochester Medical Center, New York, led that work.

The brains of many people with dementia teem with small lesions, called microinfarcts, reflecting tissue damage from occluded blood vessels. Moreover, epidemiological research links vascular injury with heightened risk for Alzheimer’s disease, and a recent study found faster cognitive decline in people with particles clogging their cerebral arteries (ARF related news story on Purandare et al., 2012). However, researchers were unsure if such obstructions cause cognitive impairment or simply coexist with it. To find out, first author Andy Shih and colleagues clotted single vessels in the brains of live rats and looked for effects on neuronal function and behavior. Previously a postdoc in Kleinfeld’s lab, Shih is now an assistant professor at the Medical University of South Carolina, Charleston.

Visualizing subcortical blood vessels and cells in anesthetized rats (Shih et al., 2012), the researchers identified the neurons that respond to sensory signals from the animals’ whiskers. Rats use these tactile sensors to make navigational judgments, including whether to jump across a gap for a reward. After training rats to do just that, the scientists induced lesions at individual microvessels (see image below) near the responsive neurons. They used photosensitive molecules that produce free radicals under laser light (Schaifer et al., 2006). Less than a week later, the rats “could no longer make a jump/no-jump decision based on whisker touch,” Kleinfeld told Alzforum. Brain tissue surrounding the blocked vessel became hypoxic and increasingly unresponsive to hindlimb stimulation, as evidenced by calcium waves reflecting runaway activity of dying neurons.
Little Clot, Big Trouble
A single arteriole (yellow) dives from the brain surface to penetrate a column of brain tissue. Blocking just one such vessel can harm the brain and lead to cognitive defects.
*Image courtesy of David Kleinfeld Lab, UC San Diego*

Some scientists think the rat model has potential implications for microinfarcts in people. “The findings suggest that microinfarcts may not be so silent,” noted William Van Nostrand of Stony Brook University Medical Center in New York. “Although there may not be overt signs of impairment, subtle deficits could occur, accumulate, and, over time, manifest as vascular cognitive impairment,” he said.

It is hard to tell how these findings will translate to humans. The rat experiments examined consequences of a single manipulation in healthy animals; however, most human studies involve people who are already quite compromised. It is challenging to draw conclusions with so many comorbidities, Kleinfeld noted. Furthermore, the rat cortex has nearly three times as many venules as arterioles, whereas the ratio is opposite in the human brain.

Regardless, Kleinfeld thinks the silver lining in this study was the memantine findings. When the rats were injected with memantine or another NMDA-type glutamate receptor antagonist (MK-801), fewer neurons died. By blocking NMDA receptors, these compounds protect neurons from excitotoxic damage. “Instead of a dead cylinder of cells roughly a half-millimeter wide, we saw just a small scar about 100 microns in diameter,” Kleinfeld said. Cognitive deficits were milder as well.

Could these drugs protect people with cerebrovascular disease? Although they showed no benefit in clinical trials for large ischemic strokes, “perhaps they may prove more efficacious for limiting microinfarct damage,” Van Nostrand wrote in an e-mail to Alzforum (see full comment below).

The Journal of Neuroscience report lends support to that idea. Nedergaard used a mouse model of multiple microinfarcts ([Rapp et al., 2008](#)), which the scientists think may be more representative of what is going on in the brains of people with vascular disease. First author Minghuan Wang and colleagues found that neuronal death progresses slowly over 28 days or more. “This is remarkably different from regular stroke, were the damage is done within hours,” senior author Nedergaard wrote in an e-mail. This
suggested to him that the mechanism of neuronal loss differs and, “most importantly, that the therapeutic window is much longer [for mini-strokes].”—Esther Landhuis.

References:


Comments on News and Primary Papers
Primary Papers: The smallest stroke: occlusion of one penetrating vessel leads to infarction and a cognitive deficit.

Comment by: William Van Nostrand
Submitted 21 December 2012 | Permalink Posted 21 December 2012

This article by Shih et al. is an elegant study that addresses the pathological and cognitive consequences of cerebral microinfarcts. Using rats, the authors created microinfarcts targeting individual penetrating arterioles and venules, and showed that a column of pathological changes associated with infarcts radiated from the occluded vessels. There are several notable and novel findings in this study.

First, the authors demonstrate that infarcted penetrating venules exhibit very similar consequences as observed with infarcted penetrating arterioles, including loss of neuronal function, oxidative damage, activation of neuroinflammatory cells, and blood-brain barrier compromise. On the other hand, infarction of deep microvessels appeared rather innocuous, producing little tissue damage.

Second, administration of the NMDA receptor antagonists MK-801 and memantine markedly reduced the infarct size, whether in penetrating arterioles or venules.

Third, a rather interesting part of the study were the experiments to address cognitive deficits of microinfarcts. In this case, the authors targeted penetrating vessels that lie within a single cortical column associated with the vibrissa primary sensory cortex. Infarction of a specific penetrating vessel within this specific cortical column impaired the sensory response to allow the rat to make a decision. Of note, these experiments indicate that this type of microinfarct can indeed have deleterious cognitive consequences. However, reducing the infarct-associated damage with NMDA receptor antagonists can prevent this type of cognitive deficit.

Finally, one of the more significant findings in this report is that the damage associated with numerous microinfarcts, within proximity to one another, can actually combine to form a larger infarct lesion. The NMDA receptor antagonists MK-801 and memantine were shown to restrict this coalescing of numerous microinfarcts.

Even though these studies were performed in a rat model, they may have potential implications for microinfarcts in humans. For example, the findings suggest that micro-/silent infarcts may not be so silent. Although
there may not be overt signs of impairment, subtle deficits could occur, accumulate, and, over time, manifest as vascular cognitive impairment. Under conditions where multiple microinfarcts might occur, they could possibly cause synergistic damage resulting in consequences reflecting that of a more serious infarct that results in palpable clinical symptoms. Although NMDA receptor antagonists were not successful in human clinical trials for larger ischemic strokes, perhaps they may prove more efficacious for limiting microinfarct damage. However, a significant hurdle to overcome would be an effective and timely way to detect micro-/silent infarcts, since there would likely be a limited window for therapeutic intervention.

**Primary Papers: The smallest stroke: occlusion of one penetrating vessel leads to infarction and a cognitive deficit.**

**Comment by:** Roy O. Weller  
Submitted 21 December 2012 | Permalink Posted 21 December 2012

In this paper from the group of David Kleinfeld, the authors address whether microinfarcts in the elderly brain have significant consequences for neurological and cognitive function. Using a rat model, individual blood vessels were occluded on the cortical surface of the brain by activation of the circulating photosensitizer, rose bengal. Deep microvessels were occluded using a pulsed laser. Occlusion of individual cortical penetrating arterioles and venules resulted in microinfarcts that led to cognitive dysfunction in a behavioral task. One of the most interesting observations in this paper is that damage caused by both single and coalesced microinfarcts could be ameliorated by post-occlusion application of memantine, a drug that is used for the treatment of Alzheimer's disease and vascular dementia. There was also a significant improvement in cognitive function following the administration of memantine.

The main significance of this paper is *firstly*, that targeted vascular occlusion leading to microinfarcts in specific areas can be used to produce measurable neurological deficits; *secondly*, that even small infarcts can produce neurological and behavioral defects; and *thirdly*, that the reduction in size of the infarcts by the administration of memantine also results in amelioration of neurological and behavioral function.

As the authors of this paper point out, the anatomical arrangement of vessels penetrating the cerebral cortex is very similar in rodents and humans. This emphasizes the importance of this study for human stroke medicine, particularly in the prevention of microinfarcts and their prompt treatment.