



# ARTICLE OF THE MONTH

## Ischemic Stroke Injury is Mediated by Aberrant Cdk5

Meyer DA, Torres-Altoro MI, Tan Z, Tozzi A, Di Filippo M, DiNapoli V, Plattner F, Kansy JW, Benkovic SA, Huber JD, Miller DB, Greengard P, Calabresi P, Rosen CL, Bibb JA.

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For the October edition of the SNACC “Article of the Month”, we present you with a bit of a change of pace. Until now, most of our featured articles have focused on aspects of neuroscience and neuroanesthesiology which purport to have more or less of a direct clinical applicability. This month, in keeping with our society’s mission (and, in fact, our name) to promote and incorporate neuroscience at even the basic science level, we have chosen an article which deals with a “laboratory” topic. The issue at hand relates to neuronal injury in a rodent stroke model and its mediation by an aberrant protein kinase (Cdk5). We are honored to have a commentary on this paper written by a basic science researcher and SNACC member since 1995, Dr. Raymond Roginski. Dr. Roginski is Clinical Assistant Professor of Anesthesia and Critical Care at the University of Pennsylvania and a Staff Anesthesiologist at the Philadelphia VA Medical Center. Notably, he discovered what is now known as the GCOM1 gene in 1998, and has been studying its role in the brain since then, including its role in neurodegenerative diseases, such as Alzheimer’s Disease and Parkinsonism. We hope you will enjoy this latest installment of the SNACC “Article of the Month” and will join in the conversation by clicking on the [SNACC LinkedIn Group](#).

-John F. Bebawy, MD

## Commentary

Reviewer: Raymond S Roginski MD PhD

The development of effective strategies to achieve perioperative neuroprotection has been one of the Holy Grails of neuroanesthesia, neuro-intensive care, neurology and the broader field of neuroscience. Many mechanisms and candidate strategies have been identified and evaluated in animal models. However, currently there is no reliable way to protect the human brain after traumatic or ischemic insults (except intracerebral arterial TPA in acute embolic stroke) or during the onset and progression of chronic neurodegenerative diseases such as Alzheimer’s (AD) and Parkinsonism (PD).

In their study Meyer et al (2014) examined the effect of aberrant Cdk5 on ischemic stroke injury in a mouse MCAO model. Middle cerebral artery occlusion is the most frequently occurring type of ischemic stroke in humans. Therefore this is a relevant model. The authors began with the established paradigm that intracellular calcium overload (mediated by excessive activation of NMDA receptors by glutamate released during ischemia) activates calpain which contributes to ischemic damage. One of the substrates of calpain is Cdk5r1 (aka p35), the activating cofactor of Cdk5. When calpain cleaves the amino-terminal 10 kDa peptide from p35, generating p25, the resulting Cdk5/p25 complex becomes neurotoxic and has been implicated in neuronal damage in AD and PD. Therefore the authors hypothesized that blocking the production of the Cdk5/p25 complex would be neuroprotective.

The study employed several methods to prove this point. After demonstrating that the focal ischemia MCAO model resulted in significant stroke volumes in aged rats and generated robust amounts of Cdk5/p25 after oxygen-glucose deprivation (OGD) in aged rat brain slices, they went on to show that the dysregulation of Cdk5 in brain slices is dependent upon calpain. After confirming these key aspects of their model system, they removed calcium from the medium and in a related experiment added inhibitors of calpain, both of which revealed the same effect, that the generation of p25 was significantly decreased. Next they showed that inhibition of Cdk5 was neuroprotective in acute brain slices using specific inhibitors of Cdk5. In addition, they revealed an effect which may be relevant to the emotional changes seen after some strokes in humans, the preservation of dopaminergic neurotransmission after an ischemic insult by inhibitors of Cdk5. The final study reported in this paper employed conditional knock-out mice genetically engineered to reduce the expression of the Cdk5 gene in the entire forebrain after treatment with 4-hydroxytamoxifen for 14 days. When subjected to MCAO, these mice demonstrated profoundly decreased infarct volumes compared to littermates not treated with 4-OH tamoxifen. In particular, striatal infarct volumes were reduced 2.6 fold.

Overall Meyer et al (2014) showed that Cdk5 promotes ischemic injury and the death of neurons after an ischemic insult and that inhibition of Cdk5 is profoundly neuroprotective in their models. This work is potentially very significant, although they have not identified a clear path leading to human clinical trials. But such trials should be possible if a suitable inhibitor of CDK5 (the human gene symbol for this gene) can be found. The CDK5 cascade interacts with the glutamate system, which has long been a target for neuroprotection. Unfortunately, with one or two possible exceptions, none of the direct acting Glu receptor antagonists have shown efficacy in human clinical trials. Therefore the strategy of indirectly interfering with Glu excitotoxicity, such as via the CDK5 pathway, seems promising. Intriguingly, the possibility of cross-talk between the CDK5 cascade and the GCOM1/GRINL1A pathway, which confers neuroprotection against NMDA and Glu toxicity (*NeuroReport* 19: 1721, 2008) by an indirect effect on the NMDA receptor, is suggested by the occurrence of two pairs of shared interacting genes (GRIN2A/GRIN1 and CCNB1/CCNB1IP1 for CDK5 and GCOM1, respectively).