# Creatine as a neuroprotector

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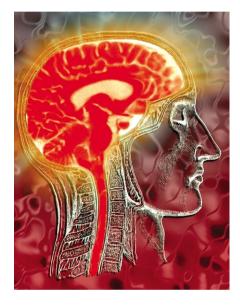
The devastating effects of many neurological disorders can all be lessened with creatine, a compound taken mainly for muscle building. These include Parkinson's disease, amyotrophic lateral sclerosis, Huntington's disease, traumatic brain injury and ischemic stroke. Robert Friedlander, an Associate Professor at Brigham and Women's Hospital and Harvard Medical School, MA, USA (http://www.bostonneurosurg.org/faculty/friedlander.html) and colleagues have now showed that a month-long prophylactic regimen of creatine prevented some of the damage caused by stroke in mice [1].

## **Neurological protection**

After cerebral ischemia, mice that were fed a 2% creatine-supplemented diet suffered an infarct, or damaged area, that was dramatically smaller than in mice fed no creatine. How creatine improves cells' chances of survival remains unclear, but the report suggests that neurons withstand the shock of ischemic insult because they are better bio-energetically equipped. Friedlander said; 'Those mice were protected from a neurologic point of view. When the cell is more robust,' he suggests, 'it can protect itself better against injury.'

Constantino ladecola, not involved in the work, is Head of the Division of Neurobiology at Weill Medical College of Cornell University, NY, USA (http://www.med.cornell.edu/research/iadecola/). He agrees that creatine probably 'enhances the ability of the brain to withstand an energy crisis. Stroke is a problem of energy – you get depletion of blood, oxygen,

glucose, etc. But unlike other organs, the brain has no reserves of energy.' Feeding the mice creatine 'allowed the brain to better withstand energy depletion. But how that happens is very difficult to understand.'



## The key role of mitochondria

That understanding might lie in another link between the chronic diseases and acute brain injury – the apoptotic pathway. Neurons of creatine-fed mice maintained higher ATP levels, and also showed diminished signs of apoptosis, in the form of reduced cytochrome *c* release and caspase-3 activation. In the choice between survival and apoptosis, Friedlander says, 'Mitochondria play a very key role. What creatine might be doing is blocking the breakdown of mitochondria, because once that happens, the cell goes down the cell-death pathway.'

There are currently two strategies to combat stroke: one is to prevent or lessen the injury event itself, the other is to minimize the damage done by the insult. Creatine falls into the

second, neuroprotective category, explains ladecola. 'Is this going to prevent the stroke 100%? No, probably not. The brain still undergoes the same amount of stress, but the neurons are able to withstand the insult.' Whereas other neuroprotective agents, such as glutamate receptor blockers and nitric oxide inhibitors, have had good results in animal models, none has panned out in human patients. Tissue plasminogen activator (tPA), 'the clot-busting drug, works the other way around - it decreases the amount of damage by opening blood vessels.' tPA is currently the only drug effective against stroke in humans.

### A prophylactic against stroke

ladecola raises the caveat for creatine: 'Whether this is going to work in humans is an open question.' But Friedlander has hopes that an identified population of patients at high risk can use creatine as a prophylactic against stroke, 'much like people taking aspirin.' Ironically, Friedlander laments that some of the biggest advantages of creatine - its low cost, ready availability, and proven safety - might turn out to impede its use. 'The disadvantage is that if pharmaceutical companies don't have an interest, it won't go to trials.' But he is hoping that the lure of an effective agent against stroke damage will send creatine on the path to use by patients.

#### Reference

1 Zhu, S. et al. (2004) Prophylactic creatine administration mediates neuroprotection in cerebral ischemia in mice. J. Neurosci. 24, 5909–5912