Neurosupportive Potential of Creatine Orotate

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Abstract

By serving as a biosynthetic precursor for both pyrimidine nucleotides and carnosine in the brain, supplemental orotic acid has the potential to support neuronal membrane biogenesis – of key importance to efficient cognitive function – while providing neuroprotection from ischemia, trauma, and oxidative neurodegeneration, and promoting brain healing. Creatine orotate may be a superior delivery vehicle for orotic acid, as brain creatine aids bioenergetics while limiting mitochondrial superoxide production. A supplement boosting brain levels of pyrimidines, carnosine, and creatine may have valuable neurosupportive activity, while concurrently promoting physical strength and endurance.

Orotate for Support of Neuronal Membrane Biogenesis

Supplemental orotic acid is converted to pyrimidines in the liver.[1, 2] The uridine synthesized in this way is released into the blood, and can be transported through the blood-brain barrier and into brain neurons to serve as a precursor for neuronal pyrimidines.[3] Cytidine nucleotides play an essential role in the synthesis of the phospholipids of neuronal membranes. Wurtman and colleagues have proposed that efficient neuronal membrane biogenesis, by supporting formation of neurites and dendritic spines, aids the formation of new synaptic connections that is crucial for learning and memory formation.[4] They have shown that joint administration of uridine and the omega-3 fatty acid DHA (a major component of neuronal membranes), with or without a supplemental source of choline, enhances the formation of dendritic spines and neurites in healthy gerbils, boosting their cognitive performance.[5-7] Rodent studies dating back several decades analogously reported that administration of certain orotate complexes could aid long-term potentiation and learning in rodents.[8-11] Clinical studies are needed to determine whether such supplementation may also aid cognition in young or aging humans.

Orotate as a Brain Antioxidant

Pyrimidines produced from supplemental orotic acid are ultimately catabolized in the liver to yield beta-alanine, much of which is released to the blood.[12-14] Beta-alanine is the rate-limiting precursor for the synthesis of the antioxidant/buffer carnosine (beta-alanyl-L-histidine), produced within skeletal muscle, heart, and the brain; this reflects the fact that the affinity of carnosine sythetase for histidine is far higher than its affinity for beta-alanine.[15] Glia within the brain can synthesize carnosine and release it to the extracellular space; both neurons and astrocytes, which do not synthesize their own carnosine, can then import the the carnosine manufactured within glia.[16-18] The utility of carnosine in the brain may reflect its potent and versatile antioxidant activity – scavenging oxidants, sequestering transition metals so that they are less likely to catalyze hydroxyl radical production, and reacting covalently with labile breakdown products of lipid peroxidation, lessening their pathogenic impact.[19-22] Studies in which carnosine is administered to rodents, or added to brain cell cultures, report that it provides protection in models of ischemia (with or without reperfusion), Alzheimer's, and Parkinson's disease, while dampening LPS-mediated microglial activation.[23-34]

Studies in which carnosine is administered to rodents are of somewhat dubious clinical relevance, as carnosine in the plasma of rats is relatively stable, and can be taken into cells intact. In contract, serum carnosinase activity is much higher in most humans, such that the half-life of plasma carnosine after carnosine ingestion is very short; in some clinical studies, intact carnosine can't be measured in plasma after carnosine supplementation.[35] Hence, studies in which beta-alanine or orotate is administered to rodents would be much more clinically pertinent; beta-alanine should be employed in cell culture studies. Unfortunately, few such studies have been done to date focusing on neuroprotection; there is a report that intraperitoneal orotic acid, administered from two hours before to 24 hours after global cerebral ischemia in gerbils provides some protection from neuronal damage.[36]

Orotate's Potential for Brain Healing

The capacity of supplemental orotic acid to support both antioxidant activity and membrane biogenesis in the brain suggests that it might have value for aiding brain repair after trauma or ischemia. Long-chain omega-3 fats, likewise supportive of brain membrane biogenesis, and possessing anti-inflammatory properties, have been found to be protective in rodent brain repair models;[37-42] it is reasonable to suspect that orotic acid might function as an effective cofactor for such supplementation.

Orotic Acid Supplementation

Administered as a complex with magnesium, orotate has shown a favorable effect on the survival of patients with severe heart failure; the dose employed in this one-year study was 6 g daily for 1 month, and 3 g daily for the subsequent 11 months.[43] It is probably reasonable to presume that doses in this range might also have some utility of boosting brain levels of pyrimidines and carnosine.

Administering orotic acid as the complex creatine orotate may be of particular value for brain health. Although creatine supplementation has been studied primarily with respect to its favorable impact on skeletal muscle performance, creatine also is a key catalyst of bioenergetics in neurons and the brain as well. Moreover, the creatine pool within neurons exerts an antioxidant effect on mitochondria, as creatine kinase activity situated near the inner membrane adenine nucleotide translocase converts newly generated ATP back to ADP, such that mitochondrial membrane potential is kept relatively low and respiratory chain generation of superoxide is minimized.[44, 45] Indeed, a large and growing literature, involving both rodent and clinical studies, indicates that supplemental creatine can at least modestly boost brain creatine levels,[46] and that this can provide benefits for cognitive performance, as well as providing neuroprotection in brain trauma and in neurodegenerative disorders.[47-70] Of particular interest is a report that dietary creatine supplementation (1%) beginning at one year of age increases mean healthy lifespan of mice by about 9%, an effect likely mediated by its impact on the brain; such supplementation is associated with decreased brain lipofuscin, a reduction in markers for oxidative stress, and up-regulation of BDNF and other neuroprotective proteins.[58]

Hence, concurrent administration of creatine and orotate – which apparently has never been studied before with respect to its impact on brain function – may have interesting potential for neuroprotection and optimization of cognitive function. Orotic acid constitutes about 54% of the weight of the creatine orotate complex, so 6-7 g daily, perhaps administered in fluid,would provide quite meaningful doses of each agent. Tricreatine orotate is currently used by some body builders and athletes as a supplemental source of creatine, but creatine orotate is not currently marketed.

Supplemental uridine-5'-monophosphate – an approved food additive – has brain-supportive potential analogous to that of orotic acid. The latter may however be preferable, owing to lower cost and the undesirability of further increasing the dietary phosphate load.[71, 72]

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