Effect of alpha-ketoglutarate and oxaloacetate on brain mitochondrial DNA damage and seizures induced by kainic acid in mice.


Source
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Abstract
The effects of alpha-ketoglutarate and oxaloacetate on brain mitochondrial DNA (mtDNA) damage and seizures induced by kainic acid were examined both in vivo and in vitro. An intraperitoneal (ip) injection of kainic acid (45 mg/kg) produced broad-spectrum limbic and severe sustained seizures in all of the treated mice. The seizures were abolished when alpha-ketoglutarate (2 g/kg) or oxaloacetate (1 g/kg) was injected intraperitoneally in the animals 1 min before kainic acid administration. In addition, the administration of kainic acid caused damage to mtDNA in brain frontal and middle cortex of mice. These effects were completely abolished by the ip preinjection of alpha-ketoglutarate (2 g/kg) or oxaloacetate (1 g/kg). In vitro exposure of kainic acid (0.25, 0.5 or 1.0 mM) to brain homogenate inflicted damage to mtDNA in a concentration-dependent manner. The damage of mtDNA induced by 1.0 mM kainic acid was attenuated by the co-treatment with alpha-ketoglutarate (2.5 or 5.0 mM) or oxaloacetate (0.75 or 1.0 mM). Furthermore, in vivo and in vitro exposure of kainic acid elicited an increase in lipid peroxidation. However, the increased lipid peroxidation was completely inhibited by cotreatment of alpha-ketoglutarate or oxaloacetate. These results suggest that alpha-keto acids such as alpha-ketoglutarate and oxaloacetate play a role in the inhibition of seizures and subsequent mtDNA damage induced by the excitotoxic/neurotoxic agent, kainic acid.

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