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Cyclocreatine (1-carboxymethyl-2-iminoimidazolidine) Inhibits the Replication of Human Herpes Viruses.

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The creatine kinase/creatine phosphate (CK/CrP) system plays an important role in cellular energy homeostasis. CK isoenzymes, which reversibly generate ATP from CrP, are compartmentalized at cellular sites where energy is produced or utilized. It has been noted that the expression of CK is induced in cells infected by several DNA viruses, implicating a role for cellular energy modulation as an important step for efficient viral replication. A CK substrate analog, 1-carboxymethyl-2-iminoimidazolidine (cyclocreatine; CCr), was tested *in vitro* for antiviral activity against a variety of DNA and RNA viruses. Several members of the human herpesvirus family were found to be sensitive to CCr, including herpes simplex virus types 1 and 2 (HSV-1 and HSV-2), varicella-zoster virus, and cytomegalovirus. In the murine vaginal HSV-2 model, CCr (administered as 1% of the diet) significantly reduced mortality, reduced vaginal lesion scores, and lowered the titers of recoverable virus. This treatment, combined with acyclovir (100 mg/kg/day), appeared to enhance the antiviral effects of acyclovir. In the murine HSV-2 encephalitis model, CCr therapy resulted in a significant increase in survival compared to placebo.

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Cyclocreatine Improves the Structural Integrity of the Retina in Human Cytomegalovirus-Induced Chorioretinitis in the Rabbit Model.

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Cyclocreatine (CCr), a creatine analog, has been demonstrated to have antiviral activity against herpesviruses *in vitro* and against HSV-2 *in vivo*. *In vitro* analyses suggest that human cytomegalovirus (HCMV) is one of the most sensitive viruses to CCr. We tested the activity of CCr in a rabbit model of HCMV-induced chorioretinitis. Levels of up to 3 mM CCr in the serum and up to 10 mM CCr in the eye were obtained by constant infusion. Rabbits were inoculated by intravitreal injection of HCMV AD169 (10^5 PFU), and CCr therapy was initiated approximately 2-6 hr post-inoculation (PI). Positive control animals were treated with DHPG (10 mg/kg/day) and placebo control rabbits were treated with saline. Animals were sacrificed 3, 4, and 5 days after the start of therapy. The efficacy of CCr was evaluated by indirect ophthalmoscopic examination, assessment of recoverable virus by culture, and by histopathology. CCr therapy reduced the development of vitreal, chorioretinal and optic nervehead pathology in HCMV-inoculated animals compared to placebo treatment, and resulted in a moderate decrease in retinal virus titers on days 3-5 PI compared to placebo retinas. Histological analysis of retinas of animals treated with CCr demonstrated significant protection compared to retinas of the placebo-treated rabbits. At sacrifice, only 4 of 22 eyes of rabbits treated with CCr demonstrated greater than moderate areas of HCMV disease in the retina. The preservation of the retinal architecture approached the effectiveness observed with DHPG therapy.