

Species-specific responses to creatine supplementation

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CREATINE IS A NATURALLY OCCURRING guanidino compound that is synthesized in the liver and kidney or obtained in small quantities from the diet primarily from meat and fish. Oral creatine monohydrate supplementation (e.g., 20 g/day \times 5 days) has been reported to increase muscle creatine and phosphocreatine (PC) content by 15–40%, enhance the cellular bioenergetics of the phosphagen system, improve the shuttling of high-energy phosphates between the mitochondria and cytosol via the creatine phosphate shuttle, and enhance the activity of various metabolic pathways influenced by creatine kinases. For this reason, there has been significant interest in determining whether creatine supplementation can enhance exercise and/or training adaptations as well as provide therapeutic benefit for various patient populations. Most studies indicate that short-term creatine supplementation can improve high-intensity exercise performance and improve gains in strength, power, and muscle mass during training. Consequently, creatine has become a popular nutritional supplement among athletes. More recently, the potential therapeutic benefits of creatine supplementation have been evaluated in patients with a variety of metabolic disorders, neuromuscular diseases, and recovery after musculoskeletal injury. These findings have indicated that creatine may serve as a promising ergogenic aid for athletes as well as offer some clinical benefit for certain patient populations.

The only clinically significant side effect that has been consistently reported in the literature has been weight gain. However, concerns have been raised regarding whether creatine supplementation may promote long-term suppression of creatine synthesis, increase renal stress, promote muscle and liver damage, alter fluid and electrolyte status, and/or cause unknown long-term side effects. Although recent studies examining the safety of creatine in humans have not substantiated these concerns (2, 4–7), several reports have indicated that long-term creatine supplementation in mice may alter liver pathology (3) and/or promote renal disease progression in hypertensive rats (Han:SPRD) (1). Understanding the mechanisms of action of creatine in healthy and diseased models as well as the possible long-term side effects from creatine supplementation is important to determining whether

creatine may serve as an effective therapeutic nutrient for various clinical populations.

The study in this issue of the *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology* by Tarnopolsky and colleagues (8) represents an important contribution to our understanding of how creatine monohydrate supplementation may differentially affect health outcomes in various species. In this regard, the researchers carefully evaluated the pathological and toxicological effects of long-term creatine monohydrate supplementation ($\frac{1}{3}$ to $\frac{1}{2}$ their life span) in nontransgenic mice (CD-1), SOD1 G93A transgenic mice that have a mutation in the Cu/Zn superoxide dismutase gene that results in an increased level of oxidative stress and serve as a good model to study amyotrophic lateral sclerosis, and Sprague-Dawley rats. Results indicated that long-term creatine monohydrate supplementation (equivalent to 8–12 times the doses used in long-term human trials for $\frac{1}{3}$ to $\frac{1}{2}$ the animals' life span) in mice increased the incidence of hepatitis lesions with no apparent effects on the remaining 18–20 tissues evaluated. However, long-term creatine monohydrate supplementation in rats at supraphysiological doses did not induce hepatic inflammatory changes or affect the pathology of other tissues examined. These findings are important because they indicate that different species may respond uniquely to creatine supplementation. Therefore, care must be taken to consider species-specific responses when 1) designing studies to assess the potential therapeutic role of creatine monohydrate supplementation on various human medical disorders; 2) assessing the pharmacological effects of various medications that may involve creatine metabolism; and 3) attempting to extrapolate results from long-term creatine feeding studies in animals to humans. Additionally, because neither the mice nor rats experienced renal or other tissue pathological changes after long-term creatine supplementation, these findings provide additional evidence that creatine supplementation does not appear to adversely affect renal function or health outcomes supporting recent clinical trials in humans.

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