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Pharmacokinetics of the Dietary Supplement Creatine

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Abstract

Creatine is a nonessential dietary component that, when supplemented in the diet, has shown physiological benefits in athletes, in animal-based models of disease and in patients with various muscle, neurological and neuromuscular disease. The clinical relevance of creatine supplementation is based primarily on its role in ATP generation, and cells may be able to better handle rapidly changing energy demands with supplementation.

Although the pharmacological outcome measures of creatine have been investigated, the behaviour of creatine in the blood and muscle is still not fully understood. Creatine is most probably actively absorbed from the gastrointestinal tract in a similar way to amino acids and peptides. The distribution of creatine throughout the body is largely determined by the presence of creatine transporters. These transporters not only serve to distribute creatine but serve as a clearance mechanism because of creatine 'trapping' by skeletal muscle. Besides the

pseudo-irreversible uptake by skeletal muscle, creatine clearance also depends on renal elimination and degradation to creatinine.

Evidence suggests that creatine pharmacokinetics are nonlinear with respect to dose size and frequency. Skeletal muscle, the largest depot of creatine, has a finite capacity to store creatine. As such, when these stores are saturated, both volume of distribution and clearance can decrease, thus leading to complex pharmacokinetic situations. Additionally, other dietary components such as caffeine and carbohydrate can potentially affect pharmacokinetics by their influence on the creatine transporter. Disease and age may also affect the pharmacokinetics, but more information is needed.

Overall, there are very limited pharmacokinetic data available for creatine, and further studies are needed to define absorption characteristics, clearance kinetics and the effect of multiple doses. Additionally, the relationship between plasma creatine and muscle creatine needs to be elucidated to optimise administration regimens.

Creatine supplementation has become a popular ergogenic aid to enhance exercise performance. In 1998, approximately $US200 million was spent on creatine monohydrate.[1] In the late 1990s, the benefits of creatine supplementation were extended from the exercise performance arena into the clinical setting. Creatine supplementation has been, and continues to be, investigated as a possible therapeutic approach for the treatment of muscular, neurological and neuromuscular diseases (table I). The continued success of creatine in the treatment of various diseases is dependent on the understanding of its behaviour with respect to absorption, distribution, elimination and pharmacodynamic outcomes. The former three points are essential in the development of therapeutic regimens to maximise the benefits of creatine, minimise any possible adverse effects, and prevent overspending on these supplements. The majority of research on creatine supplementation has focused predominantly on pharmacodynamic outcomes, whereas few studies have investigated the pharmacokinetics of supraphysiological doses of creatine. Those studies that have investigated plasma creatine versus time relationships in humans[2-9] did not fully report pharmacokinetic parameters (i.e. volume of distribution, clearance, bioavailability, mean residence time, absorption rate and half-life). Understanding the pharmacokinetics of creatine can provide a foundation for better understanding of creatine pharmacodynamics. Because of the limited information on creatine pharmacokinetics in humans, this review will be based on available human data, relevant animal data and *in vitro* work.

1. Clinical Relevance

There is an increasing amount of research using creatine in the treatment of various clinically relevant diseases and disorders. The clinical pharmacol-

Table I. Application of creatine supplementation in human disease and animal models of disease

Amyotrophic lateral sclerosis[10,11]
Arthritis[12]
Congestive heart failure[13-15]
Disuse atrophy[16]
Gyrate atrophy[17-19]
Huntington's disease[20-22]
McArdles disease[23,24]
Miscellaneous neuromuscular diseases[25-27]
Mitochondrial diseases[28-30]
Muscular dystrophy[31-34]
Neuroprotection[35-42]

ogy of creatine supplementation has been previously reviewed.[43] The underlying rationale for utilising creatine supplementation is to increase phosphocreatine. The fundamental role of phosphocreatine is the maintenance of adenine nucleotide homeostasis in tissues. Part of this role is to produce/regenerate ATP. ATP can be derived from fatty acid oxidation, carbohydrate oxidation, glycolysis and phosphocreatine. The key for understanding the relationship between cellular viability and ATP production is the quantity and rate of ATP production. Fat oxidation yields the largest quantities of ATP, but at the slowest rate.[44] Conversely, phosphocreatine can produce ATP very quickly, but has a lower capacity to generate ATP compared with fat and carbohydrate metabolism.[44] When a cell is energetically 'challenged' by the environment (e.g. exercise, ischaemia), phosphocreatine is the first system recruited. However, due to its small capacity, this system is rapidly depleted of its ATP-generating capacity. In order to increase the ATP-generating capacity of this system, creatine supplementation has been implemented and shown to increase total creatine (creatine + phosphocreatine) concentrations in skeletal muscle[4,45-49] and in nervous tissue.[50-52] Increasing the ATP-generating capacity allows a cell to better handle energetic challenges, thus preventing cell damage or death and improve cellular functioning. The increase in creatine appears to aid in the recovery of phosphocreatine after exercise,[47,49,53] but other studies have found no difference in recovery of phosphocreatine after exercise.[54]

2. Creatine Metabolism

The metabolism of creatine has been previously reviewed[55,56] (figure 1). Creatine (α-methylguanidinoacetic acid) is distributed throughout the body, with >95% of total creatine found in skeletal muscle and the remaining creatine pool located in the brain, eye, kidney and testes.[56] Creatine can be obtained through the diet with the consumption of meat (~5g of creatine in 1kg of meat) and is synthesised in the liver, kidney and pancreas. A total of approximately 2g of creatine is produced and/or consumed per day, with equal contribution from synthesis and diet (k_{input} = 2 g/day). Adequate dietary intake of creatine can result from a wide range of individual dietary habits.[57] Creatine and phosphocreatine are nonenzymatically degraded to creatinine at a rate of 2 g/day, based on a total body creatine of a 70kg human with a total creatine pool of 120g and a rate constant (k_{Crn}) of 0.017 day^{-1}.[56] Creatinine and creatine are both eliminated from the body via the kidney (figure 2). Supplementation with exogenous creatine has also been shown to reduce endogenous production in humans; however, normal rates return upon termination of supplementation.[56]

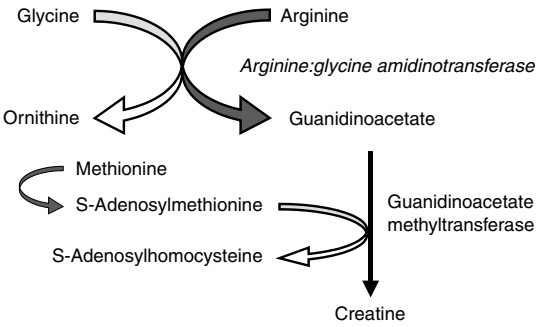

Fig. 1. Biosynthesis of creatine (reproduced from Stockler et al.,[58] with permission).

The formation of creatinine is almost exclusively from creatine, and elevating muscle creatine stores increases the amount of circulating levels of creatinine.[5,59,60] Increases in plasma creatinine would suggest a reduced creatinine clearance, thereby raising some concerns of potential renal impairment with creatine supplementation. However, kidney function does not appear to be affected by creatine supplementation,[61-63] thus questioning the validity of creatinine clearance estimates during creatine use.

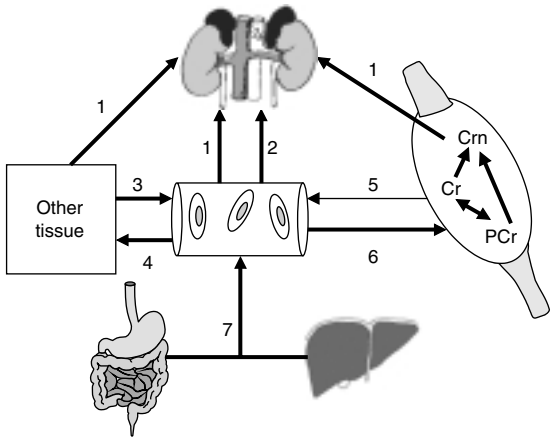

Fig. 2. Determinants of systemic plasma concentrations of creatine and creatinine. 1 = formation and renal elimination of creatinine (rate constant k_{Crn}); 2 = renal elimination of creatine (k_{Cr}); 3 = release of creatine from non-muscle tissue into the interstitial/vascular space (k_{NE}); 4 = uptake by non-muscle tissue of creatine (k_{EN}); 5 = release of creatine from muscle tissue into interstitial/vascular space (k_{ME}); 6 = uptake of creatine by muscle (k_{EM}); 7 = formation and ingestion of creatine (k_{input}). **Cr** = creatine; **Crn** = creatinine; **PCr** = phosphocreatine (reproduced with permission).

3. Absorption

Creatine is typically sold as a powder and taken orally as a solution or suspension. In addition, creatine has been formulated as a capsule and chewable tablets. The bioavailability of the capsules and chewable tablets may be limited by dissolution rate and solubility (13 g/L) and only recently has a study examined the relative bioavailability of various creatine dosage forms.[57] This study compared creatine in solution, suspension, lozenge and meat and found differences in peak concentration (C_{max}), with solution > suspension = lozenge > meat, and in time to C_{max} (t_{max}). Comparisons were made for area under the concentration-time curve (AUC), an important determinant for bioequivalence, which indicated that solution and meat have similar AUC but that solution has a significantly higher AUC compared with lozenge or suspension. However, AUC calculations only extended over the measured timepoints and were not extrapolated to infinity, which is necessary to fully demonstrate bioequivalence.

The mechanism of creatine absorption in the gastrointestinal tract is unclear. Current techniques have identified the mRNA for a creatine transporter in the gastrointestinal tract.[64] Although the creatine transporter protein has yet to be located on the apical side of the mucosal layer, the presence of the mRNA would suggest the possibility of active transport mechanisms. Furthermore, creatine is structurally similar to basic amino acids (e.g. arginine and lysine) and may enter the systemic circulation through the amino acid transporter or peptide transporters located in the proximal small intestine. Creatine is a hydrophilic and polar molecule containing carboxyl and guanidino functional groups possessing negative and positive charges, respectively (figure 3). The charge on these functional groups would hinder passive diffusion of creatine through membranes. A study in Caco-2 cell layers demonstrated poor apical-to-basolateral movement of creatine,[65] further supporting active processes.

The absolute oral bioavailability (F) of creatine is also unknown due to the lack of intravenous data, but there are several possible reasons to conclude that bioavailability is less than 100%. Although creatine is not subject to first-pass metabolism, other routes are possible for decreasing systemic creatine exposure after oral administration. First, the rate of formation of the degradation product, creatinine, is

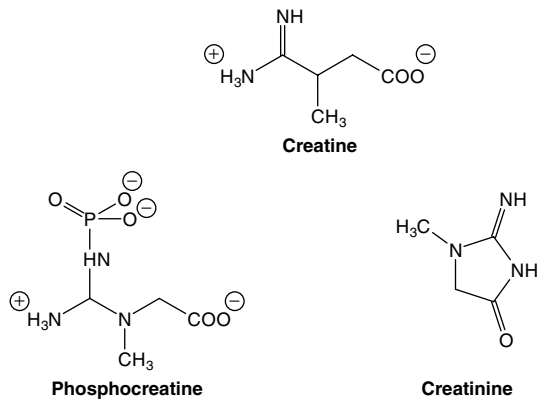

Fig. 3. Structure of creatine, phosphocreatine and creatinine.

increased in the presence of acid[66-68] and therefore accelerated degradation is possible in the lower pH of the stomach. However, creatine degradation to creatinine occurs at its maximal rate at pH 3–4.[67] The degradation half-lives for the conversion of creatine to creatinine at pH values 1.4, 3.7 and 6.8 are 55, 7.5 and 40.5 days, respectively. At these rates, less than 0.1g of a 5g dose would be lost in 1 hour. Therefore, the conversion to creatinine in the gastrointestinal tract is probably minimal regardless of transit time. Secondly, if creatine is absorbed by active mechanisms in the small intestine, these systems may be saturable thus leading to nonlinear absorption with respect to administered dose. Third, there is some evidence that faecal excretion of creatine is increased with a higher creatine intake.[69] Finally, there is experimental evidence of gut microflora having the ability to metabolise creatine into creatinine.[70]

As previously mentioned, the absorption of creatine may demonstrate nonlinear kinetics based on possible transporter uptake. Theoretically, if sufficiently high amounts of creatine are ingested, apparent zero-order absorption may occur with the rate of absorption approaching the maximal transport velocity (V_{max}) of the transporters. On the contrary, the transporter affinity (K_m) for intestinal absorption can be large and elicit first-order absorption. However, neither scenario has been demonstrated experimentally.

Creatine t_{max} in humans can be <2 hours for doses of <10g[3-7,9] (table II). At doses above 10g,

Table II. Reported and approximated pharmacokinetic values for creatine from published data after oral administration. AUC and $t_{½β}$ were estimated with the Kinetica software package (Innaphase, Champs sur Marne, France) from graphs after subtraction of baseline creatine values. CL/F was calculated as dose/AUC, where AUC is through infinity for the first dose or over one dosage interval for all other doses. Vd/F was calculated as $t_{½} \times CL/F \times 1/\ln 2$

Study (no. of subjects)	Dose (g)	t_{max}(h)	C_{max}(mg/L)	AUC (mg • h/L)	$t_{½β}$ (h)	CL/F (L/h)	Vd/F (L)	Dose no.	Comment
Green et al.[7] (6)	5	0.83	160	340	0.89	14	18	1	
	5	1.5	70	175	0.68	29	28	1	+ CHO
	5	0.83	220	570	2.1	8.7	26	13	
	5	2.2	95	260	0.94	19	26	13	+ CHO
Harris et al.[4] (3)	5	1	98	260	1.7	19	47	1	
Rawson et al.[9] (8 and 7)	5	1.3[a]	67[a]	183[a]	1.2[a]	27	47	1	Young
	5	1.6[a]	87[a]	282[a]	1.4[a]	18	36	1	Elderly
Schedel et al.[5] (1)	2.5	1	50	140	1.7	18	44	1	Female
	5	1.25	110	340	1.3	15	27	1	Female
	10	1.25	120	360	0.94	28	38	1	Female
	15	3	280	ND	ND	ND	ND	1	Female
	20	4	280	ND	ND	ND	ND	1	Female
Steenge et al.[3] (12)	5	1	120	300	1.2	17	42	1	
	5	1.25	95	280	1.2	18	31	1	+ CHO
	5	1	140	380	2.1	13	39	4	
	5	1	120	370	2.1	14	42	4	+ CHO
Vanakoski et al.[6] (8)	7	1.53[a]	160[a]	580[b]	2.9[a]	14	59	10	– Caffeine

a Reported value.

b Reported value without baseline creatine level.

AUC = area under the concentration-time curve; **CL/F** = apparent systemic clearance; **C_{max}** = peak concentration; **ND** = not determined because of insufficient data; **t_{max}** = time to C_{max}; **$t_{½β}$** = elimination half-life; **Vd/F** = apparent volume of distribution; **+** = with; **-** = without.

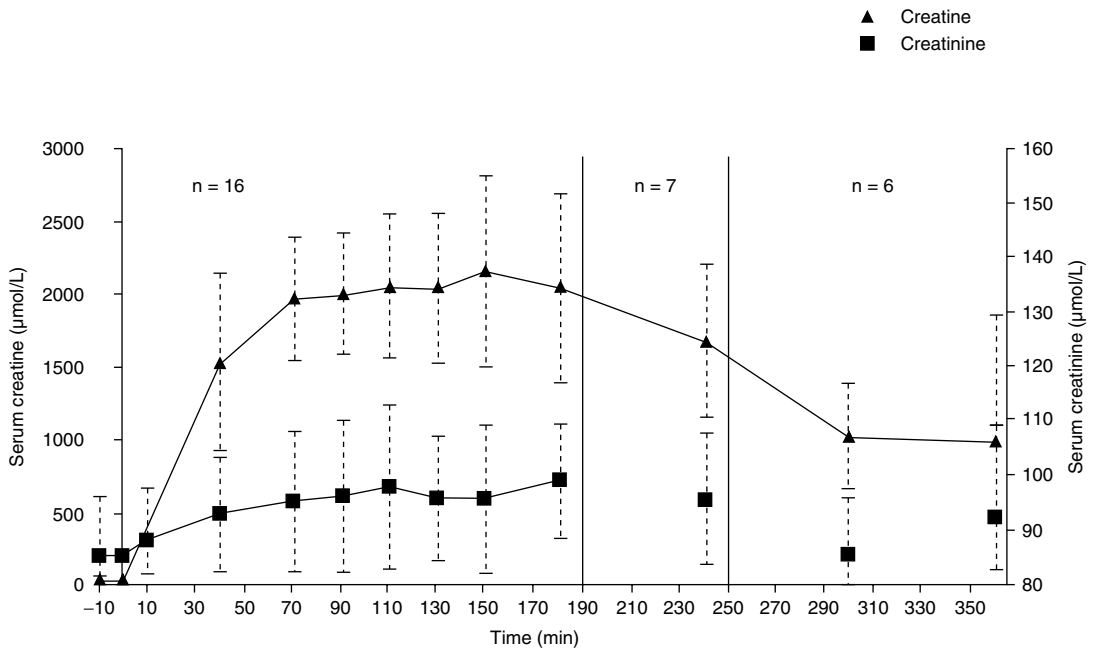

Fig. 4. Plasma levels following a single oral dose (arrow) of creatine 20g. Apparent steady state is attained, suggesting zero-order absorption at high doses (reproduced from Schedel et al.,[5] with permission from Elsevier Science).

t_{max} increases to >3 hours.[5] Furthermore, a 20g dose can show a steady-state-like plateau (figure 4).[5] The steady-state-like plateau of creatine suggests zero-order absorption, probably as a function of saturation of gastrointestinal transporters. t_{max} tends to increase with the coadministration of carbohydrate.[7] It is unclear if absorption or elimination is responsible for the variability in t_{max} seen with dose quantity or with the ingestion of carbohydrate.

In conclusion, to date, absorption mechanisms and kinetics have not been studied in detail. However, current evidence for transporters and the physicochemical properties of creatine suggest active processes for the uptake of creatine from the gastrointestinal tract. The kinetics of uptake may be dependent on the dose, resulting in nonlinearity in the rate and extent of absorption. Future studies are needed to identify the cellular location of transporters and/or absorption windows in the gastrointestinal tract and their role in creatine absorption.

4. Distribution

Following administration, creatine can be taken up by a variety of cells, including blood cells, the brain/nervous tissue, cardiac muscle, spermatozoa and the retina; however, the predominant absorption site is skeletal muscle.[55] The polar nature of the creatine molecule suggests that if distribution is based solely on diffusion, the apparent volume of distribution should probably not exceed extracellular water. Plasma protein binding is also expected to be negligible due to the hydrophilicity of the molecule.[71] As such, low protein binding results in high free levels of creatine available as substrates for the creatine transporter. The presence of the creatine transporter suggests a volume of distribution greater than the predicted extracellular water, approaching that of total body water (~45L), as shown in table II. Interestingly, studies have shown that skeletal muscle, the main reservoir for creatine, has a finite storage capacity.[4] Therefore, as creatine accumu-

lates in the muscle with repeated administration and eventually saturates the storage capacity, it is possible that the volume of distribution will decrease. The accumulation and subsequent saturation may be a result of possible downregulation of creatine transporter number or function. The next section will discuss what is known about regulation of the creatine transporter.

4.1 Creatine Transporters

Creatine is transported into tissues against a large concentration gradient through a sodium- and chloride-dependent transporter that is similar in structure to the transporters for dopamine, γ-aminobutyric acid (GABA) and taurine, and has been previously reviewed.[72,73] The mRNA for the first creatine transporter gene (CreaT1) has been found in a variety of tissues, including kidney, heart, skeletal muscle, brain, testes, colon and intestine.[64,74,75] Another creatine transporter gene (CreaT2) has been located, but the expression of this transporter, which shares 97% homology with CreaT1, may be limited to the testes.[76] Two creatine transporter isoforms (70 and 55 kDa) have been identified in humans and in other species.[77,78] The two isoforms differ in amount of glycosylation and may be responsible for different cellular targeting, leading to the identification of the creatine transporter protein in plasma membranes, sarcolemma, microsomes and mitochondria.[72]

Creatine appears to be a specific substrate for the creatine transporter, with one of the most efficient competitive substrates (i.e. highest affinity) being the creatine analogue β-guanidinopropionic acid.[64,74,75] Other endogenous compounds do not appear to compete efficiently with creatine for the creatine transporter binding site.[64,74,75,79-81] The kinetics of CreaT1 depend on the species and location of the transporter (red blood cell, macrophage, muscle fibre type).[74,75,82-86] Blood levels of creatine vary between species with humans < rabbit < mouse < rat.[87] Human blood levels range from 7–13 mg/L. Excluding humans, the creatine transporter in most species is close to saturation based on the K_m of the transporter and resting blood levels.[72] The species differences in blood and K_m values for creatine and the creatine transporter, respectively, may hinder the usefulness of animal models to elucidate human creatine pharmacokinetics. Tissue and species differences after supplementation have also been reported.[51]

The regulation of the creatine transporter is not fully understood, but transport activity appears to be influenced by total creatine content, various hormones, and exercise. The CreaT1 protein has several sites for glycosylation and phosphorylation, which may be responsible for its regulation. Human muscle total creatine levels can range from 110–160 mmol/kg dry mass (14–20 g/kg dry mass),[88] with 60% in the form of phosphocreatine,[4,45,46,49] but content is dependent on the skeletal muscle fibre type.[46,89,90] Differences in muscle creatine content could influence transporter activity, as individuals with lower creatine levels at the start of a supplementation period respond with larger increases in creatine content in muscle compared with those with higher initial starting creatine levels.[4] This varying response to creatine uptake may be a function of the creatine transporter density at the membrane or other regulatory modifications (e.g. phosphorylation) to the transporter.

Various endogenous compounds influence creatine uptake into skeletal muscle cells. Studies in cell culture show that catecholamines, thyroid hormone, insulin-like growth factor 1 (IGF-1) and insulin can influence the uptake of creatine into skeletal muscle.[91] The increases in creatine uptake in cell culture can be 1- to 3-fold higher, depending on the compound and concentration.[91] Human studies with insulin and compounds that elicit an insulin response (e.g. high-glycaemic carbohydrates) have shown similar results to the cell culture experi-

ments.[2,3,7,48] For this reason, high-glycaemic carbohydrates (e.g. glucose, glucose polymers) are typically consumed with creatine to elicit an insulin response to enhance uptake. The use of carbohydrates not only appears to enhance the rate of uptake but may affect the overall storage capacity of the muscle.[48]

Increase in creatine uptake with exercise was hypothesised to result from enhanced blood flow, but changes in transport kinetics have not been ruled out.[4] The hydrophilic nature of creatine means that it would generally be thought of as 'permeability-limited' with regards to distribution. However, if blood flow limits muscle uptake, skeletal muscle may serve as a 'high extraction' organ with its innate ability to remove creatine from the blood being far greater than the blood flow supplying the muscle. This is probably not the case, as data from Robinson et al.[92] suggest that enhanced muscle blood flow during recovery or exercise is unlikely to be important. These investigators suggest that the most likely reason for the increase in creatine uptake following exercise is an increased activation of the creatine transporter, perhaps by a change in phosphorylation state. Additionally, it is also possible that exercise will increase the translocation of the creatine transporter to the muscle membrane, similar to the effect seen with exercise and translocation of the glucose transporter GLUT-4.[93]

In summary, distribution of creatine occurs in large part due to the creatine transporter. The creatine transporter is specific for creatine and appears to be influenced by hormones, exercise and muscle creatine content. The creatine content of muscle has an upper limit, and could affect pharmacokinetics by reducing the apparent volume of distribution with repeated administration. This finite storage capacity may be due to changes in transporter number and function; however, the exact regulatory mechanism of the creatine transporter is not fully understood.

5. Clearance

In general, creatine can be removed from the blood by skeletal muscle (CL_M) and kidney (CL_R), so that (equation 1):

$$CL_{total} = CL_M + CL_R$$

The relative contribution of these pathways may be dependent on both dose and dose frequency. Nonlinear pharmacokinetics may be the result of changes in the contribution of each of the possible clearance mechanisms. For example, with the first dose, creatine clearance can rely on both muscle and kidney, but after a number of doses, when muscle creatine stores are saturated, clearance may occur only via the kidney. Each clearance mechanism will be discussed in more detail in the following sections.

5.1 Skeletal Muscle

The creatine transporter not only serves to distribute creatine throughout the body but, once creatine is intracellular, it appears to be 'locked' in the muscle, unable to diffuse out or diffusing out at an extremely slow rate (figure 2; $k_{EM} >>> k_{ME}$).[94] The pseudo-irreversible uptake of creatine by skeletal muscle and subsequent conversion to phosphocreatine and degradation to creatinine can therefore serve as a clearing mechanism similar to the relationship of haemopoetic growth factors and bone.[95] The majority of creatine conversion to creatinine occurs in the muscle compartment and appears to be a minor pathway of clearance, with CL_{Crn} estimated at 0.032 L/h (based on $k_{Crn} = 0.017$ day^{-1}[67] and a volume of distribution of 45L or total body water). Conversely, it has been suggested that creatine turnover in non-muscle compartments occurs at a faster rate than the muscle counterpart.[94]

Clearance of creatine by muscle would be affected by the same features that affect the creatine transporter: (i) molecules such as insulin, catecholamines and IGF-1; (ii) exercise; and (iii) muscle creatine levels. Furthermore, the amount or percent-

Table III. Selected administration regimens for creatine supplementation in humans

Study	Dose (g)	Frequency (per day)	Duration	Population
Andrews et al.[13]	5	4	5 days	Congestive heart failure
Bermon et al.[96]	5	1	52 days	Elderly healthy (>60 years)
Hespel et al.[16]	5 (atrophy period)	4	2 weeks	Disuse atrophy
	5 (rehabilitation)	3	3 weeks	
	5 (maintenance)	1	7 weeks	
Hultman et al.[45]	3	1	>30 days	Young healthy (<30 years)
Klopstock et al.[28]	5	4	20 days	Mitochondrial disease
Mazzini et al.[11]	5	4	7 days	Amyotrophic lateral sclerosis
	3	1	6 months	
Rawson and Clarkson[97]	5	4	5 days	Elderly healthy (>60 years)
Rawson et al.[98]	5	1	30 days	Elderly healthy (>60 years)
Tarnopolsky et al.[25]	10	1	5 days	Neuromuscular disease
	5 (maintenance)	1	5–7 days	
Vannas-Sulonen et al.[18]	0.5	3	5 years	Gyrate atrophy (adults)
	0.25	3	5 years	Gyrate atrophy (children)
Volek et al.[99]	5	5	7 days	Young healthy (<30 years)
	5 (maintenance)	1	11 weeks	
Vorgerd et al.[23]	150 mg/kg	1	7 days	Myophosphorylase deficiency
Walter et al.[34]	10	1	8 weeks	Muscular dystrophy (adults)
	5	1	8 weeks	Muscular dystrophy (children)

age muscle mass of an individual may also affect clearance. A larger muscle mass would correlate to more transporters and greater potential storage area for creatine. Therefore, individuals with larger muscle mass should demonstrate larger clearance values. Because of the possible relationship between clearance and muscle mass, it may be more appropriate to scale the dosage of creatine to bodyweight, ideal bodyweight or lean body mass. Currently, few studies adjust creatine dosage for bodyweight (table III).

There are currently no values or estimates of CL_M in humans or animals. The only available data to estimate CL_M are the Michaelis-Menten parameters for the uptake of creatine, V_{max} and K_m, for intact isolated rodent muscle and/or cloned human and animal creatine transporter. These enzymatic values can be used as a gross estimation of the intrinsic clearance (CL_{int}) by skeletal muscle with the relationship in (equation 2):[100]

$$CL_{int} = V_{max} / K_m$$

V_{max} values for intact rodent soleus and extensor digitorum longus (EDL) muscles of 77 and 100 nmol/h/g wet weight (10 and 13 μg/h/g wet weight), respectively, have been reported.[86] Combined with the respective K_m values of 73 and 160 μmol/L (9.4 and 21 mg/L), the resulting values of CL_{int} would be 1.06 and 0.63 L/h/kg wet weight for soleus and EDL, respectively. Human skeletal muscle is composed of mixed fibre types, unlike rodent where the soleus is predominantly slow-twitch and EDL is predominantly fast-twitch, and therefore the average value of intrinsic clearance (0.84 L/h/kg wet weight) would be a better estimate for humans. Applying the 'well-stirred' model with assumptions of: (i) zero plasma protein binding; (ii) 40% of bodyweight being skeletal muscle; and (iii) skeletal muscle blood flow of 60 L/h at rest, the value of CL_M in humans would be 0.24 L/h/kg body mass, or 17 L/h for a 70 kg person. As can be seen in table II, the calculated CL_M of 17 L/h is similar to the estimated CL_{total} in humans. The proximity of these values

suggests that skeletal muscle is the predominant contributor to clearance for early doses.

5.2 Renal Elimination

The second pathway of creatine elimination is by the kidney. Early research estimated that the rate of renal excretion was close to glomerular filtration rate (GFR),[101] although others have found that creatine is reabsorbed in the kidney.[102] This is supported by the low concentrations of creatine in the urine in unsupplemented conditions and the location of the creatine transporter in the kidney. CL_R can be calculated by (equation 3):

$$CL_R = \text{rate of excretion} / C_p$$

where C_p is the midpoint plasma concentration. Given that creatine has little protein binding and assuming no active renal secretion, CL_R would approach GFR (125 mL/min or 7.5 L/h). Poortmans and colleagues[62,63] reported normal CL_R values of 0.3–0.8 L/h, suggesting extensive reabsorption. With supplementation, CL_R increased to 9–22 L/h, indicating that under conditions of supplementation CL_R can range from close to GFR to well above GFR, implying active secretion. However, one of these studies was based on self-reported estimates of creatine ingestion of 2–30 g/day for 10 months to 5 years.[62] In a second study by this group, subjects ingested 5g four times a day for 5 days and plasma levels increased from 9 to 36 mg/L, but the renal excretion rate reached an unrealistic 682.5 μmol/min or >5 g/h (or >128 g/24 hours).[63] The problem with these estimations is that urine was collected for 24 hours and compared with the midpoint blood level. These calculations would be a gross estimate, and smaller windows of urine collection and blood sampling would be required to compute a better estimate of the renal creatine clearance.

Vanderberghe et al.,[103] found that women exhibited a rate of excretion of creatine under unsupplemented conditions of 1–1.5 mg/h. Other studies have found values between 1 and 40 mg/h.[9,48,96,104,105] Supplementation with creatine (>10 g/day) has been shown to increase urinary creatine levels, and after more than 3 days of loading at 4×5 g/day (20 g/day) the rate of excretion was 416–460 mg/h, but steady-state blood levels were not assessed to calculate CL_R.[9,48,96,103]

To summarise, creatine can be cleared by degradation, renal filtration and irreversible uptake into skeletal muscle. The percent contribution of each component is unknown, but the low rate of creatine conversion to creatinine and the small reported renal clearances suggest that skeletal muscle would represent the largest contribution. The contribution of skeletal muscle may decrease with increasing number of doses because of muscle saturation, allowing a higher contribution of renal elimination.

6. Pharmacokinetic Studies: Single and Multiple Dose

The lack of intravenous data has limited the ability to interpret disposition of creatine in the blood. Some investigators have administered low doses of creatine as an intravenous infusion in humans,[106] and there are few available intravenous bolus studies in humans. Fitch and colleagues[8] injected small amounts (<3mg) of radiolabelled creatine into five patients with various muscular disorders. They reported a half-life in plasma of 20–70 minutes. Creatine concentration followed a mono-exponential decline in three of the five patients, and the remaining two exhibited a bi-exponential decline with a distribution phase of less than 40 minutes. It is difficult to interpret these findings, because the dose administered was small compared with the doses that are currently being ingested. Additionally, patients who showed a bi-exponential decline were heavier and slightly older than the other three patients in this study. Age might affect creatine pharmacokinetics by a reduction in the creatine transporter. This possibility will be discussed later in Section 8.

Several studies have examined the plasma creatine concentration-time profile after a single oral dose of creatine.[2,4-7,9] Most of these did not perform full pharmacokinetic analysis, but their reported values, as well as our estimations of the remaining parameters, are given in table II. Apparent volume of distribution is close to total body water, and clearance values are similar to those predicted for the contribution of skeletal muscle to overall clearance.[1]

There is even less information on pharmacokinetics after multiple doses. Based on initial work by Harris et al.,[4] creatine administration typically follows a regimen of a 'loading' phase of 4 × 5 g/day (20 g/day) for 2–6 days and then a maintenance dosage of 3–5 g/day. This type of loading phase has been found to increase intramuscular total creatine levels by at least 17–20%.[4,15,45,47,49] Approximately 20% of this increase in total creatine is due to phosphocreatine.[4,15,45,46,103] Clinical studies have used different administration regimens than those previously mentioned, and vary in amount and duration of supplementation (table III).

Green and coworkers[7] investigated the effect of 2 days of loading with the 4 × 5 g/day (20 g/day) regimen on creatine AUC. On day 3, C_{max} after a 5g dose showed a ~35% increase compared with day 1, but there was no difference in baseline creatine levels and no difference in the 6-hour AUC. The large increase in C_{max} suggests accumulation, but the lack of difference in AUC contradicts accumulation. The lack of change in AUC may be a function of changes in clearance and/or bioavailability, and changes in C_{max} could be a function of absorption kinetics. Steenge et al.[3] examined AUC from 0 to 220 minutes after a single oral dose and after the fourth oral dose and found no increases in AUC but found increases in C_{max} and baseline creatine (figure 5). The lack of change in AUC in both studies suggests no accumulation, but this contradicted by changes in C_{max}. Based on estimated clearance values in table II, it appears that there is a small reduction in both clearance and volume of distribution with repeated doses. This is consistent with accumulation of creatine in the skeletal muscle compartment.

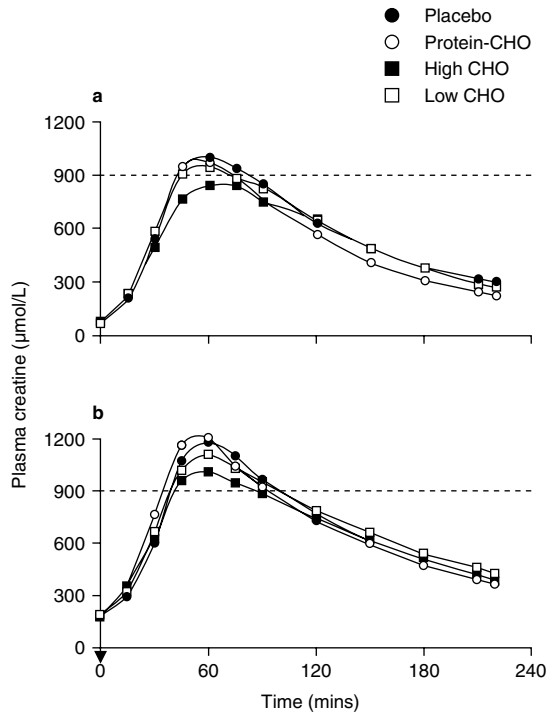

Fig. 5. Plasma creatine concentration following ingestion of creatine 5g followed 30 minutes later by the ingestion of 5g of carbohydrate (placebo), 50g of protein + 47g of carbohydrate (Protein-CHO), 94g of carbohydrate (High CHO) or 50g of carbohydrate (Low CHO). (**a**) First oral dose; (**b**) fourth oral dose. Values are mean and standard error. Dotted lines are used to facilitate comparisons (reproduced from Steenge et al.,[3] with permission).

Typically, multiple-dose regimens result in steady-state drug concentrations. It has never been experimentally proven that the current administration regimen for creatine results in steady-state blood concentrations. However, steady-state blood concentrations may not be necessary in the case of

1 Since the time of writing this review, Persky et al., published results from a clinical study that supports many of the hypotheses from this review.

creatine supplementation. Skeletal muscle has a limited capacity to store creatine[4,46] and the saturation of these stores can be accomplished quickly with a typical loading phase, or more slowly by taking 3 g/day over 30 days.[45] Even when using a loading phase, maximal accumulation of intramuscular creatine is believed to occur after about 2 days, and amounts of 20 g/day after this time may be unnecessary.[107] Further evidence suggesting that 20 g/day may be unnecessary is reflected in the progressive increase in urinary creatine with continuous high doses.[4,96,103,108] By day 3 of a 5-day loading period ingesting 4×5 g/day, urinary loss of creatine can be up to 60% based on 24-hour urine collection.[4] Additionally, creatine levels in humans can remain elevated for up to 1 month post-supplementation,[45] in part due to lack of passive movement of creatine out of the cell and the slow turnover of creatine to creatinine. Given a half-life of 40 days and an upper limit of 160 mmol/kg dry mass (20 g/kg dry mass), then about 2.5–3 g/day will be lost and therefore ingesting 2–3 g/day may be sufficient to maintain saturated muscle stores. A similar dosage (2 g/day) has previously been used to maintain skeletal muscle levels.[45]

Fitch et al.[94] proposed a schematic model and estimated rate constants after creatine administration in patients with muscular dystrophies, neuromuscular disease or polymyositis. This is one of the few proposed mathematical models to describe creatine pharmacokinetics in humans. A model using nonlinear tissue binding was proposed for intravenous bolus administration in rabbits.[109] However, this is not the most likely model, since the hydrophilic nature of creatine would suggest little tissue binding. Mathematically the nonlinear tissue binding model may be similar to a two-compartment body model. A two-compartment model may be used to describe intravenous bolus data and may be a better model based on distribution into muscle. For oral administration, a one-compartment body model may work depending on the length of the distribution phase. The input parameters can vary among apparent zero-order input, first-order input or Michaelis-Menten kinetics, and elimination can be a combination of first-order and Michaelis-Menten kinetics.

7. Effect of Diet on Pharmacokinetics: Carbohydrate and Caffeine

As discussed in section 4, data from cell culture suggests that insulin enhances creatine uptake into muscle. Based on this information, studies have investigated the effect of insulin and carbohydrate on the AUC after oral administration of creatine. Steenge et al.,[2] enterally infused creatine (100 mmol/L, 2.5 mL/min or ~1.97 g/h) along with insulin at various rates and followed plasma creatine. Steady-state plasma creatine reached ~ 95 mg/L with an insulin infusion rate of 105 mU/m^2/min, and ~135 mg/L with an insulin infusion of 5 mU/m^2/min (table IV). These data suggest an apparent clearance

Table IV. Pharmacokinetic values in healthy adults after nasogastric infusion of creatine at a rate of 1.97 g/h[2]

Insulin infusion (mU/m^2/min)	t_{max}(h)	C_{ss}(mg/L)	CL/F[a] (L/h)	AUC[b] (mg • h/L)	ΔtCr (mg/kg dry mass)
5	1.83	135	15	390	328
30	1.83	120	16	342	380
55	1.83	110	18	314	603
105	1	95	21	304	1101

a Estimated from infusion rate/C_{ss}.

b AUC from 0–220 minutes without baseline creatine (9.8 mg/L).

AUC = area under the concentration-time curve; **CL/F** = apparent systemic clearance; $\mathbf{C_{ss}}$ = steady-state plasma creatine; Δ**tCr** = change in muscle total creatine; $\mathbf{t_{max}}$ = time to C_{max}.

(CL/F) of 15–20 L/h depending on infusion rate, with the slower insulin rate eliciting a smaller clearance. Additionally, higher infusion rates caused greater change in muscle total creatine in a possible maximal-effect (E_{max}) relationship (table IV). The time to steady-state in this study was approximately 120 minutes after the start of creatine infusion, thus suggesting a half-life of ~25 minutes (5 half-lives). This finding would coincide with earlier work reporting that patients without primary muscle disease had a creatine half-life of ~20 minutes after small doses (<3mg) administered by intravenous bolus.[8]

Green et al.,[7] found a near 3-fold reduction in plasma creatine AUC if a 5g dose of creatine was ingested with a simple sugar solution (table II). C_{max} decreased 2-fold and t_{max} was slightly prolonged. The effect of carbohydrate has been attributed to enhanced removal of creatine from blood caused by the stimulatory effect of insulin on creatine uptake by skeletal muscle. An alternative explanation of the decrease in AUC could be a decrease in bioavailability. Rate of change in skeletal muscle creatine could support the former reasoning for a decrease in AUC, as suggested by a previous study.[2] Others have shown that the ingestion of carbohydrate and/or protein increases whole body creatine retention by decreasing plasma AUC (figure 5) and decreasing urine output.[3] These stimulatory effects of insulin on creatine disposal appear to diminish within 24 hours of beginning creatine supplementation.[3] Although the addition of carbohydrate can decrease gastric emptying time,[110] there is little evidence to suggest carbohydrate would decrease the bioavailability of creatine.

Based on work on the stimulatory effects of β-agonists on creatine uptake in cell culture,[91] Vanakoski et al. investigated the pharmacokinetics of creatine with and without caffeine ingestion.[6] Subjects were supplemented for 3 days with creatine 100 mg/kg 3 times daily (~20 g/day). After 3 days, a single dose of 100 mg/kg (6–7g) was administered orally. C_{max} without caffeine ingestion was 160 mg/L with a t_{max} of 92 minutes and a terminal half-life of 172 minutes. The concomitant administration of caffeine had no statistically significant effect on creatine pharmacokinetics. The lack of change in pharmacokinetics is supported by data suggesting that caffeine ingestion does not increase creatine loading into muscle.[111] The lack of effect could be due to the fact the pharmacokinetic analysis was performed after three days of loading, which would increase muscle creatine and thus reduce skeletal muscle clearance and target total clearance predominantly to the kidney. With a reduced ability of skeletal muscle to take up creatine, any stimulatory effect of caffeine would be reduced. Additionally, this study was a crossover design with a 1-week washout between treatments. This would further taint the analysis, because elevated muscle total creatine levels can last up to 28 days[45] and the accumulation of muscle creatine would reduce clearance and volume of distribution.

Dietary intake of carbohydrate and caffeine can potentially influence creatine pharmacokinetics by affecting skeletal muscle clearance. However, the effects of carbohydrate and caffeine may only influence pharmacokinetics during early doses (first day) when the contribution of skeletal muscle clearance may be the greatest, as demonstrated by Steenge et al.[3] The increase in clearance with carbohydrate appears to be a function of the insulin response. The evidence for an effect of caffeine is not substantiated, and further research is needed.

8. Special Populations

Most studies on creatine have focused on young, healthy populations. Emerging research is showing possible usefulness for creatine supplementation in special populations. The evidence of the ergogenic effects in the elderly are equivocal, with some studies showing an exercise performance benefit[112,113] whereas others have shown no benefit.[97,98] This

lack of an effect may be attributed, at least in part, to a difference in pharmacokinetics, resulting in a lack of increase in phosphocreatine. Rawson et al.[9] compared blood levels of creatine after a 5g dose in young and elderly (>60 years) healthy men. They found no statistically significant difference in terminal half-life, AUC, C_{max} or t_{max} between groups (table II), but did find in elderly men that intramuscular phosphocreatine levels did not increase with supplementation. Both populations also had similar renal excretion rates of creatine. However, despite the lack of difference in AUC, table II shows approximately a 35% difference in calculated CL/F between the two age groups. Since both groups had similar renal excretion rates, the difference in clearance may be attributable to skeletal muscle differences.

Patients with muscular dystrophy can have hypercreatinaemia and creatinuria, along with lower muscle levels of creatine and phosphocreatine.[94] Patients and animals with failing hearts[77] and populations with myopathies[78] have shown lower CreaT1 content and lower creatine and phosphocreatine muscle levels. Inborn errors in creatine metabolism have been reported, as in the case of gyrate atrophy that leads to tubular aggregates and type II fibre atrophy, both of which are relieved by creatine supplementation.[19] It has been suggested that diseases that cause defects in creatine or phosphocreatine levels may be caused by ineffective 'trapping' of creatine in muscle, or by lack of uptake.[94]

As discussed in section 6, Fitch et al.,[8] examined the pharmacokinetics of an intravenous bolus of creatine in five patients, three patients with primary muscle disease and two patients without primary muscle disease. Patients with primary muscle disease demonstrated an average half-life of 50 minutes, and the patients without primary muscle disease had an average half-life of 24 minutes. This further supports other work by this group showing differences in creatine uptake by skeletal muscle and decreases in creatine 'trapping' by skeletal muscle in specific patient populations.[94] Further studies in the elderly and patient populations are needed to examine the impact of changes in creatine transporter activity and total creatine content on pharmacokinetics and pharmacodynamic outcomes.

9. Conclusion and Dosage Recommendations

Creatine pharmacokinetics are far from being elucidated. Current data suggest that clearance is dependent on skeletal muscle and kidney function. The contribution of these systems may be dependent on dose and dose frequency. Part of the difficulty in characterising the pharmacokinetics of creatine arises from differences in study design (dose, single versus multiple doses, oral administration or infusion, effect of diet). Creatine kinetics may in fact be nonlinear as a result of transporter-based mechanisms in the gut, skeletal muscle and kidney, and therefore dose-dependency has to be fully understood. Not only does the behaviour of creatine in the blood need to be understood, but more importantly the relationship between blood concentrations and muscle concentrations needs to be defined. With an understanding of the relationship between plasma creatine and muscle creatine and vice versa, administration regimens can be tailored to reach therapeutic muscle levels quickly and maintain these levels, possibly allowing 'drug holidays' to maintain both endogenous production and creatine transporter levels.

Given the available data, it is difficult to recommend an administration regimen because the plasma concentrations needed to obtain a maximal uptake velocity by skeletal muscle are unknown. However, current regimens of a loading phase followed by a maintenance phase appear to be effective in reaching therapeutic muscle levels. A short loading phase of 2–3 days taking 0.071 g/kg bodyweight (equivalent to 5g for a 70kg person) four times a day is

suggested. Creatine should be taken with a high-carbohydrate meal or beverage, but high-fructose components (e.g. fruit juice) should be avoided because fructose does not elicit a significant insulin response. After the loading phase, creatine can be taken once daily at a dosage of 0.029 g/kg bodyweight to maintain muscle levels.[45] This regimen should cause rapid increases in muscle creatine without overuse of the supplement.

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