Heart, Lung and Circulation (2017) xx, 1–10
1443-9506/04/$36.00
http://dx.doi.org/10.1016/j.hlc.2016.12.020

REVIEW

Creatine Phosphate Administration in Cell Energy Impairment Conditions: A Summary of Past and Present Research

Q1 A.V. Gaddi, MD [a*], P. Galuppo [b], J. Yang, MD [c]

Q2 [a]Caravelli Laboratories & Techonios EuroGenLab, Bologna, Italy
Q3 [b]International Medical Affairs Department, Alfa Wasserman, Milan, Italy
Q4 [c]Department of Cardiology, Beijing Hospital, National Center of Gerontology, China

Received 2 December 2016; accepted 20 December 2016; online published-ahead-of-print xxx

Q6 Creatine phosphate (CrP) plays a fundamental physiological role by providing chemical energy for cell viability and activity, especially in muscle tissue. Numerous pathological conditions, caused by acute or chronic ischaemic situations, are related to its deficiency. For these reasons, it has been used as a cardioprotective agent in heart surgery and medical cardiology for many years. Many recent preclinical and clinical trials with CrP have provided further interesting information on the pharmacological role of this molecule.

This article gives a brief overview of the main characteristics of exogenous CrP. Besides CrP's well known cell energy and function restoring properties, new evidence is emerging regarding its antioxidant and anti-apoptotic properties. Use of CrP is well established clinically as an intraoperative and perioperative adjuvant in heart operations (valve replacement, coronary artery bypass grafting, congenital heart defect repair), and as an additional agent in medical cardiology therapy for acute myocardial infarction and acute Q7 and chronic heart failure. In particular, there are promising potential new CrP uses in neurology, such as in cerebral ischaemia and hypoxic ischaemic encephalopathy.

Keywords Creatine phosphate • Cardioplegia • Cardiac surgery • Myocardial infarction • Heart failure • Cerebral ischaemia

Introduction

Q8 Eggleton (1927) isolated creatine phosphate (CrP)[a] in animal muscle tissue [1]. However, subsequent advances in biochemistry showed that it was also biosynthesised in Q9 humans.

Creatine is phosphorylated into CrP in peripheral tissues by the enzymatic action of creatine kinase (CK) through the Q10 following reversible reaction: Creatine (Cr) + ATP (adenosine triphosphate) ⇔ H^+ + CrP + ADP (adenosine diphosphate). Muscle tissue contains about 90% of all the creatine phosphate found in the organism [2].

Cain and Davies (1962) inhibited CK in experimental models and observed that ATP levels rapidly decreased to the point that muscle contractions could no longer occur owing to the lower supply of this substance in the actomyosin contractile process [3]. This confirmed that the CrP/CK system is fundamental in promoting rapid synthesis of ATP, which is particularly important in situations of high metabolic demand.

Gudbjarnason (1970) reported that high-energy phosphate (HEP) compounds, such as ATP and CrP are rapidly depleted [4] during ischaemia. Moreover, altered HEP metabolism has been seen in different experimental models of cardiac pathology [5], including human cardiac pathology [6,7]. High-energy phosphate depletion coincides with the Q11 destruction of the sarcolemma and irreversible cell damage [8].

Q5 *Corresponding author at: Caravelli Laboratories & Techonios EuroGenLab, Bologna, Italy, Via Zamboni 8, 40100, Bologna, Italy., Email: profgaddi@gmail.com

Please cite this article in press as: Gaddi AV, et al. Creatine Phosphate Administration in Cell Energy Impairment Conditions: A Summary of Past and Present Research. Heart, Lung and Circulation (2017), http://dx.doi.org/10.1016/j.hlc.2016.12.020

Jun et al. (2014) also observed altered HEP metabolism in cerebral ischaemia. They revealed a depletion in ATP and CrP in the cerebral cortex and hippocampus following a prolonged cardiac arrest and ischaemic condition [9].

The aim of this review is to describe the current therapeutic indications of CrP, and new prospects for CrP use in heart and brain diseases with impaired cell energy metabolism.

Q12 [a] *2-[methyl-[(E)-N′-phosphonocarbamimidoyl]amino]acetic acid (IUPAC)*

Biological Activity of CrP

The CrP Shuttle

Creatine phosphate plays an essential role in all human tissues with high-energy requirements (heart, skeletal muscle, brain). Although the ultimate energy compound used for muscle contraction is ATP, the primary energy transport medium is CrP [10], which acts as a shuttle molecule between ATP production and utilisation sites [11]. Adenosine triphosphate is initially produced in the cell mitochondrion and the site of ATP utilisation in muscle contraction is the myofibril. However, since the direct transport of ATP molecules across the mitochondrial membranes is hindered, the chemical energy is moved through Cr phosphorylation into CrP: this is the ''CrP shuttle''. Creatine receives a high-energy phosphate group from ATP in the mitochondrial membrane, and then donates it to ADP in the sarcoplasm (i.e. ATP + Cr) to make muscle contractions possible. Adenosine triphosphate and CrP availability is regulated through the ''CrP shuttle'' on the basis of tissue energy requirements [11].

Adenosine triphosphate is required in the heart for cell viability and the myocardial pump function. Since there is very little ATP in the heart compared with demand, myocardial cells must continuously resynthesise it to maintain cell viability and contractile function.

CrP Reduction in Cells: Physiopathological Aspects

Several studies in the history of cardiology have focussed on the role of altered HEP metabolism, firstly in experimental heart disease models and then on humans with heart diseases.

Preliminary experiments by Hearse (1979) [12] and Whitman (1985) [13], with isolated hypoxic rat hearts and ischaemic rabbit hearts respectively, revealed a decrease in myocardial CrP, contractile activity and slower fall in ATP. More recently, Ye et al. (2001) observed a decrease in CrP/ATP ratio and creatine kinase isoenzyme release in a porcine model of cardiac hypertrophy and failure, in keeping with the degree of cardiac hypertrophy [14].

These experimental data have been confirmed in human pathology. Hardy et al. (1991) observed a decrease in the myocardial CrP/ATP ratio in patients with dilated-cardiomyopathy [6]. Myocardial CrP/ATP ratio was also shown to be a significant independent predictor of cardiovascular mortality (5% with CrP/ATP ratio >1,6; 10% if CrP/ATP ratio is <1.6) in a multivariate analysis of patients with heart failure [7].

Neubauer et al. (1992) reported that a decrease in myocardial CrP/ATP ratio correlates with the severity of heart failure, and that the CrP/ATP ratio increases after CrP treatment leading to improvement in the patient's New York Heart Association (NYHA) status [15].

New studies performed with biochemical heart failure markers, like plasma B-type natriuretic peptide level [16], have demonstrated that the CrP/ATP ratio negatively correlates with the severity of heart failure.

Lastly, brain tissue is also susceptible to ischaemic injury due to its high metabolic rate, limited intrinsic energy stores, and critical dependence on the aerobic glucose metabolism [17].

Jun et al. (2014) demonstrated in animals that partial depletions of ATP and CrP developed in the cerebral cortex and hippocampus after prolonged ischaemia-inducing cardiac arrest, thus showing the importance of adequate amounts of CrP to avoid brain damage after ischaemia/reperfusion [9].

The Use of Exogenous CrP in Preventing Cell Energy Impairment

Creatine phospate is the first molecule to be depleted in ischaemia, anoxia and toxic cardiomyopathies [18,19], whereas in stress conditions, such as hypoxia, the myocardial cells increase their uptake of exogenous CrP [20,21].

This suggests that extracellular administration of CrP may compensate for the energy deficiency [22]. Several experimental studies have, therefore, been carried out to evaluate the effects of exogenous CrP in cell energy impairment conditions.

Creatine phosphate has been shown to inhibit adenosine monophosphate (AMP) catabolism enzymes: AMP deaminase and 5′-nucleotidase [23]. If 5′-nucleotidase activity is inhibited, the adenine structure is preserved in the form of AMP, and since the adenylate kinase reaction in ADP formation is reversible, ADP (and ATP) still forms.

Creatine phosphate also preserves the adenine nucleotide pool by working on de novo synthesis. Creatine phosphate removes ADP's inhibition of phosphoribosylpyrophosphate (PRPP) synthase, the enzyme which catalyses the formation of PRPP from ribose 5-phosphate + ATP, leading to the neosynthesis of adenine nucleotides [23].

One in vitro and in vivo study in the ischaemic myocardium [24] showed that a 10 mmol concentration of exogenous CrP reduced the accumulation of lysophosphatidylcholine and lysophosphatidylethanolamine in cells, thus stabilising the myocardial cell membranes and preventing arrhythmias.

Furthermore, CrP is able to protect membrane structure through direct interaction with membrane phospholipids. In this electrical interaction, endogenous and exogenous CrP behaves like a zwitterion [23]. Its opposite charges interact with the charged phospholipids located on both sides of the sarcolemma [25] leading to sarcolemma stability.

Please cite this article in press as: Gaddi AV, et al. Creatine Phosphate Administration in Cell Energy Impairment Conditions: A Summary of Past and Present Research. Heart, Lung and Circulation (2017), http://dx.doi.org/10.1016/j.hlc.2016.12.020