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Perspective

Creatine Kinase Activity as an Indicator of Energetic Impairment and Tissue Damage in Fish: A Review

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Abstract: Creatine kinase (CK) is an enzyme that produces and uses phosphocreatine to transfer energy to maintain tissue and cellular energy homeostasis, being considered the main controller of cellular energy homeostasis. Its activity in plasma/serum has been commonly used to evaluate tissue damage, since CK is released into the bloodstream during damage. This review summarizes the current knowledge regarding the use of CK activity in fish, focusing on its potential as an indicator of the impairment of energetic homeostasis and tissue damage during stressful situations, such as exposure to contaminants (metals, pesticides, microplastic), hypoxia, thermal stress, and diseases (fungal, parasitic, and bacterial). Based on the data, we can conclude that tissue CK activity can be used as a suitable indicator of the impairment of energetic homeostasis in fish exposed to different aquaculture challenge conditions, while serum/plasma CK activity can be used as the first evidence of possible tissue damage, due to its release into the bloodstream.

Keywords: phosphotransfer network; energy; phosphocreatine; bloodstream

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1. Introduction

Creatine kinase (CK) belongs to a very conserved family of phosphagen guanidino kinases and is considered the main controller of cellular energy homeostasis, due to its reversible conversion of creatine into phosphocreatine. It is an extremely important enzyme in tissues with large and variable energy demands, like the brain and muscle [1,2]. Serum/plasma CK is also an indicator of tissue damage, because CK leaks into the bloodstream when tissue is damaged [2]. CK appeared very early in metazoan evolution, hundreds of millions of years ago, to overcome spatial obstacles in intracellular adenosine triphosphate (ATP) transport; CK genes are found in Porifera, the simplest group of animals [3]. The reaction catalyzed by this enzyme is:

$$\text{MgADP} + \text{Phosphocreatine} + \text{H}^+ \Leftrightarrow \text{MgATP} + \text{Creatine}$$

CK is present at high levels in the cytoplasm and mitochondria of tissues with high energy demands, and is highly compartmentalized, with isoenzymes in cytoplasmic (cytosolic CK) and mitochondrial (mitochondrial CK) subcellular locations [4]. The fact that there are specific isoenzymes of CK in tissues and cell compartments is related to its functions in cellular energy metabolism [1]. The interplay between CK isoenzymes from the cytoplasm and mitochondria is related to its multiple roles in cellular energy homeostasis. Both isoenzymes participate in the build-up of the intracellular reserve of phosphocreatine, acting as an efficient temporal energy buffer and preventing a rapid decrease in cellular global ATP levels. Additional functions of CK are related to the subcellular compartmentation of CK isoenzymes and adenine nucleotides [1]. CK is directly or indirectly associated with ATP-providing or ATP-consuming processes, building microcompartments that facilitate the direct exchange of adenosine diphosphate (ADP) and ATP. This differential microcompartmentalization of CK isoenzymes allows high local [ATP]/[ADP] ratios to be maintained

close to those of cellular ATPases and, at the same time, a low [ATP]/[ADP] ratio in the mitochondria, to stimulate oxidative phosphorylation. Thus, the CK/phosphocreatine-system can provide a spatial "energy shuttle" or "energy circuit", connecting places of energy consumption with places of energy production [1,5].

2. Creatine Kinase as an Indicator of Impairment in Energetic Homeostasis

CK, an enzyme belonging to the phosphoryltransfer network, is considered a central controller of cellular energy homeostasis via the reversible conversion of creatine into phosphocreatine, playing an important role in tissues with large and fluctuating energy demands, like the gills, brain and muscle [1]. Thus, its measurement is considered an interesting strategy for the evaluation of energetic homeostasis in these tissues, as well other tissues with lower energy requirements (Table 1). The determination of CK activity in serum or plasma has been commonly used to evaluate tissue damage, since CK is released into the bloodstream during damage (Table 2).

Table 1. The use of creatine kinase (CK) activity as an indicator of impairment in energetic homeostasis in fish submitted to several stressors.

Fish Species	Stress/Condition	Tissue	Result	Reference
Rhamdia quelen	Bacterial infection (*Pseudomonas aeruginosa*)	Gills	Inhibition of cytosolic and mitochondrial CK activities	[6]
Ctenopharyngodon idella	Bacterial infection (*Pseudomonas aeruginosa*)	Gills	Inhibition of cytosolic and mitochondrial CK activities	[7]
Rhamdia quelen	Parasitic infection (*Ichthyophthirius multifiliis*)	Spleen	Inhibition of cytosolic and mitochondrial CK activities	[8]
Rhamdia quelen	Bacterial infection (*Streptococcus agalactiae*)	Brain	Inhibition of cytosolic and mitochondrial CK activities	[9]
Oreochromis niloticus	Bacterial infection (*Providencia rettgeri*)	Gills	Inhibition of cytosolic and mitochondrial CK activities	[10]
Ctenopharyngodon idella	Fungal infection (*Saprolegnia parasitica*)	Gills	Inhibition of cytosolic and mitochondrial CK activities	[11]
Rhamdia quelen	Exposure to organophosphate trichlorfon	Gills	Inhibition of cytosolic and mitochondrial CK activities	[12]
Rhamdia quelen	Exposure to organophosphate trichlorfon	Muscle	Inhibition of cytosolic and mitochondrial CK activities	[13]
Cichlasoma amazonarum	Exposure to copper	Gills	Inhibition of mitochondrial CK activity; increase in cytosolic CK activity	[14]
Ctenopharyngodon idella	Exposure to methylmercury chloride	Gills	Inhibition of cytosolic and mitochondrial CK activities	[15]
Lophiosilurus alexandri	Hypoxia	Gills	Inhibition of cytosolic and mitochondrial CK activities	[16]
Oreochromis niloticus	Hypoxia	Gills	Inhibition of cytosolic and mitochondrial CK activities	[17]
Brycon amazonicus	Air exposure	Gills	Inhibition of cytosolic and mitochondrial CK activities	[18]

Table 2. The use of serum/plasma creatine kinase (CK) activity as indicator of fish tissue damage.

Fish Species	Stress/Condition	Tissue	Result	Reference
Cyprinus carpio	Exposure to polyethylene microplastic	Plasma	Increase in CK activity	[19]
Labeo rohita	Exposure to decabromodiphenyl ether	Serum	Increase in CK activity	[20]
Danio rerio	Exposure to copper oxide nanoparticles	Serum	Increase in CK activity	[21]
Oncorhynchus mykiss	Exposure to cypermethrin	Serum	Increase in CK and CK-MB activities	[22]
Oncorhynchus mykiss	Bacterial infection (*Flavobacterium psychrophilum*)	Serum	Increase in CK activity	[23]
Oncorhynchus nerka	Exposure to bitumen	Serum	Increase in CK activity	[24]
Scophthalmus maximus	Thermal stress	Plasma	Increase in CK activity	[25]
Oreochromis niloticus	Water pollution	Serum	Increase in CK activity	[26]

2.1. Creatine Kinase as an Indicator of the Negative Effects on Energetic Homeostasis in Fish during Bacterial, Fungal, and Parasitical Infections

Bacterial, fungal, and parasitical diseases are recognized as the main impediments of aquaculture development, causing severe economic impairments to fish farming and contributing to the development of antimicrobial resistance and environmental contamination due to the excessive use of drugs to combat these infections [27,28]. Recently, some studies have demonstrated that bacterial, fungal, and parasitical diseases cause alterations in glucose, lactate, and ATP levels, which affect fish energy metabolism [29]. However, the mechanism responsible for these alterations remains unknown. The first evidence of the involvement of CK activity on the impairment on energetic homeostasis was demonstrated by Baldissera et al. [6] in silver catfish (*Rhamdia quelen*) experimentally infected with *Pseudomonas aeruginosa*, where the authors showed that both branchial mitochondrial and cytosolic CK activities were severely inhibited by infection. The authors concluded that the inhibition of both enzymes contributed directly to the impairment of the synthesis and release of ATP in the gills, which may be related to the consequences of this disease. It is important to emphasize that the decrease in cytosolic CK enzymes may lead to an increase in mitochondrial CK enzymes, and vice-versa, in a mechanism known as energy compensation. The relationship between these enzymes contributes to efficient intracellular energetic communication, balancing cellular ATP consumption and production and maintaining energetic homeostasis [30]. The same response was found in the gills of grass carp (*Ctenopharyngodon idella*) experimentally infected by the same bacterium [7], where the authors concluded that the inhibition of CK activities is linked to oxidative damage caused by infection. The authors indicated that the excessive production of reactive oxygen species (ROS) is considered a physiopathological mechanism by which fish counteract infection, since ROS may be used to damage bacterial cell structures, killing the pathogen. However, the strategy is only efficient when ROS are generated at low concentrations for a brief period, because the production of high ROS concentrations for a long period of time can damage fish lipids and proteins, thereby affecting cell structures. The authors also observed a reduction in sulfhydryl (SH) amino acids, which are linked to the scavenging of excessive ROS production found at the active site of CK. The inhibition of CK enzymes may be due to the direct oxidation of SH groups located in the active site of CK.

Similar results were found in other fish species affected by different diseases, such as the inhibition of splenic cytosolic and mitochondrial CK activities in silver catfish naturally infected by the parasite *Ichthyophthirius multifiliis* [8], the inhibition of cerebral cytosolic and mitochondrial CK activities in silver catfish experimentally infected by *Streptococcus agalactiae* [9], the inhibition of branchial cytosolic and mitochondrial CK activities in Nile tilapia (*Oreochromis niloticus*) experimentally infected with *Providencia rettgeri* [10], and the inhibition of branchial cytosolic and mitochondrial CK activities in grass carp naturally

infected by *Saprolegnia parasitica* [11]. In summary, the detrimental involvement of CK activity in energetic homeostasis in fish that are naturally or experimentally infected by bacterial, fungal, or parasitic diseases is clear, as is its contribution to the pathophysiology of diseases.

2.2. Creatine Kinase as an Indicator of the Negative Effects on Energetic Homeostasis in Fish Exposed to Contaminants

Exposure to contaminants, such as metals and pesticides, has been considered an important concern associated with fish health, as well as the environment [31]. For example, the organophosphate trichlorfon is often used in aquaculture facilities against fish parasites such as *Ergasilus* sp., *Lernea* sp., *Dactylogyrus* sp., and *Trichodinas* sp. [32], but its abusive use has been associated with gill toxicity in freshwater fish [12]. A study conducted by Baldissera et al. [13] concluded that silver catfish exposed to environmentally relevant concentrations of trichlorfon showed significantly lower branchial cytosolic and mitochondrial CK activities compared to non-exposed fish, a condition that caused a decrease in branchial ATP levels and the consequent impairment of gill metabolism. In summary, the authors concluded that the bioenergetic impairment observed during exposure to sublethal trichlorfon concentrations was due to the inhibition of both CK isoforms, as well as the lack of any reciprocal compensatory mechanism between them. Moreover, the authors revealed that oxidative stress can be involved in the inhibition of CK enzymes during trichlorfon exposure. The same condition (the inhibition of CK enzymes and the involvement of oxidative stress) was found in the muscle of silver catfish exposed to environmentally relevant concentrations of trichlorfon [13], concluding that CK activity is involved in the bias in energy metabolism linked to ATP during exposure to pesticides.

The population growth and consequential increase in the release of domestic, industrial, and mining residues into the environment has increased metal contamination, which has aroused public concern due to their prolonged persistence in the environment, toxicity, and tendency towards bioaccumulation [33]. Exposure to relevant concentrations of copper (750 and 1500 ug/L) for 96 h affected branchial bioenergetic homeostasis in *Cichlasoma amazonarum* due to the decrease in ATP levels elicited by the disruption of mitochondrial CK activity [14]. The same authors demonstrated that these waterborne Cu levels impaired the energetic balance associated with ATP metabolism of the gills, an organ with high and variable energy requirements, through the inhibition of key enzymes of cellular and tissue homeostasis. The lower branchial mitochondrial CK activity compromised the delivery of high-energy phosphoryls from mitochondria to the nucleus, negatively affecting the communication between places of ATP production and its utilization, suggesting that the excess of ROS and lipoperoxidation may be associated with alterations in CK activity. Moreover, a study conducted by Baldissera et al. [15] demonstrated that exposure to methylmercury chloride inhibited the mitochondrial electron transport chain and cytosolic and mitochondrial CK activities after exposure to environmentally relevant concentrations over 48 h, a condition that caused a reduction in ATP branchial levels and a negative effect on the activity of ATP-dependent enzymes, like Na^+/K^+-ATPase and H^+-ATPase. In summary, exposure to water contaminants, such as pesticides and metals, can affect the bioenergetics and the homeostasis of fish via a disruption of CK activity, which is important for the production and utilization of ATP.

2.3. Creatine Kinase as an Indicator of Negative Effects on Energetic Homeostasis in Fish Exposed to Hypoxia and Air

The level of dissolved oxygen is an important parameter for fish in aquatic environments, and several energetic alterations have been related to hypoxia, including alterations in CK activity. Pacamã (*Lophiosilurus alexandri*) exposed to hypoxia (dissolved oxygen at 2.0 mg/L) for 48 h showed the inhibition of both cytosolic and mitochondrial fractions of branchial CK activity, demonstrating the impairment of intracellular energetic communication to maintain a balance between cellular ATP consumption and ATP production, which was related to the lower activity of ATP-dependent enzymes such as Na^+, K^+-ATPase, and

H^+-ATPase [16]. This study revealed that the inhibition of both CK fractions, as well as the lack of a reciprocal compensatory mechanism between them, in *L. alexandri* subjected to hypoxia, contributes to an impaired bioenergetic homeostasis. The same result was found by Baldissera et al. [17] in *Oreochromis niloticus* (Nile tilapia) exposed to hypoxia for 72 h (dissolved oxygen at 1.5 mg/L), concluding that a reduction in CK impairs fish energetic homeostasis. Moreover, a similar result was found by Baldissera et al. [18], who showed a significant inhibition of branchial CK activity (cytosolic and mitochondrial fractions) in *Brycon amazonicus* (matrinxã) exposed to air for 30 and 60 min, revealing that the decrease in CK activity elicited by air exposure (which led to tissue hypoxia) disrupted the branchial energetic balance via a reduction in the availability of ATP in the gills, impairing Na^+, K^+ATPase activity, contributing to a disruption in gill energetic homeostasis.

3. Creatine Kinase as an Indicator of Damage

CK is a dimeric molecule that has M and B subunits, the combination of which forms isoenzymes. There are four main CK isoenzymes: CK-1, a BB isoenzyme, found mainly in the brain, with lesions in this tissue possibly increasing CK-1 activity in the central nervous system but rarely resulting in an increase in total serum CK activity; CK-2, an MB isoenzyme, which is present to varying degrees in the heart (mostly) and skeletal muscles; CK-3, an MM isoenzyme, which is mainly found in skeletal muscle, but also in the heart muscle; and the CK-Mt isoenzyme, which is present between the inner and outer mitochondrial membranes. Disruption of the cell membranes due to any injury such as hypoxia releases CK from the cellular cytosol to the blood. Thus, serum/plasma CK activity is elevated when the brain, skeletal and heart muscles, gills, and the kidney are damaged [34].

Plasma and serum CK activity is extensively used as an indicator of damage during the investigation of aquatic contaminants, such as pesticides, microplastic, and metals [19,20]. Recently, a study conducted by Banaei et al. [19] investigated the possible toxic effects of different concentrations of polyethylene microplastics (175, 350, 700, and 1400 µg/L) in common carp (*Cyprinus carpio*) and used CK activity as an indicator of damage. According to these authors, the highest plasma CK activity was detected in the fish exposed to 1400 µg/L, with this increase being attributed to lesions in the muscles and kidney of fish, as CK is released into the bloodstream when the cells are damaged. Kumari et al. [20] evaluated the possible toxic effects of a persistent organic pollutant, decabromodiphenyl ether, in rohu carp (*Labeo rohita*) at a concentration of 9.8 µg/g feed for 24, 48, 72, and 96 h; they observed a significant increase in serum CK activity in a dose-dependent manner. According to these authors, the increase in serum CK activity is an interesting indicator of extensive tissue damage during exposure to decabromodiphenyl ether. Serum CK activity was also used as indicator of damage during exposure to copper oxide nanoparticles. According to Mani et al. [21], zebrafish (*Danio rerio*) exposed to 1 and 3 mg/L presented a significant increase in serum CK activity, a condition that is considered to be an indicator of tissue damage and which was confirmed due to elevated levels of tissue ROS and oxidative stress. A study conducted by Ucar et al. [22] confirmed that CK (total CK) and CK-MB were significantly higher in rainbow trout (*Oncorhynchus mykiss*) exposed to 2.05 ug/L cypermethrin pesticide for 96 h compared to the control fish. This is a condition compatible with tissue damage in general, as well as to heart damage due to elevated CK-MB activity. These authors hypothesized that the increase in lactate dehydrogenase due to this pesticide affected membrane permeability and caused the release of these enzymes directly into the blood.

Plasma CK activity can also be used to investigate tissue damage during bacterial infections, as evaluated by Rivas-Aravena et al. [23] in rainbow trout experimentally infected with 100 µL *Flavobacterium psychrophilum* (3.7×10^4 CFU/fish). The authors observed a significant increase in plasma CK activity in fish exposed to bacteria and concluded that this condition suggests skeletal muscle degradation induced by *F. psychrophilum*, which was corroborated by the damage observed in muscle histopathological analyses.

Studies related to water contamination also used the evaluation of serum CK activity as an indicator of damage, as in Pacific salmon (*Oncorhynchus nerka*) exposed to bitumen (a heavy type of crude oil). The fish were exposed to 66.7 µg bitumen/L water for 1 and 4 weeks, with a significant increase in serum CK activity being observed, a condition linked to muscle damage and shown by the decreased performance of fish in swimming tests [24]. Another study evaluated the blood chemistry of Nile tilapia under the impact of water pollution using fish collected from three stations along Lake Maryut (Egypt) [25]. These authors observed a significant increase in plasma CK activity in fish collected in areas with higher metals levels (cadmium, copper, iron, mercury, zinc, and nickel), concluding that an increase in plasma CK activity and other enzymes related to damage (lactate dehydrogenase, alkaline phosphatase, and aspartate aminotransferase) was linked to liver damage during exposure to polluted waters [25].

Plasma CK activity was used to evaluate the damage caused by thermal stress in *Scophthalmus maximus* exposed to low temperatures. There was a significant increase in plasma CK activity in the fish exposed to low temperatures, in a dependent manner, that is, the CK activity increased as the temperature decreased. Concomitantly, a significant increase was observed in lactate dehydrogenase, aspartate aminotransferase, and alanine aminotransferase, enzymes that indicate damage when found at elevated levels [26].

4. Conclusions

Based on the data, we can conclude that tissue CK activity can be used as a suitable indicator of an impairment of energetic homeostasis in fish exposed to different aquaculture challenge conditions, while serum/plasma CK activity can be used as the first evidence of possible tissue damage due to its release into the bloodstream.

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