Review Article

The Antioxidative Function of Alpha-Ketoglutarate and Its Applications

Shaojuan Liu¹,², Liuqin He¹,² and Kang Yao¹

¹Key Laboratory of Agro-Ecological Processes in Subtropical Region, Institute of Subtropical Agriculture, Chinese Academy of Sciences, National Engineering Laboratory for Pollution Control and Waste Utilization in Livestock and Poultry Production, Hunan Provincial Engineering Research Center for Healthy Livestock and Poultry Production, Changsha, Hunan 410125, China
²University of Chinese Academy of Sciences, Beijing 100049, China

Correspondence should be addressed to Kang Yao; yaokang@isa.ac.cn

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Alpha-ketoglutarate (AKG) is a crucial intermediate of the Krebs cycle and plays a critical role in multiple metabolic processes in animals and humans. Of note, AKG contributes to the oxidation of nutrients (i.e., amino acids, glucose, fatty acids) and then provides energy for cell processes. As a precursor of glutamate and glutamine, AKG acts as an antioxidant agent as it directly reacts with hydrogen peroxide with formation of succinate, water, and carbon dioxide; meanwhile, it discharges plenty of ATP by oxidative decarboxylation. Recent studies also show that AKG has alleviative effect on oxidative stress as a source of energy and an antioxidant in mammalian cells. In this review, we highlight recent advances in the antioxidative function of AKG and its applications in animals and humans.

1. Introduction

Reactive oxygen species (ROS) are oxygen-containing chemical species including superoxide anion, hydrogen peroxide (H₂O₂), and hydroxyl radicals, and most of which are produced by mitochondria and nicotinamide adenine dinucleotide phosphate (NADPH) oxidases [1]. Of note, excess of ROS could lead to oxidative stress in cells. Oxidative stress is associated with the disorder of proteins, lipid oxidation, and nucleic acid breaks, which may further impair cellular physiological functions. Numerous studies suggested that oxidative stress may result in some pathogenic diseases, such as cancer [2], neurological disorders [3], age-related diseases [4], atherosclerosis [5], inflammation [6], and cardiovascular diseases [7]. Mammals have evolved a series of antioxidant defenses to protect vital biomolecules from oxidative damage. On the one hand, antioxidant agents, such as antioxidant enzymes like superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH-Px), or nonenzymatic agents, such as glutathione (GSH), vitamin C, and vitamin E, can clean off most of ROS [8]. On the other hand, the excess ROS can also activate many signaling pathways such as mitogen-activated protein kinase (MAPKs), NF-erythroid 2-related factor/antioxidant response element (Nrf2/ARE), and peroxisome proliferator-activated receptor γ (PPARγ), which play a vital role in cellular redox homeostasis and contribute to antioxidative defense [9].

Glutamate, as a precursor of GSH, exerts alleviative effects on oxidative stress in medicine and surgery [10]. AKG, as a precursor of glutamine, is cheaper and more stable than glutamine and acts as an antioxidant instead of glutamine in many cellular processes. Many reports demonstrated that AKG can be converted into glutamate by glutamate dehydrogenase (GDH) and glutamine synthetase (GS), which is a sign of antioxidative function. It is evident that AKG could improve antioxidative capacity by promoting glutamine content and antioxidative systems [11, 12]. Additionally, Chen et al. showed that AKG could significantly improve SOD activity but reduce malondialdehyde (MDA) level, suggesting an improvement of intestinal antioxidative capacity [13]. Recently, more and more studies indicated that AKG could improve antioxidative function against oxidative imbalance in cells, which further contributed to the prevention and treatment of various diseases induced by oxidative stress.
Therefore, in this review, we aim to summarize the recent advances of the antioxidative function of AKG and its applications.

2. Biochemical Characteristics of AKG

AKG is a weak acid containing two carboxyl groups and a ketone group which is also called 2-ketogluutaric acid or 2-oxoglutaric acid. AKG possesses many physiological functions. On the one hand, AKG could react with ammonia and then be converted into glutamate; subsequently, the glutamate further reacts with ammonia and generates glutamine (Figure 1). On the other hand, AKG reacts with $\text{H}_2\text{O}$ as a result of the conversion of succinate, carbon dioxide ($\text{CO}_2$), and water ($\text{H}_2\text{O}$), eventually achieving elimination of $\text{H}_2\text{O}$ (Figure 2) [14]. Additionally, AKG could produce plenty of ATP in the TCA cycle and provide energy for intestinal cell processes. Furthermore, AKG performs positive effects on oxidative stress damage in intestinal mucosal cells and contributes to cell redox homeostasis [15]. It has been reported that enteral AKG was oxidized and used by intestinal mucosa, thereby, as an energy donor and antioxidative agent via the TCA cycle. Apart from the above, AKG also exerts antioxidative defense by enzymatic systems and nonenzymatic oxidative decarboxylation.

3. Antioxidative Function of AKG

3.1. Antioxidants Activities. The balance between oxidants and antioxidants plays an important role in physiological functions in cells and biomolecules. Antioxidant system comprises enzymatic and nonenzymatic agents. Antioxidative enzymes include SOD, CAT, GSH-Px, and nonenzymatic agents include GSH, vitamin C, vitamin E [10]. AKG is an antioxidative substance which exhibits a vital role in scavenging ROS in organism [16]. Growing studies suggest that AKG serves as a natural antidote of scavenging ammonia by exerting its antioxidative capacity. It has been reported that AKG inhalation showed a protective role in ammonia-induced lung damage in rats [17]. The mechanism may be caused by reducing the levels of lactate dehydrogenase (LDH) and MDA and improving the activities of SOD and CAT and GSH level. Lipid peroxidation is susceptible to ammonia or trauma like burns and eventually produces MDA resulting in membrane injury and even cell apoptosis, while antioxidants such as SOD and GSH-Px are beneficial to prevent the lipid peroxidation and injury [18]. AKG could prevent the lipid peroxidation by increasing SOD, GSH-Px, and CAT activities to facilitate fat metabolism, and then alleviate ethanol-induced hepatotoxicity and hyper-ammonemia induced by ammonium acetate in rats [19, 20]. Similarly, AKG also performs chemopreventive role in hepatocarcinogenesis induced by N-nitrosodiethylamine (NDEA) in rats by modulating the levels of antioxidants and lipid peroxide to access normal levels [21]. Furthermore, AKG shows high resistance to ammonia-N stress in hybrid sturgeon as it enhances antioxidant enzymes activity and HSP 70 and HSP 90 gene expression [22]. Besides, cyanide-induced oxidative stress could lead to neurotoxicity, the lipid peroxidation, and dysfunction of membrane especially in brain and kidney of animals like rats [23]. And cyanide is evident to inhibit antioxidative defense such as reducing SOD activity and GSH level [24]. Interestingly, AKG is considered as a natural antagonist of cyanide poisoning because of its chemical structure that is able to bind with cyanide to produce cyanohydrin and further prevent cyanide poisoning or cyanide lethality [25, 26]. In rat in vitro and vivo models, AKG reduces GSH depletion and DNA damage induced by cyanide [27]. Furthermore, studies demonstrate that AKG alone could prevent brain and liver from cyanide-induced oxidative damage by increasing GSH, SOD, and GSH-Px levels and reducing MDA level in rats, especially when combined with sodium thiosulfate [28, 29]. Additionally, a recent study indicates that AKG could enhance freeze-thaw tolerance and prevent cell death induced by carbohydrate stress in yeast, and the protective pathway may be involved in the enhanced antioxidant defense [30].

3.2. Nonenzymatic Oxidative Decarboxylation in $\text{H}_2\text{O}_2$ Decomposition. In regard of antioxidative defense, some studies show that AKG exerts its function by other redox regulatory mechanisms rather than antioxidant activities. A number of
AKG has been widely used in animals and humans as a feed additive and medicine. In animal industry, AKG could effectively improve growth performance, nitrogen utilization, immunity, bone development, intestinal mucosal injury, and oxidative system [35–39]. In humans, AKG is extensively used in trauma, aged diseases, postoperative recovery, and other nutritional diseases [40]. In terms of antioxidative function, AKG exhibits a crucial role in multiple diseases involved in aging, cancer, cardiovascular diseases, and neurological diseases. It has been reported that AKG develops its antioxidant capacity to fight against ethanol toxicity and enhance cold tolerance in the model of Drosophila melanogaster, other animals, and humans, which provides a strong evidence for the H2O2-scavenging ability of AKG [34]. Thus, AKG can be used as a potent scavenger in nonenzymatic oxidative decarboxylation in H2O2 decomposition.

5. Summary and Perspective

AKG serves as a pivotal intermediate and is widely applied in animals and humans. Particularly, AKG primarily exerts its antioxidative function by the following: (1) enhancing antioxidative enzymes activities and nonenzymatic agent levels against oxidative stress and lipid peroxidation, especially in intervention of ammonia and cyanide poisoning; (2) participating in nonenzymatic oxidative decarboxylation in H2O2 decomposition to scavenge ROS and protect organism from various ROS-induced diseases. And AKG provides a promising therapeutic intervention for clinical diseases in animals and humans (Figure 3). Besides the above antioxidative pathways, Nrf2/ARE is an important regulator of antioxidative process that aids to keep redox homeostasis, and it has been proved to perform a vital role in various diseases (i.e., liver injury, traumatic brain injury, and inflammation) induced by oxidative stress [53]. Of particular interest, glutamine has been verified to improve the gene expression of Nrf2 by activating Nrf2/ARE signaling pathway to suppress ROS generation, elevate GSH levels, and prevent apoptosis in intestine [54, 55]. However, as a precursor of glutamine, whether AKG could directly activate Nrf2/ARE signaling pathway to alleviate oxidative stress or not, relevant research about that is not reported and further study is needed.
**Abbreviations**

| Abbreviation | Description |
|--------------|-------------|
| AKG          | Alpha-ketoglutarate |
| ROS          | Reactive oxygen species |
| H₂O₂         | Hydrogen peroxide |
| NADPH        | Nicotinamide adenine dinucleotide phosphate |
| SOD          | Superoxide dismutase |
| CAT          | Catalase |
| GSH-Px       | Glutathione peroxidase |
| GSH          | Glutathione |
| MAPKs        | Mitogen-activated protein kinase |
| Nrf2/ARE     | NF-Erythroid 2-related factor/antioxidant response element |
| PPARγ        | Peroxisome proliferator-activated receptor γ |
| GDH          | Glutamate dehydrogenase |
| GS           | Glutamine synthetase |
| MDA          | Malondialdehyde |
| CO₂          | Carbon dioxide |
| H₂O          | Water |
| LDH          | Lactate dehydrogenase |
| NDEA         | N-Nitrosodiethylamine |

**Conflicts of Interest**

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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