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Research Progress of Astaxanthin on Contrast agent induced acute kidney injury

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ABSTRACT

Contrast agent induced acute kidney injury (CI-AKI) is a leading cause of hospital-acquired acute kidney injury as a result of more and more iodinated contrast-media use for diagnostic purposes. Previous studies have demonstrated that oxidative stress and apoptosis are established processes contributing to contrast agent induced acute kidney injury. Astaxanthin (ATX), a carotenoid found in microalgae, fungi, complex plants, seafood, flamingos and quail has been confirmed have anti-oxidant, and anti-apoptosis effects. Experimental investigations in a range of species using a contrast agent induced acute kidney injury model demonstrated kidney preservation when ATX is administered prior to the induction of contrast agent. ATX, as an natural antioxidant, is capable to prevent CI-AKI effectively, and the mechanism is possibly related to anti-oxidant and anti-apoptosis. In this mini review, we briefly summarize the potential for ATX as a protector against CI-AKI pathologies.

Introduction

Astaxanthin(ATX) is a xanthophyll carotenoid of predominantly marine origin, with potent antioxidant and anti-apoptosis effects demonstrated in both experimental and human studies. Many studies have proven that astaxanthin has a preventive effect on various kidney diseases[1-5]. Oxidative stress and apoptosis are common pathophysiological features of contrast agent induced acute kidney injury (CI-AKI), hence ATX may have a potential therapeutic role in this condition. This review will summarize the available evidence suggesting ATX may be of therapeutic value in CI-AKI.

Potential Mechanisms of ATX for CI-AKI Protection

Anti-oxidative effects

Oxidative stress damage is caused by an imbalance between oxidation and anti-oxidation in the body, which causes tissue damage caused by excessive generation of ROS and reactive nitrogen free radicals in the body. The appropriate amount of ROS can be used as a signal molecule to promote wound healing and tissue repair, reduce the production of malignant pathogens. On the contrary, excessive ROS can react with proteins, lipids, and DNA through a chain reaction, thereby destroying homeostasis and causing tissue damage[6, 7]. The exact mechanism of CIAKI is not fully understood. It has been suggested that CM increases osmotic load, decreases renal blood flow, and induces renal arterial constriction. Such a condition promotes generation of ROS and results in ischemic tubular injury, and can be a reason for direct tubular toxicity[8, 9]. Contrast agents

make the imbalance between oxygen supply and demand, resulting in hypoxia of the medulla and hypoxic injury. A large number of animal experiments have found that after the use of contrast agents, the products of lipid peroxidation in animals will increase significantly, such as malondialdehyde and isoprostane. At the same time, a multiple increase in ROS can be detected in the urine of patients undergoing coronary angiography. ROS can prevent the vasodilatory effects of NO, resulting in ischemic injury and immune-mediated tissue damage[10]. After the angiography, hyperosmotic environment is formed outside the cell, and oxidative stress caused by ROS induces apoptosis of renal tubular epithelial cells.

ATX is well documented to have antioxidative activity as a scavenger of free radicals and a quencher of reactive oxygen species (ROS)[11-13]. The finding that spin trapping of ROS species by carotenoids, increases with increasing carotenoid oxidation potential[14].That decreasing scavenging rate of free radicals decreases with decreasing oxidation potential. The oxidation potential of ATX being significantly higher than that of β-Carotene, thus the scavenging rate of ATX is much higher than that for β-Carotene and exhibits Pro-oxidative character which includes reduction of Fe3+ to Fe2+[15, 16]. The antioxidative activity of ATX on cells is greater than that of β-carotene, vitamin C, vitamin E, lutein, lycopene, and other catechins[17, 18]. Recently, Kim et al.[19] suggested ATX effectively suppressed including lipid peroxidation, total reactive species (RS), superoxide (•O2), nitric oxide (NO•), and peroxynitrite (ONOO-). Studies have confirmed that the antioxidant activity of ATX plays a protective role in various kidney diseases. For instance, nephrotoxicity induced by CMS might be due to oxidative damage. The improvement by ATX is related to their antioxidant properties[20]. Pretreatment of ATX is effective in preserving renal function and histology against ischemia/reperfusion via antioxidant activity[4].The nephrotoxic effect of cisplatin was diminished by the antioxidant effect of ATX[21].ATX is useful for the prevention of Fe-NTA-induced renal tubular oxidative damage[22].ATX plays an important role in reduction of oxidative damage and could prevent pathological changes in diabetic rats suggesting promising application of ATX in diabet treatment[23]. Thus, ATX provides protection against oxidative attacks in experimental renal diseases. We speculate that ATX has a protective effect on contrast, and its mechanism may be through antioxidant activity, and it has been verified in my previous experiment[24].

Anti-apoptosis effects

Apoptosis is a process of programmed cell death that occurs in multicellular organisms. Caspase-3, a protease, is the most important terminal cleavage enzyme in apoptosis. Contrast medium (CM)-induced renal epithelial cell apoptosis is an important underlying cause of renal failure[25, 26]. Previous studies have shown that CM induces apoptosis of tubular cells by activating intrinsic or mitochondrial pathway, which down-regulates anti-apoptotic genes and up-regulates pro-apoptotic genes. The expressions of apoptosis-related proteins such as caspase3 are detected significant increase in the contrast nephropathy model[27-33].

In addition to the antioxidant effects, it has been reported in literatures that ATX has an anti-apoptotic

Table 1. Animal studies investigating the nephrotoxicity effects of astaxanthin.

Studies	Animal	Model	Mechanism of astaxanthin
Augusti PR *et al.* 2008[1]	Male Wistar rats(eight weeks-old)	mercuric chloride inducedkidney function impairment	anti-oxidation
Wang X *et al.* 2014[2]	Male Wistar rats(eight weeks-old)	trivalent inorganic arsenic-induced renal injury	anti-oxidation
Guo SX *et al.* 2015[3]	Adult male Sprague-Dawley rats (weighing approximately 220–250 g)	severe burns induced early acute kidney injury	anti-oxidation and anti-apoptosis
Qiu X *et al.* 2015[4]	○11Male ICR mice weighing 20-25 g ○22Human tubular epithelial cells (HTECs)	ischemia/reperfusion induced renal injury	anti-oxidation and anti-apoptosis
Mosaad YO *et al.* 2016[5]	Male albino rats (weighing 210±10 g)	gentamicin-induced nephrotoxicity	anti-oxidation
Kim YJ *et al.* 2009[19]	Porcine proximal tubular epithelial cell line	high-glucose-exposed proximal tubular epithelial cells	anti-oxidation and anti-apoptosis
Ghlissi Z *et al.*2014[20]	Male *Wistar* rats(weighing 250 ± 20 g)	colistin-induced nephrotoxicity	anti-oxidation
Akca G *et al.* 2018[21]	Male Sprague Dawley rats (aged 3–5 months and weighing 264.83 ± 7.39 g)	cisplatin-induced nephrotoxicity	anti-oxidation
Okazaki Y *et al.* 2017[22]	Male Wistar rats (4 weeks old)	ferric nitrilotriacetate-induced renal oxidative injury	anti-oxidation
Sila A *et al.* 2015[23]	Male Wistar rats (~200 g)	diabetic nephropathy	anti-oxidation
Liu N *et al.* 2018[24]	Adult male Sprague-Dawley rats (weighing approximately 160–200 g)	contrast agent-induced acute kidney injury	anti-oxidation and anti-apoptosis
Liu G *et al.* 2015[36]	Male Balb/c mice(aged 8–10 weeks and weighing around 20–25 g)	adriamycin-induced focal segmental glomerulosclerosis	anti-oxidation

effect[34, 35]. Studies have shown that the protective effects of astaxanthin against many kidney diseases is related to anti-apoptosis[3, 4, 36]. Considering the crucial role of oxidative stress in inducing pathological changes of IR and the antioxidant properties of ATX, ATX might alleviate tubular necrosis/ apoptosis and inflammation via scavenging free radical[19]. We infer that anti-apoptotic is another important mechanism that ATX moderate CI-AKI which may involve direct action of ATX (direct action on apoptotic molecules) and indirect action (mediated antioxidation). The specific mechanism that ATX moderate CI-AKI via the anti-apoptosis effects still needs further study.

ATX confers multiple renal protective effects in various experimental models of kidney diseases (Table 1).

Conclusion

The protective effects of ATX are associated with its anti-oxidative and anti-apoptotic effects. ATX is a safe nutrient, with no toxic effects when it is consumed with food. Furthermore, as a natural powerful antioxidant, ATX is an excellent candidate for treating CI-AKI. The mechanism and the target of its action are still uncertain. For more in-depth understanding, more relevant animal experiments and a large number of clinical data samples are needed for confirmation, which may eventually lead to ATX becoming a novel protective agent for CI-AKI.

Conflict of interest

The authors declare that they have no competing interest.

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