Research Progress of Astaxanthin on Contrast agent induced acute kidney injury

Dongmei Gao1 & Wenhua Li1,2*

1Institute of Cardiovascular Disease Research, Xuzhou Medical University, Xuzhou, Jiangsu, 221002, China
2Department of Cardiology, The Affiliated Hospital Of Xuzhou Medical University, Xuzhou, Jiangsu, 221002, China

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 diseases1-5. 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 damage6,7. 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 toxicity8,9. 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 isoprostan. 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. 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). The finding that spin trapping of ROS species by carotenoids, increases with increasing carotenoid oxidation potential. 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+. The antioxidative activity of ATX on cells is greater than that of β-carotene, vitamin C, vitamin E, lutein, lycopene, and other catechins. ATX is much higher than that for β-Carotene and exhibits antioxidative activity on cells, and oxidative stress caused by ROS induces apoptosis of renal tubular epithelial cells.

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

<table>
<thead>
<tr>
<th>Studies</th>
<th>Animal</th>
<th>Model</th>
<th>Mechanism of astaxanthin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Augusti PR et al. 2008</td>
<td>Male Wistar rats(eight weeks-old)</td>
<td>mercuric chloride induced kidney function impairment</td>
<td>anti-oxidation</td>
</tr>
<tr>
<td>Wang X et al. 2014</td>
<td>Male Wistar rats( eight weeks-old)</td>
<td>trivalent inorganic arsenic-induced renal injury</td>
<td>anti-oxidation</td>
</tr>
<tr>
<td>Guo SX et al. 2015</td>
<td>Adult male Sprague-Dawley rats (weighing approximately 220–250 g)</td>
<td>severe burns induced early acute kidney injury</td>
<td>anti-oxidation and anti-apoptosis</td>
</tr>
<tr>
<td>Qiu X et al. 2015</td>
<td>011 Male ICR mice weighing 20-25 g</td>
<td>ischemia/reperfusion induced renal injury</td>
<td>anti-oxidation and anti-apoptosis</td>
</tr>
<tr>
<td>Mosaad YO et al. 2016</td>
<td>Male albino rats (weighing 210±10 g)</td>
<td>gentamycin-induced nephrotoxicity</td>
<td>anti-oxidation</td>
</tr>
<tr>
<td>Kim Yi et al. 2009</td>
<td>Porcine proximal tubular epithelial cell line</td>
<td>high-glucose-exposed proximal tubular epithelial cells</td>
<td>anti-oxidation and anti-apoptosis</td>
</tr>
<tr>
<td>GhliSSi Z et al. 2014</td>
<td>Male Wistar rats( weighing 250 + 20 g)</td>
<td>colistin-induced nephrotoxicity</td>
<td>anti-oxidation</td>
</tr>
<tr>
<td>Akca G et al. 2018</td>
<td>Male Sprague Dawley rats (aged 3–5 months and weighing 264.83 ± 7.39 g)</td>
<td>cisplatin-induced nephrotoxicity</td>
<td>anti-oxidation</td>
</tr>
<tr>
<td>Okazaki Y et al. 2017</td>
<td>Male Wistar rats (4 weeks old)</td>
<td>ferric nitritriacetate-induced renal oxidative injury</td>
<td>anti-oxidation</td>
</tr>
<tr>
<td>Silva A et al. 2015</td>
<td>Male Wistar rats (~200 g)</td>
<td>diabetic nephropathy</td>
<td>anti-oxidation</td>
</tr>
<tr>
<td>Liu N et al. 2018</td>
<td>Adult male Sprague-Dawley rats (weighing approximately 160–200 g)</td>
<td>contrast agent-induced acute kidney injury</td>
<td>anti-oxidation and anti-apoptosis</td>
</tr>
<tr>
<td>Liu G et al. 2015</td>
<td>Male Balb/c mice(aged 8–10 weeks and weighing around 20–25 g)</td>
<td>adriamycin-induced focal segmental glomerulosclerosis</td>
<td>anti-oxidation</td>
</tr>
</tbody>
</table>
effect\textsuperscript{9,14,35}. Studies have shown that the protective effects of astaxanthin against many kidney diseases is related to anti-apoptosis\textsuperscript{3, 4, 36}. Considering the crucial role of oxidative stress in inducing pathological changes of IR and the antioxidant properties of ATX, ATX might ameliorate tubular necrosis/apoptosis and inflammation via scavenging free radicals\textsuperscript{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.

**References**


