Review Article

Role of Intracellular Ca\(^{2+}\) and Na\(^{+}/Ca^{2+}\) Exchanger in the Pathogenesis of Contrast-Induced Acute Kidney Injury

Dingping Yang\(^1\) and Dingwei Yang\(^2\)

\(^1\) Division of Nephrology, Department of Internal Medicine, Renmin Hospital of Wuhan University, Wuhan 430060, China
\(^2\) Division of Nephrology, Department of Internal Medicine, General Hospital of Tianjin Medical University, Tianjin 300052, China

Correspondence should be addressed to Dingwei Yang; dxyang0072003@163.com

Received 20 September 2013; Accepted 24 October 2013

Academic Editor: Michele Andreucci

Copyright © 2013 D. Yang and D. Yang. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

The precise mechanisms underlying contrast-induced acute kidney injury (CI-AKI) are not well understood. Intracellular Ca\(^{2+}\) overload is considered to be a key factor in CI-AKI. Voltage-dependent Ca\(^{2+}\) channel (VDC) and Na\(^{+}/Ca^{2+}\) exchanger (NCX) system are the main pathways of intracellular Ca\(^{2+}\) overload in pathological conditions. Here, we review the potential underlying mechanisms involved in CI-AKI and discuss the role of NCX-mediated intracellular Ca\(^{2+}\) overload in the contrast media-induced renal tubular cell injury and renal hemodynamic disorder.

1. Pathogenesis of CI-AKI

Contrast-induced acute kidney injury (CI-AKI) is the third leading cause of hospital-acquired acute renal failure accounting for 10–12% of all causes of hospital-acquired renal failure [1]. In general population, the incidence is 1–6%. In some special populations, such as patients with underlying hypertension, cardiovascular diseases, diabetes mellitus, or preexisting renal insufficiency, the incidence is higher and may be as high as 20–50% [2–4]. In patients undergoing coronary angiography in China, the incidence of CI-AKI is 8.7%–23.5% [5, 6]. The precise mechanisms underlying CI-AKI are not fully understood, especially its cellular and molecular mechanism. But, it is clear that disturbance of renal hemodynamics and direct toxic action on renal tubular cells are main factors responsible for CI-AKI. Previous investigations [7, 8] have shown that contrast media administration can result in initial renal vasodilatation (about 20 minutes), followed by prolonged vasoconstriction (about 20 minutes to several hours). Subsequent studies [9, 10] demonstrated that there were regional differences in the vascular response to contrast media, with a greater reduction in flow to the outer medulla. And now, it has been verified that contrast-induced selective reduction in renal medullary blood flow and the secondary hypoxia in this region is a major underlying cause of CI-AKI [10]. It has been reported that calcium channel blockers (CCB) can reverse the acute hemodynamic alterations induced by contrast administration and alleviated CI-AKI [11–13]. Furthermore, our experimental animal investigation [14] also verified that tail vein injection of an inhibitor of reverse mode of Na\(^{+}/Ca^{2+}\) exchanger (NCX) can suppress the contrast-induced ET-1 overproduction and renal vasoconstriction. These findings suggested that intracellular Ca\(^{2+}\) overload plays an important role in contrast-induced renal hemodynamic disorder. Besides changes in calcium physiology, contrast-induced vasoconstriction might also be a result of a direct effect on vascular smooth muscle [15] or from a local increase in adenosine [16] and endothelin [17] production.

It must be pointed out that, under normal circumstances, the contrast-induced renal hemodynamic disorder was not enough to induce CI-AKI based on the facts that humans as well as experimental animals without risk factors do not usually exhibit CI-AKI following contrast media injection. This is because, under physiological state, the renal circulation is subjected to autoregulation which is associated...
with neural, hormonal, paracrine, and autocrine influences. Injured autoregulation of microcirculation might be the cause that all kinds of risk factors such as preexisting renal impairment, diabetes mellitus, and hypercholesterolemia, make the kidney vulnerable to iodinated contrast media.

Renal tubular cells apoptosis is a key mechanism of CI-AKI. Studies have shown that contrast media can induce renal tubular epithelial cell apoptosis via ROS (reactive oxygen species) pathway, JNK/p38 stress kinase pathway, and intrinsic apoptotic pathways [18–20] and can also result in renal tubular epithelial cell injury by dephosphorylation (inactivation) of the kinase Akt [21]. But it is still unclear why contrast media can cause ROS overproduction and why contrast media can activate p38 Mitogen-Activated Protein Kinases (MAPK). Our recent studies showed that contrast medium can activate p38 MAPK [21]. But it is still unclear why contrast media can cause ROS overproduction and why contrast media can activate p38 MAPK [21].

Recent animal model experiments [14, 37] also showed that pretreatment with tail vein injection of KB-R7943 markedly and dose-dependently suppressed the increase in renal ET-1 production and the reduction in renal blood flow induced by contrast medium administration and prevented contrast-induced acute renal failure, which suggested that Ca\textsuperscript{2+} overload via the reverse mode of NCX system is involved in contrast-induced renal tubular epithelial cell apoptosis.

Recent animal model experiments [14, 37] also showed that pretreatment with tail vein injection of KB-R7943 markedly and dose-dependently suppressed the increase in renal ET-1 production and the reduction in renal blood flow induced by contrast medium administration and prevented contrast-induced acute renal failure, which suggested that Ca\textsuperscript{2+} overload via the reverse mode of NCX system is involved in contrast-induced renal tubular epithelial cell apoptosis.

3. The Role of Na\textsuperscript{+}/Ca\textsuperscript{2+} Exchanger System in the Pathogenesis of CI-AKI

NCX is a bidirectional plasma membrane transporter that catalyzes the exchange of 3 or 4 Na\textsuperscript{+} for 1 Ca\textsuperscript{2+}, depending on the electrochemical gradients of the substrate ions [28, 29] and is encoded by a multigene family comprising 3 NCX isoforms: NCX1, which is expressed in various organs including the kidney [30]; and NCX2 and NCX3, which are expressed mainly in the brain and skeletal muscle [31, 32]. Under physiological conditions, NCX can pump the Ca\textsuperscript{2+} outside the cell using the Na\textsuperscript{+} concentration gradient across the cell membrane to keep a low intracellular Ca\textsuperscript{2+} level, which is referred to as the forward-mode operation of the exchanger. In pathological conditions, NCX can reversely extrude Na\textsuperscript{+} for Ca\textsuperscript{2+} influx and result in intracellular Ca\textsuperscript{2+} overload, which is referred to as the reverse mode of calcium influx mode of NCX. In the normal kidney, NCX plays an important role in the active calcium transport in distal convoluted tubules [33]. In the ischemia-reoxygenation renal tubular epithelial cells, NCX reversely extrudes Na\textsuperscript{+} for Ca\textsuperscript{2+} influx and results in intracellular Ca\textsuperscript{2+} overload and tubular epithelial cell injury [34, 35].

It has been verified that contrast media can induce renal tubular epithelial cell apoptosis via ROS pathway, JNK/p38 pathway, and intrinsic apoptosis pathway [18, 20]. Our recent in vitro studies [19, 36] demonstrated that contrast-induced ROS overproduction, p38 activation, and apoptosis in renal tubular cell were associated with the increase of intracellular Ca\textsuperscript{2+}. The inhibitor of reverse mode of NCX, KB-R7943, can alleviate contrast-induced renal tubular apoptosis through suppressing the increase of intracellular Ca\textsuperscript{2+} and subsequent ROS overproduction and p38 activation. These data demonstrate that intracellular Ca\textsuperscript{2+} overload via the reverse mode of NCX system is involved in contrast-induced renal tubular epithelial cell apoptosis.

Recent animal model experiments [14, 37] also showed that pretreatment with tail vein injection of KB-R7943 markedly and dose-dependently suppressed the increase in renal ET-1 production and the reduction in renal blood flow induced by contrast medium administration and prevented contrast-induced acute renal failure, which suggested that Ca\textsuperscript{2+} overload via the reverse mode of NCX, followed by renal ET-1 overproduction and renal vasoconstriction, plays an important role in the pathogenesis of CI-AKI.

4. Hypothesis about the Molecular Mechanism of CI-AKI

Based on the findings [19, 22, 36] that inhibition of the reverse mode of NCX alleviated contrast-induced renal tubular cell apoptosis through suppressing the increase of intracellular Ca\textsuperscript{2+}, ROS overproduction, p38 MAPK activation, and Caspase-3 overexpression and the findings [14, 37] that tail vein injection of inhibitor of reverse mode of NCX can exert protective effects on CI-AKI in rats through suppressing
contrast-induced renal ET-1 overproduction and renal vasoconstriction, we propose the following hypothesis regarding the molecular mechanism of CI-AKI. Contrast medium exposure activates the reverse mode of NCX1 expressed in renal tubular epithelial cells; NCX reversely extrudes Na\(^+\) for Ca\(^{2+}\) influx and results in increased intracellular Ca\(^{2+}\). The increased intracellular Ca\(^{2+}\) can stimulate Ca\(^{2+}\) release from the mitochondrial and endoplasmic reticulum and result in intracellular Ca\(^{2+}\) overload [38]. The intracellular Ca\(^{2+}\) overload via the reverse mode of NCX and VDC induced by contrast media in the renal tubular epithelial cell can result in ROS overproduction and oxidative stress. Increased ROS and intracellular Ca\(^{2+}\) can induce upregulation of p38 MAPK and p-p38 MAPK expression [36] and subsequently activate intrinsic apoptotic pathways such as bcl-2, bax, and caspase-3 and result in renal tubular epithelial cell apoptosis, which is the underlying cause of contrast-induced direct renal tubular toxicity. p38 MAPK activation via the reverse mode of NCX and VDC could also result in renal ET-1 overproduction, followed by renal vasoconstriction and renal ischemia, which is one of the underlying causes of contrast-induced renal hemodynamic abnormalities. ET-1 overproduction and renal ischemia can cause depletion of adenosine triphosphate (ATP) and development of intracellular acidosis. The accumulation of intracellular Na\(^+\), which is caused by inhibition of Na\(^+\)/K\(^+\)-ATPase activity because of
decreased ATP production [39] and activation of the \( \text{Na}^+ / \text{H}^+ \) exchange because of intracellular acidosis [40], can also activate the reverse of the mode of NCX and subsequently cause calcium overload and ET-1 overproduction, forming a vicious cycle. The diagram of the hypothesis about the molecular mechanism of CI-AKI is seen in Figure 1. Contrast media exposure activates VDC and the reverse mode of NCX expressed in the renal tubular epithelial cell and induces \( \text{Ca}^{2+} \) influx. The increased intracellular \( \text{Ca}^{2+} \) stimulates \( \text{Ca}^{2+} \) release from the mitochondrial and endoplasmic reticulum and results in intracellular \( \text{Ca}^{2+} \) overload, which induced ROS overproduction and oxidative stress. Increased ROS and intracellular \( \text{Ca}^{2+} \) activate p38 MAPK. On one hand, p38 MAPK activates intrinsic apoptotic pathways such as bcl-2, bax, and caspase-3 and induces renal tubular epithelial cell apoptosis, which is the underlying cause of contrast-induced direct renal tubular toxicity. On the other hand, activated p38 MAPK also results in renal ET-1 overproduction, followed by renal vasoconstriction and renal ischemia, which is one of the underlying causes of contrast-induced renal hemodynamic abnormalities. ET-1 overproduction and renal ischemia can cause depletion of ATP and development of intracellular acidosis, which can result in accumulation of intracellular \( \text{Na}^+ \) and further activate the reverse of the mode of NCX and subsequently cause \( \text{Ca}^{2+} \) influx and ET-1 overproduction, forming a vicious cycle.

5. Conclusion

In summary, \( \text{Ca}^{2+} \) overload via the reverse mode of NCX1 and VDC, followed by ROS overproduction, p38 MAPK activation, and ET-1 overproduction, plays an important role in the contrast-induced renal hemodynamic disorder and renal tubular epithelial cell apoptosis, which suggests that, in clinical practice, CCB should be recommended to patients with hypertension who are undergoing radiographic examination or therapy requiring contrast media and that selective inhibitors of NCX1 may be beneficial in the prevention and treatment of CI-AKI in humans.

Disclosure

This paper was not published or submitted elsewhere.

Conflict of Interests

There does not exist any financial or other conflict of interests.

Acknowledgments

This study was supported by research Grants from the National Natural Science Funds of China (81370841) and the Natural Science Fund of Hubei province (2012FFB04426).

References

[1] S. H. Hou, D. A. Bushinsky, and J. B. Wish, "Hospital-acquired renal insufficiency: a prospective study," *American Journal of Medicine*, vol. 74, no. 2, pp. 243–248, 1983.
[2] I. Goldenberg and S. Matetzky, "Nephropathy induced by contrast media: pathogenesis, risk factors and preventive strategies," *Canadian Medical Association Journal*, vol. 172, no. 11, pp. 1461–1471, 2005.
[3] Y. Itoh, T. Yano, T. Sendo, and R. Oishi, "Clinical and experimental evidence for prevention of acute renal failure induced by radiographic contrast media," *Journal of Pharmacological Sciences*, vol. 97, no. 4, pp. 473–488, 2005.
[4] E. Ledneva, S. Karie, V. Launay-Vacher, N. Janus, and G. Deray, "Renal safety of gadolinium-based contrast media in patients with chronic renal insufficiency," *Radiology*, vol. 250, no. 3, pp. 618–628, 2009.
[5] F. Gao, Y. J. Zhou, X. Zhu, Z. J. Wang, S. W. Yang, and H. Shen, "C-reactive protein and the risk of contrast-induced acute kidney injury in patients undergoing percutaneous coronary intervention," *American Journal of Nephrology*, vol. 34, no. 3, pp. 203–210, 2011.
[6] W. Ling, N. Zhaohui, H. Ben et al., "Urinary IL-18 and NGAL as early predictive biomarkers in contrast-induced nephropathy after coronary angiography," *Nephron Clinical Practice*, vol. 108, no. 3, pp. 176–181, 2008.
[7] G. L. Bakris and J. C. Burnett Jr., "A role for calcium in radiocontrast-induced reductions in renal hemodynamics," *Kidney International*, vol. 27, no. 2, pp. 465–468, 1985.
[8] R. W. Katzberg, T. W. Morris, and F. A. Burger, "Renal hemodynamics following intravenous and renal ischemia catheterization and angiography," *Investigative Radiology*, vol. 12, no. 5, pp. 381–388, 1977.
[9] A. Nygren, "Contrast media and regional renal blood flow. A study of the effects of ionic and non-ionic monomeric and dimeric contrast media in the rat," *Acta Radiologica*, vol. 378, part 3, pp. 123–135, 1992.
[10] P. Liss, A. Nygren, U. Olsson, H. R. Ulfendahl, and U. Erikson, "Effects of contrast media and mannitol on renal medullary blood flow and red cell aggregation in the rat kidney," *Kidney International*, vol. 49, no. 5, pp. 1268–1275, 1996.
[11] D. Russo, A. Testa, L. Della Volpe, and G. Sansone, "Randomised prospective study on renal effects of two different contrast media in humans: protective role of a calcium channel blocker," *Nephron*, vol. 55, no. 3, pp. 254–257, 1990.
[12] S. B. Duan, F. Y. Liu, J. A. Luo et al., "Nephrotoxicity of high- and low-osmolar contrast media: the protective role of amlodipine in a rat model," *Acta Radiologica*, vol. 41, no. 5, pp. 503–507, 2000.
[13] H. H. Neumayer, W. Junge, A. Kufner, and A. Wenning, "Prevention of radiocontrast-media-induced nephrotoxicity by the calcium channel blocker nicardipine: a prospective randomised clinical trial," *Nephrology Dialysis Transplantation*, vol. 4, no. 12, pp. 1030–1036, 1989.
[14] D. W. Yang, D. P. Yang, R. H. Jia, and J. Tan, "Na⁺/Ca²⁺ exchange inhibitor, KB-R7943, attenuates contrast-induced acute kidney injury," *Journal of Nephrology*, vol. 26, pp. 877–885, 2013.
[15] J. Karstoft, L. Bååth, I. Jansen, and L. Edvinsson, "Vasoconstriction of isolated arteries induced by angiographic contrast media. A comparison of ionic and non-ionic contrast media iso-osmolar with plasma," *Acta Radiologica*, vol. 36, no. 3, pp. 312–316, 1995.
[16] A. Pfleuger, T. S. Larson, K. A. Nath, B. F. King, J. M. Gross, and F. G. Knox, "Role of adenosine in contrast media-induced acute renal failure in diabetes mellitus," *Mayo Clinic Proceedings*, vol. 75, no. 12, pp. 1275–1283, 2000.
[17] C. Bagnis, J. M. Idec, M. Dubois et al., “Role of endothelium-derived nitric oxide-endothelin balance in contrast medium-induced acute renal vasoconstriction in dogs,” *Academic Radiology*, vol. 4, no. 5, pp. 343–348, 1997.

[18] C. Quintavalle, M. Brenca, F. De Micco et al., “In vivo and in vitro assessment of pathways involved in contrast media-induced renal cells apoptosis,” *Cell Death and Disease*, vol. 2, no. 5, article e155, 2011.

[19] D. P. Yang, R. H. Jia, G. H. Ding, and J. Zhang, “KB-R7943 decreased renal tubular cell apoptosis and p38 expression induced by contrast media,” *Chinese Journal of Experimental Surgery*, vol. 5, pp. 641–643, 2008 (Chinese).

[20] X. Gong, G. Celsi, K. Carlsson, S. Norgren, and M. Chen, “N-acetylcysteine amide protects renal proximal tubular epithelial cells against iohexol-induced apoptosis by blocking p38 MAPK and iNOS signaling,” *American Journal of Nephrology*, vol. 31, no. 2, pp. 178–188, 2010.

[21] M. Andreucci, G. Fuiano, P. Presta et al., “Radiocontrast media cause dephosphorylation of Akt and downstream signaling targets in human renal proximal tubular cells,” *Biochemical Pharmacology*, vol. 72, no. 10, pp. 1334–1342, 2006.

[22] D. P. Yang, D. W. Yang, R. H. Jia, and G. H. Ding, “Selective inhibition of reverse mode of Na+/Ca2+ exchanger attenuates contrast-induced cell injury,” *American Journal of Nephrology*, vol. 37, pp. 264–273, 2013.

[23] D. P. Yang, R. H. Jia, G. H. Ding, and D. W. Yang, “Felodipine attenuates NRK52E cell injury induced by contrast media,” *Herald of Medicine*, vol. 27, no. 10, pp. 1153–1156, 2008 (Chinese).

[24] D. R. Wilson, P. E. Arnold, T. J. Burke, and R. W. Schrier, “Mitochondrial calcium accumulation and respiration in ischemic acute renal failure in the rat,” *Kidney International*, vol. 25, no. 3, pp. 519–526, 1984.

[25] M. Carraro, W. Mancini, M. Artero et al., “Dose effect of nitrendipine on urinary enzymes and microproteins following non-ionic radiocontrast administration,” *Nephrology Dialysis Transplantation*, vol. 11, no. 3, pp. 444–448, 1996.

[26] Z. Khoury, J. R. Schlicht, J. Como et al., “The effect of prophylactic nifedipine on renal function in patients administered contrast media,” *Pharmacotherapy*, vol. 15, no. 1, pp. 59–65, 1995.

[27] B. Spangberg-Viklund, J. Berglund, T. Nikonoff, P. Nyberg, T. Skau, and R. Larsson, “Does prophylactic treatment with felodipine, a calcium antagonist, prevent low-osmolar contrast-induced renal dysfunction in hydrated diabetic and non-diabetic patients with normal or moderately reduced renal function?” *Scandinavian Journal of Urology and Nephrology*, vol. 30, no. 1, pp. 63–68, 1996.

[28] K. D. Philipson, D. A. Nicoll, M. Ottolia et al., “The Na+/Ca2+ exchange molecule: an overview,” *Annals of the New York Academy of Sciences*, vol. 976, pp. 1–10, 2002.

[29] M. Condrescu, K. Opuni, B. M. Hantash, and J. P. Reeves, “Cellular regulation of sodium-calciunm exchange,” *Annals of the New York Academy of Sciences*, vol. 976, pp. 214–223, 2002.

[30] D. A. Nicoll, S. Longoni, and K. D. Philipson, “Molecular cloning and functional expression of the cardiac sarcolemmal Na+/Ca2+ exchanger,” *Science*, vol. 250, no. 4980, pp. 562–565, 1990.

[31] Z. Li, S. Matsuoka, L. V. Hryshko et al., “Cloning of the NCX2 isoform of the plasma membrane Na+/Ca2+ exchanger,” *Journal of Biological Chemistry*, vol. 269, no. 26, pp. 17434–17439, 1994.

[32] D. A. Nicoll, B. D. Quednau, Z. Qui, Y. R. Xia, A. J. Lusis, and K. D. Philipson, “Cloning of a third mammalian Na+/Ca2+ exchanger, NCX3,” *Journal of Biological Chemistry*, vol. 271, no. 40, pp. 24914–24921, 1996.

[33] C. E. Magyar, K. E. White, R. Rojas, G. Apodaca, and P. A. Friedman, “Plasma membrane Ca2+-ATPase and NCX1 Na+/Ca2+ exchange expression in distal convoluted tubule cells,” *American Journal of Physiology—Renal Physiology*, vol. 283, no. 1, pp. F29–F40, 2002.

[34] J. Yamashita, M. Itoh, T. Kuro et al., “Pre- or post-ischemic treatment with a novel Na+/Ca2+ exchange inhibitor, KB-R7943, shows renal protective effects in rats with ischemic acute renal failure,” *Journal of Pharmacology and Experimental Therapeutics*, vol. 296, no. 2, pp. 412–419, 2001.

[35] J. Yamashita, S. Kita, T. Iwamoto et al., “Attenuation of ischemia/reperfusion-induced renal injury in mice deficient in Na+/Ca2+ exchanger,” *Journal of Pharmacology and Experimental Therapeutics*, vol. 304, no. 1, pp. 284–293, 2003.

[36] D. P. Yang, R. H. Jia, G. H. Ding, D. W. Yang, and X. L. Xiong, “Reverse mode of Na+/Ca2+ exchange inhibitor, KB-r7943 attenuates tubular epithelial cell apoptosis induced by contrast media,” *Chinese Journal of Emergency Medicine*, vol. 17, no. 7, pp. 713–716, 2008 (Chinese).

[37] D. W. Yang, D. P. Yang, R. H. Jia, and S. Lin, “Effects of selective inhibition of reverse mode of Na+/Ca2+ exchanger on rats with contrast-induced acute kidney injury,” *National Medical Journal of China*, vol. 93, no. 22, pp. 1750–1754, 2013 (Chinese).

[38] L. Yu, T. Netticadan, Y. J. Xu, V. Panagia, and N. S. Dhall, “Mechanisms of lysophosphatidylcholine-induced increase in intracellular calcium in rat cardiomyocytes,” *Journal of Pharmacology and Experimental Therapeutics*, vol. 286, no. 1, pp. 1–8, 1998.

[39] H. R. Cross, G. K. Radda, and K. Clarke, “The role of Na+/K+ ATPase activity during low flow ischemia in preventing myocardial injury: a 31P, 23Na and 87Rb NMR spectroscopic study,” *Magnetic Resonance in Medicine*, vol. 34, no. 5, pp. 673–685, 1995.

[40] W. Scholz, U. Albus, H. J. Lang et al., “Hoe 694, a new Na+/H+ exchange inhibitor and its effects in cardiac ischaemia,” *British Journal of Pharmacology*, vol. 109, no. 2, pp. 562–568, 1993.