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The Role for AVE0991 (MAS-Receptor Angiotensin II (1-7) Agonist) in Reducing Cisplatin-Induced Acute Kidney Injury on C57BL/6 Mice

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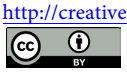

Abstract

Acute Kidney Injury (AKI) is a condition that causes nephrotoxicity in kidney tissues due to cisplatin-induced cancer treatments. Hence, it is proposed in this review that AVE0991 (a MAS-receptor Angiotensin II (1-7) agonist) may reduce cisplatin-induced acute kidney injury by promoting nitric oxide production.

Keywords

Cisplatin, Acute Kidney Injury, AKI, Cisplatin-Induced Acute Kidney Injury, Nephrotoxicity, Renal Renin Angiotensin System, RAS, AVE0991, MAS-Receptor Angiotensin II (1-7) Agonist

1. Introduction

Kidney injury is normally classified as functional disruption [1], as the decrease in Glomerular Filtration Rate (GFR) is evident [1] [2]. The adequacy of renal blood flow is important, but understanding the kidney injury model on a microvascular and macrovascular scale is essential [1]. For instance, insufficient renal perfusion occurs pre-renally on a macrovascular level during the state of shock and intra-renally on a microvascular level, during ischemic reperfusion injury [1]. Renal blood flow may or may not correlate with glomerular perfusion, because changes in glomerular perfusion are evident in periods of preserved blood pressure via differential effects on afferent and efferent arterioles [1].

In normal human physiology, the afferent arteriolar tone is controlled via tubule-glomerular feedback from the Juxtaglomerular Apparatus (JGA) mediated

by angiotensin II, thromboxane, catecholamines, Nitric Oxide (NO) and adenosine [1]. The efferent tone is controlled via angiotensin II in response to Renin Angiotensin Aldosterone System (RAAS) [1] [3]. Studies over the past 2 decades have reported changes to afferent and efferent microvascular tone altered in the diseased state, therefore, predicting with the increase in glomerular perfusion pressure leads to kidney injury [1]. Renal perfusion is important, however, there are many factors contributing to kidney injury such as the absence of hypotension and glomerular hypoperfusion may cause tubular damage and also associate with oxidative stress and inflammation [1].

Figure 1 illustrates the vast potentiality of toxic or ischemic injury to cause tubular damage resulting in cell death via complex pathways mediated by microvascular dysfunction due to increased Reactive Oxygen Species (ROS), causing oxidative stress, inflammation and immune dysregulation ultimately resulting in Acute Kidney Injury (AKI) [1] [4]. Tumour Necrosis Factor-alpha (TNF-α), Interleukin (IL) 1, 6 and 8 [5], along with Transforming Growth Factor-β (TGF-β) and Toll-Like Receptors (TLRs) causes AKI [1] [2]. Pathophysiology of AKI is very complex and nephrotoxicity is one of the major side-effects of toxic-induced renal injury. It is reported in 25% of cases of severe AKI, toxic drugs affect critically ill patients [2] [6] and 19% of failures in phase 3 clinical trial is due to kidney toxicity [2] [7]. Serum Creatinine (sCr) and Blood Urea and Nitrogen (BUN) levels are increased during AKI, causing kidneys to dysregulate electrolyte balance, hence failing to excrete fluids and waste products [8] [9]. Current therapies involving fluid strategies tentatively increase intra-abdominal pressure, thereby resulting in ischemic oedema and congestion in the renal vasculature, which increases the chances of AKI [1]. Macrophages and lymphocytes are upregulated to repair the epithelial cells from injury; however, the depletion of these inflammatory responses causes prolonged kidney injury [10]. Studies have reported regulatory T cells (T-reg) play a crucial role in limiting tissue injury via RAG-1 strain [10]. When T-reg is inhibited, then worse conditions are evident that leads to AKI caused by ischemic-reperfusion injury [10].

Toxic drugs pass through the tubular organic ion transporters (CTR1 and OCT2) across the luminal membranes of the tubule [11] and are reabsorbed again into the lumen of the tubule, generating a greater risk of injury on renal epithelial cells [11] [12]. Many cancers are treated with the aid of platinum drugs, but unfortunately cause an increase in oxidative stress, which affects renal proximal tubules resulting in AKI [4] [13] [14]. Platinum drugs such as cisplatin are identified to accumulate in the proximal tubule of the nephron, where toxic effects take place [15] [16] [17] [18]. Cell death associated with AKI may also be facilitated via genetic factors such as Bcl-2 X protein (BAX) causing the cell-cycle arrest, thereby preventing cell division as the DNA could be damaged [1] [15]. Even though studies involving animals indicated the use of B cells slowing tissue repair post-injury; in humans, the adaptive immune system and immunological memory play a crucial role in the genesis of AKI and Chronic Kidney Disease (CKD) [10].

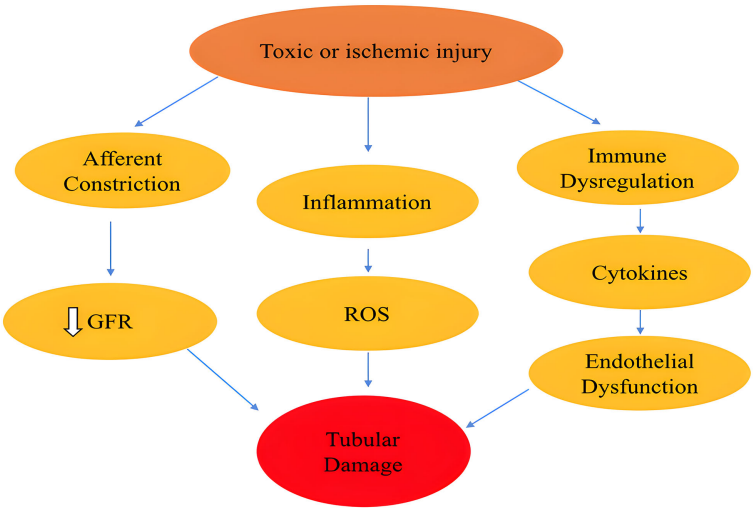

Figure 1. Toxic or ischemic injury causes tubular damage resulting in cell death via various mechanisms [1].

This review will examine the effects of cisplatin on kidney tissue and also the role of AVE0991, MAS receptor angiotensin (1-7) agonist, which may reduce cisplatin-induced AKI by promoting NO production.

2. Renal Renin Angiotensin System (RAS)

The Renin Angiotensin System (RAS) plays a crucial role in regulating blood pressure and electrolyte metabolism [19]. Several clinical studies indicate diverse involvement of RAS in various physiological and pathological processes such as cellular proliferation, inflammation and tissue fibrosis via several receptors [19]. Renin is released from the JGA cells into the blood, but some portions are filtered through glomeruli and reabsorbed by proximal tubules [3]. However synthesis of renin occurs in collecting ducts, and the release of renin is altered as regulatory production of cyclic Adenosine Monophosphate (cAMP) and cyclic Guanosine Monophosphate (cGMP) changes intracellular calcium and sodium levels [3]. Stimulation of cAMP via β-adrenergic activation releases renin from JGA cells triggering Sympathetic Nervous System (SNS), enabling prostanoids to stimulate secretion of renin via Prostaglandin E2 (EP2), Prostaglandin E4 (EP4) and Prostacyclin (IP) receptors [3]. NO and atrial natriuretic peptides are also involved in the release of renin via cGMP dependent pathway [3].

Endothelial NOS regulates vascular function and the production of NO can be enhanced by several stimuli such as [20] [21] sheer stress, Acetylcholine (ACh), bradykinin and histamine via specific receptors, increases intracellular Ca^{2+} concentration, which binds to Calmodulin (CaM) activating eNOS, that facilitates an electron flux from the reductase to the oxygenase domain of the enzyme to produce NO [20] [21]. Phosphorylation of eNOS via independent Ca^{2+} pathway is equally crucial because it binds to Ca^{2+} concentration and facilitates active electron flux causing reductase to transform into oxygenase domain to produce NO [21]. Endothelial derived NO is a vasodilator as it stimulates soluble Guany-

late Cyclase (sGC) in vascular smooth muscle cells, inducing cGMP, which primarily activates protein kinase G promoting reuptake of cytosolic Ca^{2+} into the Sarcoplasm Reticulum (SR) [21]. As the Ca^{2+} exits the cell, opening of Ca^{2+}-activated K^+ channels is identified [21]. Since cGMP is induced, decreased intracellular Ca^{2+} concentration inhibits Myosin Light Chain Kinase (MLCK) phosphorylation of myosin, resulting in smooth muscle cell relaxation as illustrated in **Figure 2** [21].

NO can also affect cellular activity independently via sGC, Stimulating sarcoplasmic/Endoplasmic Reticulum Ca^{2+} ATPase (SERCA) resulting in relaxation of smooth muscle cell [21]. Dysfunction in endothelium is not only due to decreased NO production by eNOS but a mix combination of variables, that decreases the availability of L-arginine and enzyme dysfunction resulting in increased degradation. Hence, there is a need to consider various signalling pathways and changes in bioavailability while examining the role of NO in vascular wall [21].

Release of renin is inhibited by an increase in intraglomerular hydrostatic pressure, solely depended on angiotensin converting enzyme-Ang-II Type 1 Receptors (AT_1R) [3]. Several clinical studies have indicated that a high sodium intake inhibits renin secretion and angiotensin-II inhibits renin release directly via short negative feedback loop AT_1R and indirectly via the suppression of prostanoids synthesis by Cyclo-Oxygenase 2 (COX2) [3] [10].

Angiotensinogen, when broken down by renin form Ang-I and ACE, consequently converting Ang-I into Ang-II [23], as illustrated in **Figure 3** [22] and cisplatin entry through ACE via AT_1R promotes sodium and water retention, oxidative stress, vasoconstriction, cell proliferation, inflammation and fibrosis [23] [24]. Activated AT_1R is phosphorylated and binds to arrestins, which mediate rapid receptor desensitisation and internalisation [24] [25]. AT_1R couples to various soluble and receptor tyrosine kinases such as p38-Mitogen Activated Protein Kinases (MAPK), Extracellular Regulated Kinases (ERK1, ERK2) and Jun N-terminal Kinases (JNK) functioned through jak-STAT pathway, which increases ROS [24] [26] [27]. The mechanism linking AT_1R and tyrosine kinase pathway may involve de novo synthesis of cytokine and Epidermal Growth Factor (EGF) ligands to initiate signalling [24] [26]. There are many isomers for EGF receptor, however, metalloproteinase-dependent shedding of EGF ligands are crucial in Ang-II-AT_1R mediated growth, hypertrophy and proliferation of cardiac, vascular and renal cells [3] [24] [26].

RAS has demonstrated to play a crucial role in the molecular mechanism of AKI, as elevated renin activity results in ischemia, thereby increasing Ang-II via AT_1R, which decreases the vasculature of the tubular region [19] leading to endothelial dysfunction causing vasoconstriction by decreased O_2 delivery [10]. Further promoting inflammatory neutrophils and monocytes causing tubular dysfunction and affecting GFR via tubulo-glomerular feedback [10]. These imbalances indicate the relationship between arterial pressure and vascular resistance, where outer medulla of kidney is usually affected [10]. Thus, lack of NO

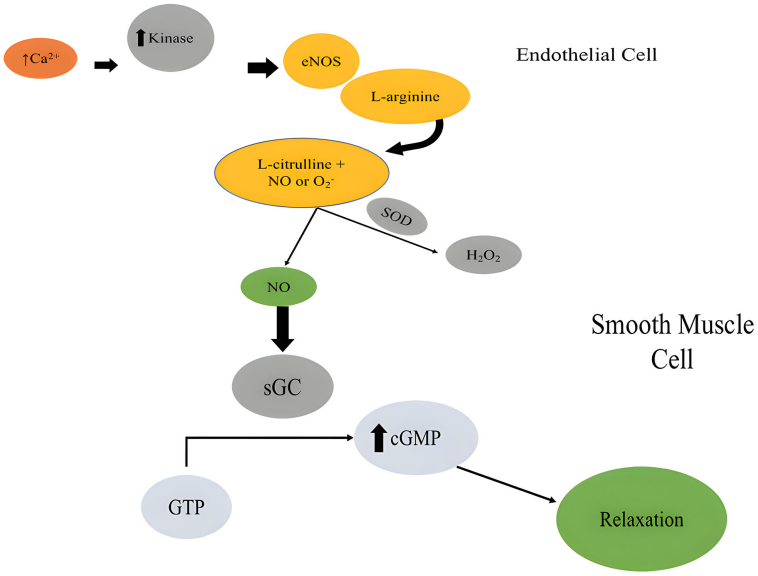

Figure 2. Increased intracellular Ca^{2+} via eNOS promotes relaxation in smooth muscle cells by eliciting NO production [20].

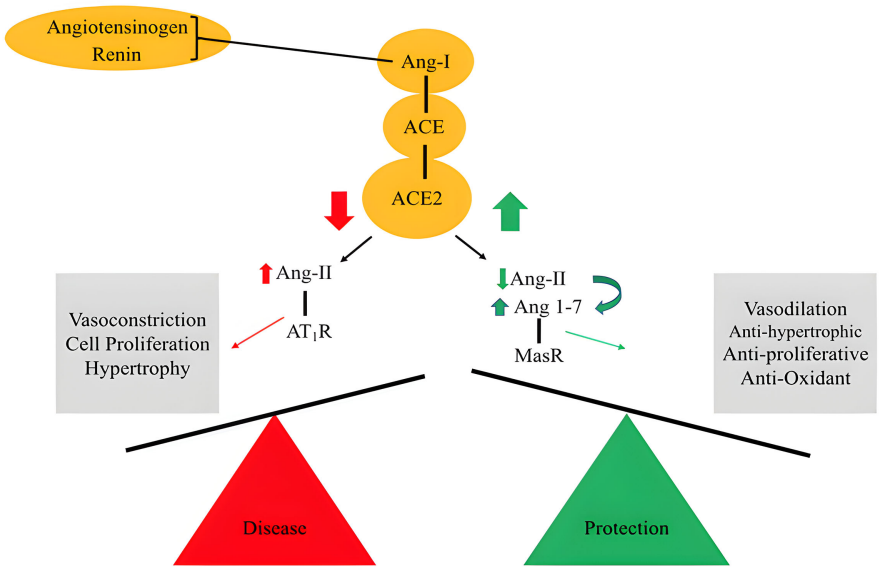

Figure 3. In kidney, angiotensinogen is broken down by ACE and renin forming ACE2 and Ang-II. An increase in Ang-II results in vasoconstriction whereas reduction of Ang-II elicits vasodilation [22].

production from blood vessels increasing vascular permeability, which causes tissue swelling [10].

The synthesis of inactive Ang-(1-9) from Ang-I and the catabolism of Ang-II to form Ang-(1-7), binding to MAS receptor (specific membrane receptor) as illustrated in **Figure 2** [22] [23], counteracts the effects of Ang-II, which is also the main functions of ACE2 [22] [23]. Ang-I is also a substrate of Neprilysin, cleaving to produce Ang-(1-7) [23]. ACE2 non classical RAS Ang-(1-7) counteracts with effects of the ACE-Ang-II-AT_1 axis [23] as specific functions include

natriuresis, reduced oxidative stress, vasodilation, anti-proliferative activity and diuresis by upregulating the concentrations of NO and prostaglandins [23] [28] [29] [30]. These processes aids in protecting the kidney from damage [23]. Ang-(1-7) is also metabolized by ACE, furthermore, accumulating evidences indicates that, ACE/ACE2 ratio regulates the production and accumulation of Ang-II and that ACE2 deficiencies leads to higher Ang-II concentrations [23] [31]. Balance between the effects of these two molecules affects the RAS and hence, the ACE/ACE2 ratio might represent the key parameter that is driving the regulation of RAS [23]. In healthy conditions, ACE2 activity increases along with ACE, whereas imbalances can develop under diseased conditions [23] [32] [33] [34]. In human kidneys, biopsies have indicated that hypertensive patients have higher ACE/ACE2 mRNA ratios [23] [34]. Batlle and colleagues suggested that ACE and ACE2 are regulated via different mechanisms and that ACE/ACE2 ratio could be misleading [35], however, Pohl and colleagues indicated ACE2 is expressed along the entire renal tubular segment, while ACE is only expressed in the brush membrane border of proximal tubule and that surface expression of ACE and ACE2 differed as a function of endocytosis [36]. Thereby indicating an increase in ACE/ACE2 ratio induced via the ACE-Ang-II-AT_1 axis leads to kidney damage, whereas renal ACE/ACE2 ratio are regulated via independent mechanisms [23].

3. Cisplatin-Induced Oxidative Stress

Cisplatin enters renal cells via passive and or facilitated mechanisms [37], either via CTR1 or Organic Cation Transporter 2 (OCT2), which are cell death promoting via MAPK, ROS, p53 or cytochrome p21 pathways [37] [38]. Generation of TNF-α productions in tubular cells, stimulates inflammatory response leading to tubular cell injury or cell death [37] [39]. Mitochondrial dysfunction, inhibition of lysosomal hydrolyse, along with phospholipid damage and increase in intracellular Ca^{2+} leads to toxic build up in proximal tubular cells, influenced directly by ROS and oxidative stress [11] [13] [40] [41]. By doing so cisplatin induces Acute Tubular Necrosis (ATN), which evidently causes oxidative stress and these conditions promotes ROS formations via two mechanisms [11] [39].

Firstly, cisplatin in its highly reactive form reacts with thiol-containing molecules including Glutathione (GSH), a well-recognised cellular antioxidant [11] [13] [39]. Inactivation or depletion of GSH and related antioxidants, generates endogenous ROS accumulation within the cells [11] [13] by activating MAPK, p53 and possibly p21, leading to renal tubular cell death [11] [13] [15] [42]. Consequently, ROS stimulates fibrotic process either directly or indirectly via enhanced inflammation [11] [13] [42].

Fibrosis and inflammation might further increase ROS formation or stimulate the production of cytokines and growth factors [11] [12] [13] [40].

Secondly, cisplatin may induce mitochondrial dysfunction and increase ROS production via its disrupted respiratory chain, reducing cellular respiration and

Adenosine Triphosphate (ATP) [11] [13] [43] [44]. ROS targets lipid components of membrane, causing peroxidation, denaturing of proteins and enzyme inactivation [11] [13] [40]. A variety of cellular enzyme systems such as NADPH oxidase, xanthine oxidase, uncoupled endothelial Nitric Oxide Synthase (e-NOS) and arachidonic acid metabolizing enzymes including cytochrome P450, lipoxygenase and COX generates ROS [16] [40] [45] [46].

Uncontrolled production of mitochondrial ROS activates the opening of the mitochondrial Permeability Transition Pore (PTP) as illustrated in **Figure 4** induces necrosis in microsomes via cytochrome P450 enzymes [11] [45] [47] [48], which activates Glucose-6-Phosphate Dehydrogenase (G6PD) and hexokinase causing an increase in free radicals and depletion of antioxidants such as Superoxide Dismutase (SOD), glutathione peroxidase and catalase [40] [47]. G6PD stimulates an increase in intracellular Ca^{2+} levels, activating NADPH oxidase, stimulating ROS production by damaged mitochondria [40] [47] [49] [50] [51] [52].

Increase in Reactive Nitrogen Species (RNS), decreases cellular defences by oxidising thiol pools, by inducing structure and function of proteins and lipid peroxidation [40].

Absorption of various plasma proteins and molecules by tubular cells may cause secretion of chemotactic and inflammatory mediators in the interstitium [11] [53]. Nuclear Factor-kappa B (NF-kB) regulates DNA transcriptase and upregulates inflammatory mediators such as Damage-Associated Molecular Patterns (DAMPs) through TLR4 [11] [53]. Manganese Superoxide Dismutase (Mn-SOD), primary mitochondrial antioxidant enzyme, essential for maintaining normal cell functions [45] decreases post-cisplatin administration, which causes cell injury, indicating poor antioxidant response for cell survival [40] [45] [54].

TNF-α is dependent on ROS and activates NF-kB via p38-MAPK pathway [40] [55]. It is mediated by tumour necrosis factor receptors TNFR1 and TNFR2 via p55 and p75 respectively [40] [55]. Cisplatin administration also increases inflammatory cytokines and chemokines such as IL-1β, IL-18, IL-6 and CX3CL1 mediated via TNFR2 [40] [49] [55]-[62]. Moreover, studies reports that cisplatin induced apoptosis in p53 deficient renal cells is via the intrinsic mitochondrial pathway resulting in cell death as p53 is observed to cause nephrotoxicity through the administration of cisplatin by inducing tubular cell apoptosis as a dependent mechanism. However, independent mechanisms may also induce apoptosis by activating BAX and releasing cytochrome c, resulting in mitochondrial damage [45] [59] [61] [63] [64].

4. Endoplasmic Reticular Stress (ERS)

Endoplasmic Reticulum (ER) performs several important functions including post-translation modification, folding, and the assembly of newly synthesised secretory and cell membrane proteins and its proper function is essential for cell survival [65] [66]. Cells tentatively functions by responding to increased ERS via

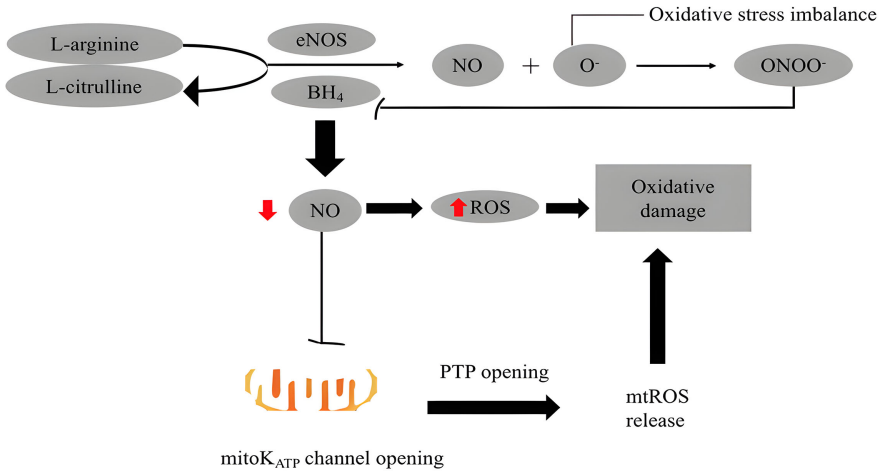

Figure 4. Decreased NO production via eNOS increases ROS resulting in oxidative stress causes mitochondrial damage [47].

Unfolded Protein Response (UPR), which aims to generate more homeostatic environment, however, can also promote cell death, if ERS is prolonged or severe [67] [68]. When ER pathway is interrupted due to an increase in oxidative stress, decreases ATP, thereby implicating inflammation in its pathogenesis [69]. ERS is a form of cellular stress caused by excessive protein accumulation at the ER [69]. Three major ERS pathways are by the accumulation of Pancreatic ER Kinase (PERK), eukaryotic initiation factor 2α (eIF2α); or Inositol-Requiring Enzyme 1 (IRE1), X-box binding protein 1 (XBP1); or by Activating Transcription Factor (ATF6) such as C/EBP Homologous Protein (CHOP), resulting in growth arrest via the activation of c-jun-NH2-terminal kinase signalling causing increased production of Transforming Growth Factor-β1 (TGF-β1), which enhances proliferation, apoptosis and DNA damage [44] [65] [66].

CHOP induces ER stress resulting in apoptosis [65] [67] [70]. Therefore, unattended ERS could result in cell death, inflammation and excessive oxidant production [69] [71]. Even though, ERS could be a result of atherosclerosis, diabetes and neurodegenerative diseases; AKI generated via hypoxia, free radical generation and decreased amounts of glucose and amino acids are few of the causes of ERS [69].

Cisplatin induces caspase 3 activation, involving Ca^{2+} and Ca^{2+} dependent calpain protease [73], which inactivates calpain-dependent ER-specific caspase 12 and upregulates Heat Shock Proteins (HSPs) subfamily; composed of four isomers HSC70-inducible isoform, HSP72, mHSP75 and GRP78 enables to restore cellular homeostasis [21] [74]. Glucose Regulated Protein 78 (GRP78) upregulation are due to the administration of platinum drugs [73] [75]. GRP78 acts in accordance with Ca^{2+} dependent pathway, which acts as the main regulator of ER function [67] [73]. Cisplatin can also induce apoptosis in enucleated mouse kidney proximal tubular cells as indicated by Yu *et al.* 2007 causing cell death via cytoplasmic signalling, which acts independently to nucleus but regulated by cyclin-dependent kinase 2 (cdk2)-E2F1 pathway as the cytoplasmic lo-

cations are in ER and Golgi complex as illustrated in **Figure 5** [72] [73] [75] [76]. Evidently, upregulation of GRP78 and CHOP via caspase 4, found in damaged tubular cells post toxic kidney injury indicates that cisplatin induces apoptosis through ERS pathway [73] [77] [78]. HSP72 and GRP78 are expressed in response to cellular stress and its induction can be as great as 15% of the total protein [74]. Studies on rat showed proteinuria in early stages, and further examinations showed accumulation of transgene substances in the ER inducing ERS and subsequent kidney injury [67]. Given that HSP72, GRP78 and CHOP are induced in renal tubules during AKI and that proximal detachment is projected to the urinary space; levels of these proteins can serve as a possible early biomarker to detect cisplatin-induced AKI and will be studied in this thesis [65] [66] [70] [74] [79] [80].

5. Cisplatin-Induced Nephrotoxicity

Cisplatin induces direct tubular epithelial cell toxicity as well as reduction in renal blood flow as a result of endothelial dysfunction and vasoconstriction [24] [27] [81]. Many cancer patients show a decrease in appetite, lowering blood pressure, consequently deteriorates and form cisplatin-induced nephrotoxicity despite routine administration of Intravenous (IV) fluids [50] [81] [82]. Patients with low blood pressure are expected to have delayed urinary excretion of cisplatin due to decrease in GFR [8] [81] [83]. Komaki reported that, patients are at high risk of AKI during intercurrent illness such as volume depletion because, the contraction of efferent arterioles is inhibited due to oxidative stress [81] [84]. RAS can also be activated by volume depletion from sodium wasting or polyuria and vascular contractions post-cisplatin administration [81]. Increase in plasma renin activity and plasma aldosterone concentrations were also identified with cisplatin administration [81] [85] [86]. Malignant transformations are associated with at least six acquired, functional capabilities: sustained angiogenesis, evasion of apoptosis, self-sufficiency in growth signals, insensitivity to anti-growth signals, tissue invasion and metastasis and limitless replicative potential [24] [37]. RAS regulates all of these capabilities; however, most prominent effects are on angiogenesis, invasion, pro-survival and proliferation [24]. Much of the increased metastasis and invasion that is associated with an activated RAS is likely to be a direct consequence of angiogenesis [24].

6. Current Therapeutic Strategies

Hydration, electrolyte replacement with saline and avoiding other nephrotoxic drugs has been the most supportive measures in reducing severe AKI [39]. GFR must be assessed routinely as well as hydration, which should have commenced prior to the treatment and continued for at least 3 days post treatment [39]. Adequacy for hydration solely depends on urine output, which needs to be maintained 3 - 4 L/day [39]. Magnesium (Mg^{2+}) also has been reported to decrease in cisplatin administration and several patients are advised to routinely

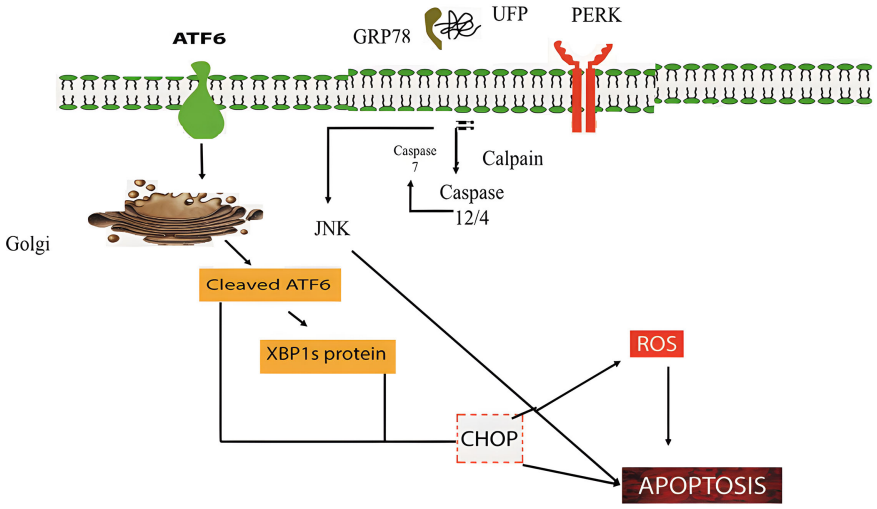

Figure 5. ER stress induces UPR resulting in apoptosis through various mechanisms [72].

assess their serum Mg^{2+} and needs to be replaced adequately [39]. However, therapeutic strategies are required to eliminate AKI completely and several researchers have tried to implement many experimental studies on animals mostly for the prevention of cisplatin-induced AKI [39] because cisplatin based chemotherapy induces nephrotoxicity in approximately 25% - 30% of patients treated for solid cancers like small cell lung carcinoma and prostate cancer [87]. Accumulative research studies indicate that autophagy from cytoplasm, organelles or membrane engulfed by double-membrane structure targeted for destruction in lysosomes, could act as a protective measure against cisplatin-induced cell death; and activation of mTOR signalling may regulate autophagy that affects tubular cell death via various mechanisms [87].

In a recent study, metformin was found as a potential protective agent by targeting cisplatin-induced tubular cell death in cultured NRK-52E cells and AKI in mice [87]. It functions by stimulating Adenosine Monophosphate Kinase alpha (AMPKα) and thus causing induction of autophagy [87]. However, this study was interesting, there was also a down regulation of AMPKα phosphorylation that led to diminished metformin promoted cell survival [87] and this study was done on cultured cell whereas it didn't express the effects on in-vivo mice model [87].

ACE2 upregulation as a treatment was based on reduced levels of ACE2 in patients with renal disease and in experimental models [28] [88] [89]. Studies in mice showed significant improvement in kidney function by lowering urinary albumin excretion rate and improved creatinine clearance [27] [28]. This improvement was associated with less severe renal fibrosis, which attributes to inhibition of excess canonical and non-canonical TGF-β signaling by ACE2 [28]. Pro-inflammatory cytokine expression and macrophage infiltration were attenuated by renal ACE2 associated with a decrease in MAPK signaling [28]. RAS activation has an important role in the pathological processes that leads to kidney injury by regulating body fluid balance and blood pressure, and inhibition of

this pathway improves renal outcomes [28] [90]. Expression of ACE2 is altered in human kidney disease [29]. Neo-expression of ACE2 is found in glomerular and peritubular capillary endothelium in various renal disorders and in renal transplants [29]. Further studies should elucidate the pathophysiological significance of these changes in ACE2 expression and explore its role as a possible protective mechanism [29]. The significance of reduction in renal ACE coupled with an increase in ACE2 proteins needs to be clarified, but it seems logical to propose such combination could attenuate Ang-II and could exert protective effect against necrosis at early stages of AKI and the increase in ACE2 should further prevent Ang-II accumulation by favoring conversion of Ang-I to Ang-(1-9) and Ang-II to Ang-(1-7) [30] [31] [91] [92].

There were several studies that linked many mechanisms that could reduce inflammation and tumour cell death that results in necrosis; however, there was not enough studies conducted on endothelial cell pathway, which could potentially increase NO production, which could cause vasodilation via cGMP pathway. Therefore, the study proposal of using AVE0991, of Ang-(1-7) mimetic could prove as a protective agent against cisplatin-induced AKI.

7. Relationship between AVE0991 and RAS

AVE0991 (5-formyl-4-methoxy-2-phenyl-1[[4-[2-ethylaminocarbonylsulfonamido) -5-isobutyl-3-thienyl]-phenyl]-methyl]-imidazole [93] [94], is a derivative of imidazole [93] and is soluble in alkaline water solutions [93]. AVE0991 is an orally active and physiologically well tolerated compound, which mimics the action of Ang-(1-7) in several tissues [93] [95]. It is also reported that, AVE0991 has a longer biological half-life and evidently more stable compared to Ang-(1-7) [96]. AVE0991 helps to release Nitric Oxide (NO) and to a lesser extent superoxide (O_2^-) in endothelial cells [93] and it is also capable of releasing 5 times as much NO as Ang-(1-7) [93] [94]. Generation of O_2^- and consequent fast reactions with O_2^- and NO forms peroxy-nitrite and other cytotoxic radicals, while the release of NO associated with low concomitant production of O_2^- might contribute to the preservation of the vasculature [93] [97] [98].

Studies on AVE0991 have shown beneficial effects in atherosclerosis and hypertension [21]. Prolonged treatment using Ang-(1-7) mimetic has led to an increase in glucose uptake and insulin resistance in rats [21].

Pinheiro reported that AVE0991 increases water reabsorption, along with a decrease in urinary volume in control mice with a rise in urine osmolarity [101]. Ang-(1-7) increases osmotic water permeability in distal nephron [101]. It is also reported of inducing concentration-dependent vasodilator effects on aortic rings and this mechanism was evidently present in intact endothelium [93] by stimulating endothelial function facilitated by release of NO [93]. Another study reported that AVE0991 attenuated inflammatory effects on ACE2-Ang-(1-7) MAS axis by attenuating an elevation of sCr, decreasing neutrophil influx in both kidney and lungs [102]. Decrease in neutrophil accumulation reduced chemokine production as identified with low circulating levels of chemokine in AVE

treated animals [102]. Administration of AVE0991 improves renal damage by significantly decreasing index of renal injury on glomerular and tubular regions [102] by attenuating glomerular sclerosis in experimental glomerulonephritis and over-expression of ACE2 in diabetic nephropathy may also be due to an increase in Ang-(1-7) levels [102]. In correlation with MAS receptor, mRNA levels are increased whereas AVE0991 may exhibit beneficial effects through various mechanisms by interacting with ACE2 by inhibiting renal activities of this enzyme [102]. An increase in MAS receptor, could represent a compensatory response to renal damage as compared to endogenous regulatory mechanisms [102]. Many studies have indicated the potentiality of MAS receptor and putative drug AVE0991 is found to stimulate ACE2-Ang-(1-7) MAS axis by promoting anti-inflammatory responses as illustrated in **Figure 6** [102].

Yuedong and colleagues indicated the potentiality of AVE0991 to reduce oxidative stress by demonstrating it on aortic banding mice [103]. Their results indicated that, vehicle treated mice had a higher expression of NADPH Oxidase 2 (NOX2) and NOX4 proteins, compared with sham-operated group [103]. Elevation in NADPH oxidase generates endothelial ROS that leads to proliferation [104]. When, AVE0991 was administered, it was found to supress the increase of NOX2 and NOX4 mRNA and protein levels indicating AVE0991 reduces oxidative stress in mice [103]. By reducing oxidative stress, indicates fewer ROS in endothelial cell, which may reduce ERS and fewer inflammatory responses that could preserve the vascular tone of the kidney tissues, as illustrated in **Figure 6**.

8. Research Rationale

Treatment with AVE0991 is found to reduce inflammation, and glomerular and tubulointerstitial damage in ischemic/reperfusion AKI-induced animals (via occlusion of the renal pedicle), thereby reducing acute and chronic kidney injury,

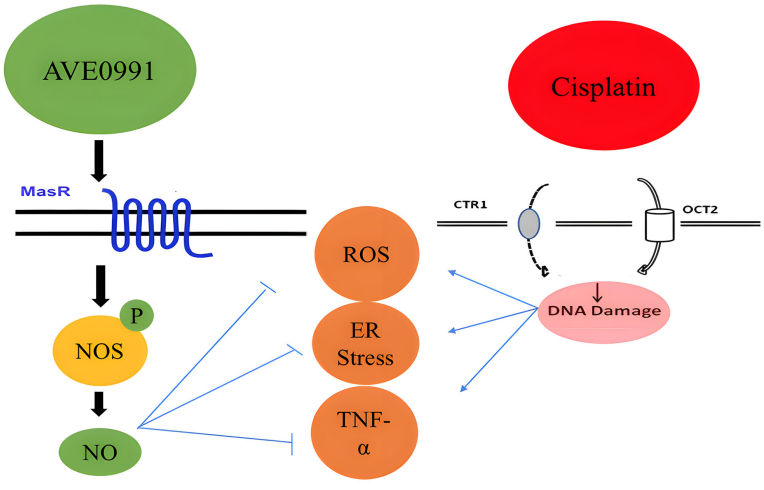

Figure 6. AVE0991 stimulates the MASR to elicit the production of NO resulting in vasodilation [99] [100], whereas cisplatin enters renal epithelial cells via the OCT2 or CTR1, induces epithelial cell death by causing DNA damage, hence, increasing the production of ROS, ER stress and TNF-α resulting in vasoconstriction [46].

hence, it is proposed that AVE0991 via stimulation of the ACE2-Ang-(1-7) MAS axis on kidney tissues can counteract the effects of cisplatin-induced AKI (as illustrated in **Figure 6**) such as anti-oxidative stress, decreased production of ROS and decreased inflammatory responses and may preserve the vasculature of kidney tissues, which may restore reno-protective mechanisms [46] [93] [96] [105].

9. Conclusion

Cisplatin is the most widely used drug in treating cancers, but can also cause many side effects such as AKI. Although this review consolidates many research studies and current therapies by illustrating the mechanisms, it showcases the pathway to reduce cisplatin-induced AKI by understanding the role of AVE0991 in decreasing ROS and inflammatory responses in preserving the kidney tissues, which may counteract the effects and provide better reno-protective mechanisms.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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