Lipid mediators of inflammation in obesity-related glomerulopathy

Eileen Nolan¹,²,³, Yvonne M. O’Meara²,³ and Catherine Godson¹,²

Correspondence and offprint requests to: Eileen Nolan;
E-mail: eileen.nolan.3@ucdconnect.ie

The interplay between chronic kidney disease (CKD) and obesity represents the convergence of two of the most common contemporary clinical issues, and is of particular interest and significance in the context of the burden presented by each at present, and the dismal projections associated with both of these conditions for the future. That obesity leads to CKD through its association with other risks, such as hypertension, type 2 diabetes mellitus and atherosclerosis, is well established; however, it is likely that obesity itself is an independent risk factor for the development of CKD. The

¹Diabetes Complications Research Centre, UCD Conway Institute of Biomolecular and Biomedical Research, Dublin, Ireland,
²School of Medicine and Medical Sciences, University College Dublin, Dublin, Ireland and
³Mater Misericordiae University Hospital, Dublin, Ireland

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aetiology of this obesity-related glomerulopathy (ORG) is not clear, but it appears to be strongly influenced by chronic inflammation, manifest as a disturbance of the balance between pro-inflammatory and pro-resolving lipid mediators, adipokines and mononuclear cells. This review examines the association between obesity and CKD, the role of inflammation therein, and the potential for pro-resolving lipid mediators to restore homoeostasis and offer therapeutic potential in ORG.

**INTRODUCTION**

A report in 1974 of nephrotic syndrome in four massively obese (ob) patients who sustained a reduction in proteinuria during dietary weight loss, and a biopsy finding in two of those patients of mesangial glomerulopathy [1], prompted a concerted effort to investigate a potential relationship between obesity and chronic kidney disease (CKD). Since then, numerous epidemiological studies have suggested a role for obesity as an independent risk factor for both the development and progression of CKD [2, 3]. The association between obesity and CKD has been demonstrated in multiple ethnicities [4–6], with no significant difference found between genders [7]. Furthermore, it was found that the incidence of biopsy-proven obesity-related glomerulopathy (ORG) increased 10-fold from the period 1986 to 2000 (in keeping with the increasing incidence of obesity) [8], raising concern for an emerging epidemic of obesity-related kidney disease affecting not only adults, but also, alarmingly, the paediatric population [9].

The predominant histological findings on renal biopsy in ORG are glomerulomegaly and secondary focal segmental glomerulosclerosis (FSGS) [7, 10]. The earliest clinical indication of ORG is microalbuminuria, which is detectable in apparently otherwise healthy subjects who are overweight or ob [11], progressing to subnephrotic- or nephrotic range proteinuria and renal insufficiency in more advanced disease [8]. Although insufficient data are available at present, it appears that clinically, ORG may be distinguishable from idiopathic FSGS by its lower incidence of nephrotic syndrome, more benign course, and slower progression of proteinuria and renal failure [8]. The pathophysiology of ORG is not certain, but potential mechanisms include altered renal haemodynamics (an increase in BMI leads to hyperfiltration and glomerular hypertrophy, a notion that is reinforced by the finding that glomerulomegaly parallels increasing weight) [11], insulin resistance, hyperlipidaemia, activation of the renin–angiotensin–aldosterone system, oxidative stress, and as we will explore in this review, inflammation [8].

**INFLAMMATION IN OBESITY-RELATED GLOMERULOPATHY**

Inflammation is a process necessary to the maintenance of health, and is essential in the defence against infection and tissue injury [12]. The chronic low-grade inflammation which is a feature of obesity, CKD, and many other diseases [13], however, is a maladaptive process, and may represent a failure of the normal resolution of inflammation [14]. Adipose tissue is an active endocrine organ which, in addition to its roles as a reservoir of lipids and a layer of thermal insulation, is capable of producing a range of hormones and signalling peptides, which are together referred to as ‘adipokines’, and include leptin, adiponectin, chemerin, tumour necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), interleukin-10 (IL-10), monocye chemoattractant protein-1 (MCP-1), plasminogen activator inhibitor-1 and resistin. Adipokines are active in regulating appetite and satiety, glucose and lipid metabolism, blood pressure homoeostasis and inflammation [15]. In obesity, adipose tissue becomes the site of a chronic low-grade inflammatory process which favours the production of pro-inflammatory adipokines. This inflammatory response is aggravated by the recruitment of macrophages which, in concert with adipocytes, perpetuate a cycle of inflammation in the obesity adipose tissue [15], leading to local tissue destruction and fibrosis, and both local and remote insulin resistance and inflammation [16].

**Leptin**

Leptin is coded by the ob gene and is produced mainly by white adipose tissue. It binds to receptors (obRb) in the hypothalamus and acts as a regulator of energy balance [17]. Obesity, however, is a hyperleptinaemic and leptin-resistant state in which leptin production correlates with increasing adipocyte size and BMI. The leptin resistance of obesity is injurious to several peripheral tissues, including the kidney [8]. In humans, higher plasma leptin levels are associated with CKD [18], whereas in rats, it has been demonstrated that leptin causes glomerulosclerosis [19]. Leptin is associated with renal injury through both direct and indirect effects on the kidney [8]. Leptin directly influences kidney function by binding to specific receptors in the glomerulus (both obRa and obRb are present but the exact role of each is not established), leading to up-regulation of pro-fibrotic transforming growth factor-beta (TGF-β) responses and increased production of components of extracellular matrix [17]. Culture of mouse mesangial cells in the presence of leptin leads to increased production of type I collagen mRNA and protein and an increase in mRNA levels of TGF-β II receptors, although it does not increase the production of TGF-β1 itself. The result is that mesangial cells are sensitized to physiological levels of TGF-β1, with exposure to a combination of TGF-β1 and leptin leading to greater production of type I collagen than either TGF-β1 or leptin alone. In cultured endothelial cells, leptin leads to cell proliferation and stimulates the synthesis of type IV collagen. Leptin also induces mRNA expression and protein secretion of TGF-β1 [17]. In combination, these findings suggest that leptin promotes renal fibrosis in a paracrine fashion, through a combination of increased TGF-β1 production by endothelial cells, and up-regulation of TGF-β receptor II in the mesangium, resulting in the synthesis of type I and type IV collagen (Figure 1) [8, 17, 20]. The pro-fibrotic effects of leptin have also been demonstrated in vivo, with a leptin infusion into normal rats leading to an increase in glomerular TGF-β1 expression and cell proliferation and an increase in glomerular
Adiponectin

Adiponectin is an anti-inflammatory and insulin-sensitizing adipokine encoded by the adipose most abundant gene transcript 1, and produced by adipocytes. Adiponectin signals through the receptors AdipoR1 and AdipoR2 [8], and acts to stimulate secretion of IL-10, block NF-κB activation, inhibit the production of TNF-α and IL-6 and promote insulin sensitivity in liver, adipose tissue and skeletal muscle [15]. Serum adiponectin levels are reduced in ob animals and humans, and it appears that this may be significant in the development of kidney disease (Figure 1). A study in ob individuals without diabetes demonstrated a significant negative association between serum adiponectin levels and low-grade albuminuria, which is independent of age, gender, blood pressure and glucose level [21].

The protective effects of adiponectin in the kidney appear to be related to podocyte function, as seen in adiponectin knockout mice (Ad−/−), which have increased albuminuria and podocyte foot process fusion; treatment of these animals with exogenous adiponectin appears to rescue kidney function, normalize albumin excretion and improve podocyte foot process morphology. Cultured podocytes exposed to adiponectin show increased AMPK activity with reduced podocyte permeability to albumin and improved podocyte function (demonstrated by zona occludens-1 translocation to the membrane) [22], suggesting that adiponectin may be directly protective towards the kidney. The role of adiponectin in podocyte injury has also been investigated in POD-ATTAC mice in which podocyte-specific apoptosis is induced, leading to significant kidney damage with foot process effacement, mesangial expansion and glomerulosclerosis. These mice, when crossed with mice lacking adiponectin, develop irreversible albuminuria and renal failure, whereas those crossed with mice overexpressing adiponectin recover their renal function rapidly and exhibit less interstitial fibrosis, suggesting that adiponectin is renoprotective after podocyte injury [23].

Recently, it has been demonstrated that the renoprotective properties associated with adiponectin may be mediated through inhibition of NF-κB signalling. Treatment of mice with celastrol, an NF-κB inhibitor, leads to increased serum adiponectin levels, decreased obesity, decreased creatinine and urinary albumin excretion, reduced mesangial expansion and expression of type IV collagen and reduced TGF-β1 activity in the kidney. Culture of a mouse podocyte cell line with celastrol, an NF-κB inhibitor, leads to increased serum adiponectin levels and decreased obesity, decreased creatinine, decreased urinary albumin excretion, reduced mesangial expansion and expression of type IV collagen and reduced TGF-β1 activity in the kidney [24].

Mononuclear cells

Both circulating monocytes and their tissue derivatives, macrophages, are fundamental cells in inflammation and homoeostasis. Macrophages are classified as having either a pro-inflammatory M1 or an anti-inflammatory M2 phenotype (with several M2 subsets identified) [25]. M1 macrophages generate TNF-α, IL-1β, reactive oxygen species and nitric oxide, and are active in the initiation of inflammation, whereas M2 macrophages produce anti-inflammatory IL-10, and are active in the resolution of inflammation and in tissue healing and repair [25]. However, as is seen in several chronic conditions, an imbalance may occur between M1 and M2 macrophages, leading to the development of maladaptive chronic inflammation [12]. In ob adipose tissue, there is an increase in pro-inflammatory M1 macrophages and a reduction in M2 cells, contributing to a chronic pro-inflammatory state and a failure of inflammatory resolution [16]. Whether the increase
in M1 macrophages results from phenotypic switching of resident cells or recruitment of inflammatory macrophages from the circulation is not certain. However, a study carried out in mice has suggested that the latter may be the case. In adipose tissue from lean mice, the resident macrophages are of an M2 phenotype and localize to the interstitial spaces between adipocytes. In diet-induced obesity, these same macrophages remain in the interstitial spaces, whereas recruited macrophages, which are of an M1 phenotype, localize in clusters around necrotic adipocytes [26]. This is interesting in the context of the phenotypic classification of monocytes, which are the circulating precursors of tissue macrophages. Monocytes are found in three subsets, namely, classical, intermediate and non-classical, with this latter population considered to be pro-inflammatory [27]. It is thought that a developmental progression occurs from a ‘resting’ or classical phenotype, through intermediate, and towards an ‘activated’ or pro-inflammatory non-classical phenotype, and that distinct monocyte subsets may give rise to different macrophage subsets in the tissues [28]. Given that obesity is associated with an expansion in the circulation of the pro-inflammatory non-classical subset of monocytes [29], it is possible that this contributes to the increase in M1 macrophage infiltration seen in ob adipose tissue, and to the imbalance between mononuclear cell subsets, which is an important factor in the cycle of adipose tissue inflammation (Figure 2).

**LIPID MEDIATORS OF INFLAMMATION**

Mediators of inflammation are substances which co-ordinate the component events of inflammation, and are categorized into seven groups according to their biochemical properties: vasoactive amines, vasoactive peptides, fragments of complement components, lipid mediators, cytokines, chemokines and proteolytic enzymes [12]. Lipid mediators are bioactive lipids and are classified on the basis of structure (Table 1) [30]. The focus of this review is polyunsaturated fatty acid (PUFA)-derived lipid mediators, which originate from either ω-3-PUFA or ω-6-PUFA. PUFA are obtained from dietary sources, such as fish oil (ω-3-PUFA) and vegetable oil (ω-6-PUFA), and are inserted into membrane phospholipids, from which they are mobilized when required. Of the three major ω-3-PUFA obtained from diet, two [docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA)] are involved in lipid mediator generation, while the role of the third, alpha-linolenic acid is not certain [31]. ω-3-PUFA give rise to groups of lipid mediators known as resolvins, protectins and maresins [32, 33]. The dietary ω-6-PUFA, linoleic acid, is converted to arachidonic acid (AA) which can be mobilized from membrane phospholipid by the action of the enzyme phospholipase A2 [34, 35]. The lipid mediators generated from ω-6-PUFA are prostaglandins, thromboxanes, leukotrienes and lipoxins [35]. Functionally, PUFA-derived lipid mediators are either inflammatory (prostaglandins, thromboxanes and leukotrienes), or resolving (lipoxins, resolvins, protectins and maresins) (Figure 3) [33, 36].

Lipid mediators are generated by transcellular synthesis, and subsequently exported extracellularly to transmit their signals to target cells, through binding to class 1 G protein-coupled receptors [37]. Lipid mediators, as a group, are distinguished by their production locally to their site of action, and

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**Table 1. Classification of lipid mediators of inflammation with selected mediators listed in each class**

<table>
<thead>
<tr>
<th>Class</th>
<th>Mediators</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatty acids</td>
<td>Derived from ω-3-fatty acids: Resolvins, Protectins, Maresins</td>
</tr>
<tr>
<td></td>
<td>Derived from ω-6-fatty acids: Lipoxins, Prostaglandins, Thromboxanes, Leukotrienes, Isoprostanes</td>
</tr>
<tr>
<td>(Lyso)Phospholipids</td>
<td>Platelet-activating factor, Oxidized phospholipids, Psychosine, Lysophosphatidic acid, Sphingosine-1-phosphate</td>
</tr>
<tr>
<td>Others</td>
<td>2-Arachidonyl-glycerol, Arachidonyl-ethanolamide, Ceramide, Ceramide 1-phosphate</td>
</tr>
</tbody>
</table>

**FIGURE 2:** Mononuclear cells contribute to adipose tissue inflammation. Circulating monocytes are activated to a pro-inflammatory non-classical phenotype in obesity. Monocytes infiltrate adipose tissue and transform into macrophages. Adipose tissue inflammation is characterized by an increase in pro-inflammatory M1, and a reduction in pro-resolving M2 macrophages, resulting in a maladaptive chronic inflammatory process. This leads to an imbalance in adipokine production, with increased pro-inflammatory adipokines such as leptin, TNF-α (tumour necrosis factor-alpha), IL-6 (interleukin-6) and IL-1β (interleukin-1-beta), and decreased levels of anti-inflammatory adipokines, such as IL-10 (interleukin-10) and adiponectin.
by their short half-life (seconds to minutes) and subsequent rapid degradation [30]. Lipid mediators can be regarded as autocoids which are generally produced ‘on demand’, although occasionally, precursors may be produced and stored to facilitate rapid mobilization when required [38]. PUFA-derived lipid mediators are generated in response to extracellular stimuli [37]; however, it is interesting to note that lipoxins, resolvins and protectins are also produced in response to exogenous aspirin administration [38], and that dietary supplementation with Ω-3-PUFA has proved beneficial in a range of experimental and clinical inflammatory conditions [31]. This suggests that some of the documented pro-resolving properties of aspirin and Ω-3-PUFA may be attributable to their promotion of pro-resolving lipid mediators in vivo.

The capacity of the PUFA family to generate an extensive repertoire of mediators from a very few precursors is one of its most remarkable features, and affords it considerable versatility in directing the process of inflammation, as the same precursor molecule frequently has the capacity to produce pathway endpoints with completely opposite functions. For example, the precursor molecule AA can give rise to pro-inflammatory leukotrienes or prostaglandins or, via different synthetic pathways, to pro-resolving lipoxins [35]. In this way, lipid mediators are capable of controlling both the initiation and the resolution of inflammation [39]. During the initial phase of inflammation, the release of pro-inflammatory mediators leads to vasodilatation (prostaglandin E2), platelet activation (thromboxane A2) and neutrophil chemotaxis (leukotriene B4) to the site of inflammation [32]. At the height of the inflammatory response, the production of pro-resolving molecules begins, which then signal to reduce vascular permeability, reduce neutrophil activation and stimulate macrophages to phagocytose apoptotic neutrophils and clear inflammatory debris [40], restoring homeostasis.

A crucial strategy employed by the PUFA family of lipid mediators is ‘class switching’ from pro-inflammatory to pro-resolving agents. In the above scenario, neutrophils which have entered the tissue to participate in the inflammatory response promote a switching of AA metabolism away from production of pro-inflammatory prostaglandins and leukotrienes, and towards pro-resolving lipoxins, which initiate the termination of inflammation. There is co-incident production of resolvins and protectins, which also promote the resolution of inflammation. Involvement of Ω-3-PUFA in ‘class switching’ has also been demonstrated in macrophages, with both EPA and DHA switching the metabolism of AA away from cyclooxygenase (COX) pathways (decreased COX-1) and towards lipoxygenase (LO) pathways (increased LO-5), leading to a reduction in pro-inflammatory mediators such as thromboxane A2, leukotriene B4 and prostaglandin E2 [31]. Through its co-ordination of the process of inflammation, therefore, the lipid mediator family is essential to the maintenance of tissue homeostasis and the promotion of inflammatory resolution.

**LIPID MEDIATORS IN ADIPOSE INFLAMMATION**

Ob adipose tissue is characterized by chronic low-grade inflammation, in which deranged lipid mediator profiles, disordered adipokine production and altered mononuclear cell phenotype feature prominently. Administration of pro-resolving lipid mediators, however, has been shown to promote the resolution of adipose tissue inflammation, with beneficial effects on adipokine and mononuclear cell profiles. The presence of receptors (FPR2, ChemR23 and GPR32) for pro-resolving mediators has been demonstrated in adipose tissue, suggesting that it is a viable target for these agents [41].

**Ω-3-PUFA-derived lipid mediators**

Obesity adversely affects the synthesis in adipose tissue of pro-resolving lipid mediators, and is associated with an impaired capacity to resolve an acute inflammatory response [42], suggesting that obesity impairs the resolution phase of inflammation. In the adipose tissue of ob mice, protectin D1 (PD1) [41-43] and resolvin D1 (RvD1) [41] are reduced or absent, as is their precursor 17-hydroxydocosahexaenoic acid (17-HDHA) [41, 43]. The resolvin E series precursor, 18-hydroxyeicosapentaenoic acid (18-HEPE) and a marker of the maresin synthetic pathway, 14-HDHA, are also decreased in ob adipose tissue [41]. Meanwhile, there is up-regulation of the enzyme 15-hydroxyoxoprostaglandin dehydrogenase/eicosanoid oxidoreductase (15-PGDH/EOR) [41], which is active in lipid mediator degradation, suggesting that both impaired synthesis and accelerated degradation of pro-resolving lipid mediators contribute to failure of resolution of adipose tissue inflammation. Treatment with dietary supplementation of Ω-3-PUFA (with or without calorie restriction), however, restores the endogenous biosynthesis of pro-resolving lipid mediators, promoting the formation in ob adipose tissue of PD1 (or PD isomers such as protectin DX) [44, 45], RvD1 and 17-HDHA [45], while simultaneously decreasing the production of inflammatory prostaglandin E2 and thromboxane B2 [45], suggesting that the impairment of inflammatory resolution seen in obesity may be remediable by dietary Ω-3-PUFA.
supplementation, and consequent adipose tissue pro-resolving lipid mediator generation.

Restoration of pro-resolving lipid mediators has beneficial effects on adipose inflammation and macrophage activity. Obesity is associated with infiltration of adipose tissue by macrophages [42, 46], which are predominantly of an M1 pro-inflammatory phenotype [47, 48]. Dietary supplementation with Ω-3-PUFA leads to a decrease in macrophage infiltration [44, 46], while exogenous administration of RvD1 [47] or DHA [48] leads to reduced inflammatory M1 macrophages and increased anti-inflammatory M2 cells in adipose tissue, the functional significance of which is a down-regulation of pro-inflammatory cytokines (TNF-α, IL-6 and MCP-1) and an up-regulation of anti-inflammatory cytokines such as IL-10 [48]. Interestingly, it appears that in vitro, exposure of peritoneal or adipose tissue macrophages to RvD1 not only promotes the M2 phenotype, but also leads to non-phlogistic phagocytic activity, which is essential for clearance of apoptotic cells and debris during the resolution phase of inflammation [48]. Monocyte inflammatory activity is also affected by obesity, with increased monocyte chemotaxis occurring in response to MCP-1 in ob mice. This chemotaxis, which is essential for mononuclear infiltration of adipose tissue, is attenuated by RvD1 and resolvin D2 (RvD2), with similar results seen in cultured human adipocytes [41].

Ω-3-PUFA dietary supplementation leads to improved insulin sensitivity in ob mice [43, 45], through up-regulation in adipose tissue of genes associated with insulin sensitivity (PPAR-γ), glucose transport (GLUT-4) and insulin receptor signalling (IRS-1) [45]. Dietary Ω-3-PUFA also partially prevent high-fat diet-induced obesity, with reductions in adiposity and adipocyte size, triglyceride levels and insulin levels observed [44]. Improved insulin sensitivity is also seen following exogenous 17-HDHA [43], RvD1 [47] or resolvin E1 (RvE1) [45] administration, with RvE1 also up-regulating IRS-1 and PPAR-γ in adipose tissue [45].

Favourable effects on the adipokine profile also result from an Ω-3-PUFA-rich diet or exogenous lipid mediator administration. A high-fat diet leads to down-regulation of expression and reduced serum concentrations of adiponectin [46]; however, an Ω-3-PUFA supplemented diet [44, 46], exogenous 17-HDHA [43], or exogenous RvD1 [47] restore levels of this adipokine. Similar effects on adiponectin levels are seen following in vitro culture of ob adipose tissue explants with RvD1, RvD2, 17-hydroxydocosahexaenoic acid (17R-RvD1) [41] or PD1 [45]. Both RvD2 alone and a mixture of multiple lipid mediators [RvD1, RvD2, 17R-RvD1 and lipoxin A4 (LXA4)] are also effective in reducing leptin production by adipose tissue explants from ob mice [41], with a trend towards leptin reduction also occurring in response to a combination of Ω-3-PUFA dietary supplementation and calorie restriction [44].

Ω-6-PUFA-derived lipid mediators

Pro-resolving lipid mediators derived from Ω-6-PUFA may also have a role in the resolution of adipose tissue inflammation and promotion of insulin sensitivity. In mice, LXA4 attenuates adipose inflammation, leading to decreased IL-6 and increased IL-10 levels. An associated increase in GLUT-4 and IRS-1 expression also occurs, suggesting that the resolution of adipose inflammation is co-incident with improved insulin sensitivity. Furthermore, LXA4 improves insulin signalling and glucose uptake in cultured mouse adipocytes, with an associated reduction in the secretion of inflammatory cytokines, including TNF-α [49].

LXA4 also appears to have a role in regulating adipokine production by ob adipose tissue, and it has been demonstrated that it is effective in increasing adiponectin production by ob mouse adipose tissue explants, either alone, or in combination with other pro-resolving lipid mediators. Conversely, the same mixture of lipid mediators can effect a reduction in leptin production, suggesting that LXA4 promotes a favourable adipokine production profile [41].

An interesting finding in ob mice is that in response to a combination of an Ω-3-PUFA enriched diet and calorie restriction, not only are Ω-3-PUFA mediators up-regulated, but increased adipose tissue levels of 15-deoxy-delta-12,14-prostaglandin J2 (15d-PGJ2) are also observed [44]. This is a somewhat unexpected finding, as 15d-PGJ2, a relatively recently described prostaglandin [50], is derived from Ω-6-PUFA precursors which are usually suppressed by Ω-3-PUFA. It is possible that this finding represents an influence exerted by Ω-3-PUFA over the Ω-6-PUFA pathways, to favour the generation of pro-resolving mediators [44].

CONCLUSIONS

Epidemiological projections suggest that the current challenges associated with obesity will be augmented with time, in which scenario, obesity-related glomerulopathy may become a very significant health issue, and for which, at present, therapeutic options are limited. Chronic adipose inflammation appears to be a significant factor in the aetiology of ORG, characterized by an imbalance between pro-inflammatory and pro-resolving lipid mediators, adipokines and mononuclear cells. Experimental evidence suggests that pro-resolving lipid mediators are beneficial in restoring homeostasis in adipose inflammation, and may represent a potential therapeutic strategy in the management of obesity-related glomerulopathy.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest to declare in relation to this manuscript. We confirm that this manuscript has not been published elsewhere and is not under consideration by another journal. All authors have approved the manuscript and agree with its submission to NDT.
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Autophagy and metabolic changes in obesity-related chronic kidney disease

Joseph Satriano
and Kumar Sharma

Correspondence and offprint requests to: Joseph Satriano; E-mail: jsatriano@ucsd.edu

ABSTRACT

Obesity is a long-term source of cellular stress that predisposes to chronic kidney disease (CKD). Autophagy is a homeostatic mechanism for cellular quality control through the disposal and recycling of cellular components. During times of cellular stress, autophagy affords mechanisms to manage stress by selectively ridding the cell of the accumulation of potentially toxic proteins, lipids and organelles. The adaptive processes employed may vary between cell types and selectively adjust to the insult by inducing components of the basic autophagy machinery utilized by the cells while not under duress. In this review, we will discuss the autophagic responses of organs to cellular stressors, such as high-fat diet, obesity and diabetes, and how these mechanisms may prevent or promote the progression of disease. The identification of early cellular mechanisms in the advent of obesity- and diabetes-related renal complications could afford avenues for future therapeutic interventions.

INTRODUCTION

Obesity continues to be a widespread public health issue. In the USA, the prevalence of obesity doubled between 1980 and 2002, affecting approximately one in three adults [1]. Adipose tissue is not merely for energy storage but is rather a complex endocrine gland that interacts with other organs. It is largely through these interactions that obesity increases the likelihood