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Minireview

IL-1 receptor antagonist in metabolic diseases: Dr Jekyll or Mr Hyde?

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Abstract Interleukin-1 receptor antagonist (IL-1ra) has been shown to play a crucial role in the prevention of various inflammatory diseases. There is also convincing evidence that IL-1ra is able to counteract inflammatory effects of IL-1 members implicated in insulin resistance and diabetes. However, the use of knock-out animal models provides evidence to the contrary and the role of IL-1ra in obesity-linked anomalies remains controversial.

This minireview gets an insight into recent findings on the implication of IL-1ra and its gene polymorphism in diabetes and obesity, discusses the potential dual effects of IL-1ra observed in different models, and comments on future directions.

Keywords: Interleukin-1 receptor antagonist; Diabetes; Obesity; Insulin resistance; Gene polymorphism; Adipocyte

1. Introduction

Many pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF-α) and IL-6 are secreted by adipocytes and have attracted considerable attention as mediators or coordinators of the insulin resistance observed in inflammatory diseases and obesity (for reviews see [1,2]). IL-1, one of the major proinflammatory cytokines, is increased in diabetic patients as well as in patients with rheumatoid arthritis or cancer [3]. IL-1 has been shown to promote β-cell destruction in the pathogenesis of type 1 diabetes [4]. Recent reports have illuminated the mechanisms of IL-1-induced insulin resistance [5] and the role of IL-1 in pancreatic β-cell destruction in non-obese diabetic (NOD) mice [6]. Since inflammatory mediators trigger islet β-cell apoptosis in both type 1 and 2 diabetes [7], anti-inflammatory therapeutic approaches could be a significant new development.

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Abbreviations: IL-1ra, interleukin-1 receptor antagonist; TNF-α, tumor necrosis factor alpha; IFNγ, interferon gamma; PPARγ, peroxisome proliferator-activated receptor gamma; NF-κB, nuclear factor kappa B; NOD, non-obese diabetic; WAT, white adipose tissue

2. IL-1ra

The interleukin-1 receptor antagonist (IL-1ra) belongs to the IL-1 family and binds to IL-1 receptors without inducing a cellular response, thereby antagonizing competitively the inflammatory effects of IL-1α and -β [8]. Thus, IL-1ra is a naturally occuring inhibitor, which is unique in the cytokine world. An excess of IL-1ra is necessary to counteract the effects of IL-1 in vitro.

Cells known to secrete IL-1ra include immune cells [9–11], epithelial cells [12,13] skin keratinocytes [14], stromal cells [15–18], hepatocytes [19] and adipocytes [20].

Since it does not induce signal transduction, the "activity" of IL-1ra is regulated only by its levels of production which are controlled by regulatory molecules (inhibitors and enhancers). A dysregulation in the balance between IL-1 and IL-1ra is one of the factors influencing the course, the susceptibility to and the severity of many diseases [21]. In the past few years, IL-1ra has attracted considerable clinical attention because its serum levels are elevated in pathologies as diverse as sepsis, cancer, metabolic diseases and auto-immune diseases [22–25]; whereas the plasma IL-1ra/IL-1 ratio in a healthy population is close to 1 and exhibits minimal variation [26]. The increase in circulating IL-1ra levels corresponds to a delayed event in response to IL-1 production and may represent a preventive mechanism in long-acting and/or excessive inflammatory response. IL-1ra is sometimes considered as an acute phase protein because its expression is regulated by proinflammatory cytokines in hepatocytes [19].

In contrast, the inflammatory site is more likely unbalanced in favor of IL-1, especially in severe lesions [27–30] and insufficient production of endogenous IL-1ra may contribute to the pathogeny of these conditions.

3. IL-1ra and diabetes

An imbalance between IL-1ra and IL-1 may predispose to the development of type 1 diabetes since very high levels of IL-1ra are required to block the IL-1-induced decrease in insulin secretion by pancreatic β-cells in vitro [31] or to inhibit the injurious effects of IL-1 on β cell function [32]. Moreover, an imbalance of IL-1ra/IL-1 in favour of the pro-inflammatory cytokine is observed in both the serum and LPS-stimulated peripheral blood cells from patients with early type 1 diabetes while an increase in circulating concentrations of IL-1ra in long-standing diabetes suggests a sustained role of IL-1ra

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against β-cell loss [33]. In vivo studies have demonstrated the protective role of IL-1ra in the development of type 1 diabetes. In mice, treatment with IL-1ra prevented streptozotocin-induced diabetes and inhibited recurrence of diabetes after pancreatic islet transplantation in spontaneously diabetic NOD mice [34,35]. More recently, IL-1ra gene delivery to human islets in culture was reported to prevent cell apoptosis [36] and to increase cell replication in rat pancreatic islets [37].

Taken together, these results suggest that an increase in IL-1ra production could be a response to immuno-inflammatory activation present at the onset of type 1 diabetes.

Recent work has demonstrated that leptin, another adipocytokine involved in the pathogenesis of insulin resistance, induces β-cell apoptosis and impairs β-cell function via IL-1β signalling in human islets [38]. Leptin decreases β-cell production of IL-1ra and induces IL-1β release. Accordingly, the expression of IL-1ra by human pancreatic β-cells is down-regulated in type 2 diabetic patients [38]. Interestingly, two independent studies show that patients with type 2 diabetes have significantly lower plasma levels of IL-1ra than non-diabetic patients while IL-1β plasma levels are similar in patients and in controls [39,40]. However, the source of systemic cytokines in these studies remains to be determined.

4. IL-1ra and obesity

In patients with hyperleptinemic obesity, serum levels of IL-1ra are 7-fold higher as compared to non-obese patients (1750 vs 250 pg/ml) and decrease after weight loss from bypass surgery [41]. In this study, IL-1ra concentrations correlated with lean body mass index, the degree of insulin resistance and leptin levels.

In morbid obesity, leptin may exert its effects through the IL-1 pathway and IL-1ra may contribute to central leptin resistance in obesity [42] because (i) IL-1ra crosses the blood/brain barrier [43]; (ii) leptin induces IL-1ra expression in the brain – including hypothalamus [44], (iii) injection of IL-1ra into the cerebral ventricles inhibits the leptin-induced reduction in food intake [45].

Recent findings showed that white adipose tissue (WAT) is a major source of IL-1ra [46]. IL-1ra is mostly secreted by the adipocyte fraction of WAT and to a minor extent by the stromal fraction [20]. In human WAT explants, IL-1ra secretion is induced by LPS, IL-1 and IFNβ through a local paracrine/autocrine action since these regulatory molecules are produced by stromal cells or by the adipocytes themselves [20]. In this study, peroxisome proliferator-activated receptor gamma (PPARγ) ligands failed to induce the secretion of IL-1ra whereas they strongly enhance IL-1ra secretion in human monocytes [47].

The adipo-insular axis plays an important role during the development of type 2 diabetes in obese patients. IL-1ra being modulated by leptin in β-cells may participate in the axis loop by regulating adipocytokines production. The cross-talk between IL-1ra and other adipocyte markers has not been reported. In particular, IL-1ra expression after leptin exposure was not investigated in human adipocytes.

5. IL-1ra regulation and metabolic factors

Few studies address the cross-talk between IL-1ra and other metabolic factors. To date, IL-1ra modulation by adiponectin has been found in human leukocytes [48] whereas IL-1ra modulation by leptin is cell-specific since leptin decreases the expression and secretion of IL-1ra in pancreatic islets but increases it in monocytes [49] and macrophages [50].

In HepG2 and THP-1 cells, the activation of the IL-1ra promoter by leptin involves the activation of MAPK and the binding of a yet uncharacterized factor to the nuclear factor kappa B (NF-κB) binding site of the IL-1ra promoter [51].

In hepatocytes, IL-1 and IL-6 stimulate IL-1ra gene transcription and this stimulation is mediated by activation of NF-κB and CEBP. Interactions between these two transcription factors have been suggested to mediate the synergistic effects of IL-1 and IL-6 on acute phase protein production [19].

Long-term IL-1α stimulation of 3T3-L1 adipocytes induces SOCS-1 and -3 while acute IL-1α treatment was recently reported to cause insulin resistance at different levels [5]: (i) by reducing tyrosine phosphorylation of IRS-1 and its association with PI3-kinase; (ii) by stimulating Ser-307 phosphorylation of IRS-1 via the activation of several serine kinases (IKK, JNK, ERK and p70S6K); (iii) by inhibiting PKB/Akt phosphorylation in synergy with IL-6.

Thus, examining signalling pathway modulation by IL-1ra is also of particular interest in order to elucidate how IL-1ra counteracts IL-1-induced insulin resistance.

6. IL-1ra knock out mice

Recently, the IL-1ra −/− mouse has proven to be a good model for investigating obesity, diabetes and lipid metabolism disorders [52,53]. As previously described [54], mice lacking IL-1ra have a lean phenotype due to a reduction in body fat mass compared with wild-type controls. Surprisingly, these mice also have an increased food intake relative to their body weight when fed with a standard diet [53]. This could be a consequence of an increased energy expenditure and of a significant reduction in blood leptin concentrations (6-fold lower when compared with wild-type mice). Despite having also decreased blood insulin levels, IL-1ra −/− mice have normal serum glucose levels because of an increased insulin sensitivity.

Whether adipocyte differentiation is altered or not in IL-1ra −/− mice is controversial. Using histological analysis of adipose tissue, Matsuki et al. previously reported that adipocytes of IL-1ra −/− mice under fed conditions exhibited normal morphology and cell volume as those of wild-type mice. According to more recent work [53], IL-1ra −/− mice have reduced adipose storage, impaired adipogenesis (associated with reduced gene expression of adipocyte differentiation markers LPL, Krox20, C/EBPα and PPARγ) and a 77% decrease in adipocyte size.

Heterozygous IL-1ra +/− mice also have impaired adipogenesis but have unaltered fat mass [53]. The authors suggest that in these mice, the adipocyte hypotrophy may be compensated by an increase in adipocyte recruitment due to a relative balance between IL-1 and IL-1ra (ratio close to 1). On the other hand, the circulating IL-1 excess in IL-1ra −/− mice prevents adipogenesis and this IL-1 oversignalling may also lead to reduced fat mass and WAT stores.

IL-1ra gene deletion in IL-1ra −/− mice did not result in a general inflammatory state since circulating levels of pro-inflammatory cytokines including IL-1 are not significantly different from those in wild-type mice. However, the resulting

imbalance of IL-1ra/IL-1 towards an excess of IL-1 signalling may explain the inhibition in LPL expression and activity, leading to the suppression of fat accumulation, and may cause the suppression of weight gain, whereas a 2.6-fold molar excess of serum IL-1ra concentration in the wild-type mice may be sufficient to block IL-1 activity at a systemic and/or local levels [53]. The decrease in insulin secretion may cause the defect in lipid accumulation found in adipose tissue of these mice. Taken together, these results suggest that endogenous IL-1ra is a pro-adipogenic factor and markedly increased circulating IL-1ra levels in obese humans might contribute to obesity-associated anomalies, including an acquired resistance to leptin.

7. IL-1ra gene polymorphism and metabolic diseases

The human IL-1ra gene (IL1RN) has a variable length polymorphism within intron 2 due to variation in the number of copies of an 86 bp sequence. To date, six distinct alleles corresponding to 1, 2, 3, 4, 5 and 6 copies of the repeat sequence have been identified [55]. The 4-repeat (IL1RN*1) and 2-repeat (IL1RN*2) alleles are those most frequently found in the general population while the other four alleles are rarely observed. The number of repeats at the polymorphism site may be of functional significance because the repeated sequence contains possible binding sites for transcription factors [56]. Indeed, IL-1ra allele 2 has a clear influence on IL-1ra circulating levels since in normal human subjects, its carrier individuals had 10-fold higher levels than the non-carrier individuals (745 ng/ml vs 627 pg/ml) [57]. Moreover, a significant increase in frequency and/or carriage rate of IL1RN*2 has been reported to be associated with more severe clinical outcome in various disorders (references in database http://www.nanea.dk/cytokinesnps/) including non-insulin dependent diabetes mellitus [58]. IL1RN*2 is the first such marker outside the MHC related to disease severity.

Although there is no evidence for overall linkage or intrafamilial association between IL-1ra polymorphism and type 1 diabetes [59], an increased frequency of the IL1RN*1/IL1RN*1 genotype was observed [60]. In this study, patients with type 1 diabetes carrying this genotype had also 30% lower levels of plasma IL-1ra compared with levels in patients carrying the IL1RN*1/IL1RN*2 genotype. This finding suggests an enhancing effect of IL1RN*2 allele on IL-1ra circulating levels in type 1 diabetes patients as observed in healthy carriers. However, this enhancing effect may be influenced by other factors including IL-1 beta genes [57].

The association between IL-1ra polymorphism and type 2 diabetes has not been reported whereas the relative risk of obesity in comparison with lean group tends to be higher in IL1RN*2 carriers but without reaching significance [61].

8. Conclusions and future directions

In recent years, an important experimental approach has been undertaken by many groups to study the role of IL-1ra in metabolic diseases (summarized in Fig. 1). It is now clear that IL-1ra has a protective role in pancreatic cells and recombinant IL-1ra, which is currently used as a therapeutic molecule in rheumatoid arthritis [62] may be a potential drug in the treatment of diabetes by controlling its local delivery in IL-1ra deficient pancreatic cells from microencapsulated genetically engineered cells [63].

In contrast, results using the generation of mouse models with altered IL-1ra result in strong adipocyte hypotrophy and decrease in blood leptin levels, suggesting that endogenous IL-1ra is a pro-adipogenic factor contributing to central leptin

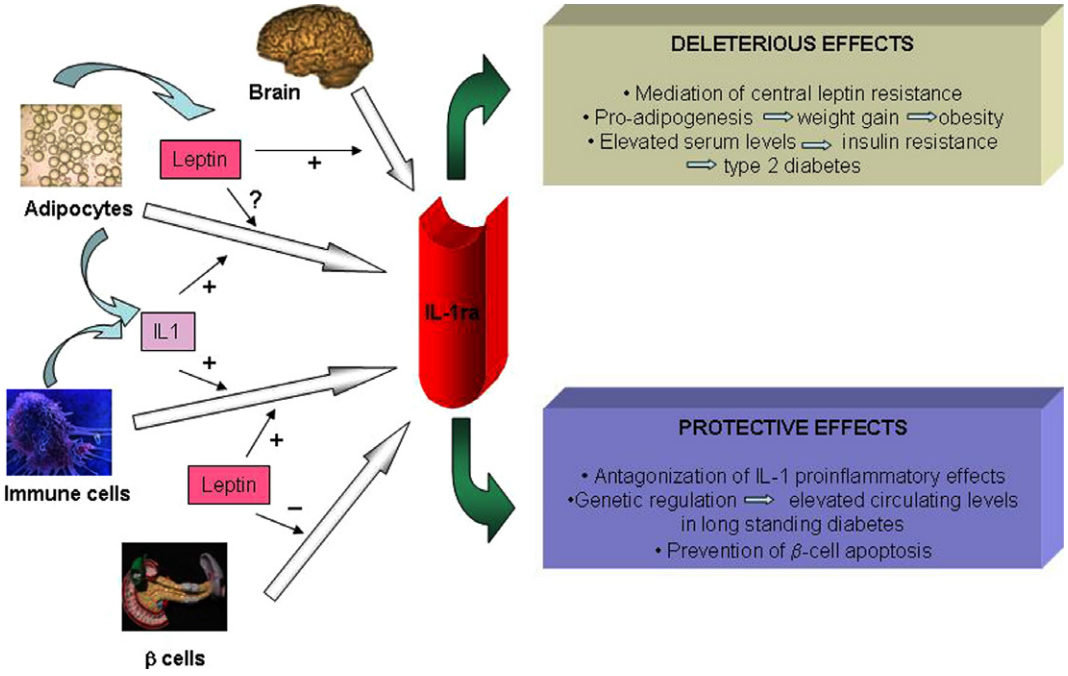

Fig. 1. Proposed model outlining the dual action played by IL-1ra in human metabolic diseases. IL-1ra is modulated by other adipocytokines (mainly IL-1 and leptin) in various cell types from different organ systems, and coordinates ubiquitous reactions leading to either harmful or protective effects. Details of the features described in this figure are given and referenced in the text.

resistance in obesity. Yet, the direct evidence that IL-1ra induces adipocyte differentiation needs to be confirmed but is likely since IL-1β, TNF-α and IL-6 inhibit 3T3 pre-adipocytes differentiation along with decreased insulin-stimulated glucose uptake, GLUT-4 and C/EBPα expression [64–66]. The inhibition of adipogenesis by IL-1 and TNF-α in these cells is mediated by suppressing PPARγ function through NF-κB activated by the TAK-1/TAB1/NIK cascade [67] and reversed by troglitazone [65]. The effect of IL-1ra on this signalling pathway (possibly in synergy with troglitazone) as well as on the expression of other adipocyte specific genes (LPL, Wnt, Pref-1, SREBP, adiponectin) should gain further important insights into the fundamental physiological process of adipogenesis regulation by the IL-1/IL1ra balance.

The discrepancy regarding circulating IL-1ra that is decreased in type 2 diabetes and increased in obesity is intriguing and may reflect different mechanisms in distinct pathologies. Obesity is characterised by an excess in blood leptin, which is now considered as a pro-inflammatory adipocytokine [68]. Increased circulating IL-1ra levels in obese patients may have a protective role in response to high leptin levels and pertain to its immunomodulatory and/or metabolic activities as described in sepsis or inflammatory disorders [2].

Recent data indicate that obese WAT is infiltrated by macrophages, which are a major source of locally-produced pro-inflammatory cytokines, including IL-1 (review in [69]). Interestingly, weight loss is associated with a reduction in the macrophage infiltration of WAT and an improvement of the inflammatory profile of gene expression. As IL-1ra concentrations are also reduced after weight loss, they probably respond to the IL-1 signal during the course of the disease and the circulating IL-1ra in obesity may come from the inflammatory cells rather than from adipocytes. In contrast, the human pancreatic β-cells are the main source of IL-1ra in type 2 diabetes, where IL-1ra expression is down-regulated. These results predict a distinct regulation of IL-1ra between the different cell types (inflammatory cells, β-cells and adipocytes) and it would be important to further characterize IL-1ra in these cells.

We have previously found a dichotomy between the systemic production of IL-1ra and its local production at the inflammatory site, and suggested separate regulatory mechanisms in different compartments [25]. In this study, the IL1RN*2 allele was shown to accentuate this dichotomy. Similarly, circulating levels of IL-1ra are elevated in type 1 diabetic patients (especially those with IL-1RN*2) while a deficiency in IL-1ra secretion takes place in the pancreatic cells and may be influenced by IL1RN*2.

Lately, the understanding of the molecular mechanisms by which the IL-1 family members modulate food intake and energy expenditure has progressed rapidly. However, many questions still remain only partly answered as contradictory results appear on the role of IL-1ra in these mechanisms: First, a role for IL-1ra in the regulation of body weight has been suggested and the balance of IL-1/IL-1ra appears crucial in this function but still, a lack of IL-1 signalling does not affect the maintenance of body weight as reported in IL-1 −/− mice [70] or in transgenic mice overexpressing IL-1ra [54]; Second, chronic central administration of recombinant IL-1ra does not affect food intake in rats [71] while IL-1ra deficient animal models suggest an effect on food intake; Third, IL-1ra prevents IL-1 mediated β-cell apoptosis in pancreatic islets but IL-1ra deficient mice show no pancreatic alteration in term of islets morphology as well as insulin storage in β-cells [72].

Further studies will be necessary to clarify these points and would allow a better general understanding on the complex regulation of IL-1ra and its implication in insulin resistance and obesity-linked diseases.

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