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Possible involvement of the (pro)renin receptor-dependent system in the development of insulin resistance

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1. ABSTRACT

It is widely acknowledged that activation of the renin-angiotensin system impairs insulin sensitivity. Pharmacological inhibition of the (pro)renin receptor-dependent system has shown beneficial effects in diabetic nephropathy, retinopathy and hypertensive cardiac damage in animal models. Previously, we showed that fructose feeding stimulated nonproteolytic activation of prorenin and subsequent production of angiotensin II in skeletal muscle in rats, and that inhibition of the (pro)renin receptor-dependent system improved the development of fructose feeding-induced insulin resistance. In addition, our current preliminary study suggests that local angiotensin II generation in skeletal muscle and adipose tissues induced by nonproteolytic activation of prorenin is involved in the development of spontaneous insulin resistance in type 2 diabetic rats. In this review, we will briefly summarize the possible contribution of the (pro)renin receptor-dependent system to the pathogenesis of insulin resistance, with a focus on how the nonproteolytic activation of prorenin contributes to the development of insulin resistance.

2. INTRODUCTION

A growing body of evidence suggests that activation of the renin-angiotensin system (RAS) impairs insulin sensitivity (1), and that hyperinsulinemia and insulin resistance promote the development of cardiovascular disorders (2, 3). In addition, clinical studies have shown that treatments with RAS inhibitors, such as angiotensin (Ang)-converting enzyme (ACE) inhibitors (4), Ang II type 1 receptor blockers (ARBs) (5) and a direct renin inhibitor (DRI) (6), prevent the development of insulin resistance in hypertensive patients, indicating that ACE, Ang II and renin contribute to the development of insulin resistance. On the other hand, it is also acknowledged that tissue RAS, such as the intrarenal Ang II levels, are regulated in a manner distinct from the systemic RAS (7). However, the mechanisms by which tissue RAS is activated during the development of insulin resistance are still unclear.

Prorenin, the enzymatically inactive precursor of renin, is expressed in various tissues (8), and has an amino-terminal prosegment that is thought to cover the

enzymatic cleft and obstruct access to its substrate, angiotensinogen. Prorenin is also known to be activated without catalytic conversion into mature renin via the (pro)renin receptor (9). The activated prorenin can generate Ang I locally, thereby accelerating the subsequent tissue production of Ang II (8). Interestingly, mature renin can also bind to (pro)renin receptor, and the amount of Ang I generated by receptor-bound renin dramatically exceeds that by unbound renin (8), suggesting that activation of both renin and prorenin is facilitated by binding to (pro)renin receptor. The locally produced Ang II acts as an autocrine/paracrine factor and induces local actions that are independent of the systemic actions induced by circulating Ang II. Ichihara et al. demonstrated that inhibition of the nonproteolytic activation of prorenin with a decoy peptide containing the handle region of the prorenin prosegment decreases Ang II formation in the heart (10) and renal tissues of hypertensive rats (11) and in the renal tissues of type 1 diabetic rats (12) without large changes in the systemic RAS. Moreover, fructose feeding induces nonproteolytic activation of prorenin and subsequent Ang II production in skeletal muscle in rats (13). Inhibition of these changes by the handle region peptide (HRP) may be involved in the attenuation of fructose feeding-induced insulin resistance. However, the roles of (pro)renin receptor in the development of insulin resistance are poorly understood. In this short review, we will briefly summarize the possible contribution of the (pro)renin receptor-dependent system to the pathogenesis of insulin resistance, with a focus on how the nonproteolytic activation of prorenin contributes to the development of spontaneous insulin resistance.

3. RAS AND INSULIN RESISTANCE

It is widely acknowledged that ACE inhibitors and ARBs blunt the progression of type 2 diabetic nephropathy (4, 5) and reduce the incidence of new onset of type 2 diabetes mellitus (14, 15) in humans. Previous studies have also shown that RAS inhibition by ACE inhibitors or ARBs improves glucose intolerance in type 2 diabetic mice (16, 17). The beneficial effects of ACE inhibitors and ARBs indicate the importance of the RAS in the pathogenesis of type 2 diabetes and its complications. In addition, recent studies have reported beneficial effects of a DRI on insulin resistance (18-21). Studies on *db/db* mice revealed that the DRI, aliskiren, exhibits organ-protective effects by improving insulin resistance and lipid abnormalities, as well as, having anti-fibrotic effects on target organs (18) and ameliorating pancreatic injury (19). These studies raise the interesting possibility that renin may be linked to insulin resistance and lipid abnormalities in type 2 diabetes mellitus. Recently, Iwai et al. (20) have demonstrated that aliskiren improves the impairment of plasma glucose in the oral glucose tolerance test (OGTT) and increases the response to insulin injection in the insulin tolerance test in diabetic KKAy mice. Aliskiren also decreases oxidative stress and inflammatory markers in insulin-sensitive organs such as skeletal muscle and adipose tissues. In addition, aliskiren can potentiate adipocyte differentiation, which may be involved in the improvement of adipocyte dysfunction and insulin sensitivity (20). Moreover, aliskiren enhances insulin secretion by restoring β cells in pancreatic islets through a reduction in oxidative stress (20). A recent study by Lastra et al. (21) showed that renin inhibition by aliskiren improves systemic insulin sensitivity, skeletal muscle insulin metabolic signaling, and glucose transport in Ren2 rats. These beneficial effects of aliskiren on insulin resistance are qualitatively similar to the effect of ARBs as previously reported by the same group (22). These *in vivo* experiments using aliskiren revealed that the DRI has a protective effect for insulin resistance and diabetic complications.

4. INSULIN RESISTANCE AND THE (PRO)RENIN RECEPTOR-DEPENDENT SYSTEM

Diabetic patients have relatively low circulating plasma renin activity (23, 24). High levels of prorenin, but low circulating plasma renin activity, are closely associated with the severity of diabetic complications (23, 24). The possible contribution of the (pro)renin receptor-dependent system to the development of insulin resistance are unclear, although insulin resistance and diabetic complications were improved by renin or prorenin inhibition using aliskiren or the HRP, respectively (6, 12). We previously suggested that the (pro)renin receptor-dependent system is activated in skeletal muscle and contributes to the development of insulin resistance in a fructose feeding-induced insulin-resistant rat model (13). HRP treatment markedly improved the glucose intolerance and caused less increase in the insulin level in response to oral glucose administration in high-fructose-fed rats. Importantly, fructose feeding augmented nonproteolytic activation of prorenin in skeletal muscle and the increased Ang II contents in skeletal muscle are also attenuated by HRP treatment. These findings indicate that nonproteolytic activation of prorenin is involved in RAS activation of skeletal muscle during the development of insulin resistance in high-fructose-fed rats. Although these observations indicate that local RAS activation mediated by (pro)renin receptors is involved in insulin resistance induced by fructose feeding, it is still unclear whether nonproteolytic activation of prorenin contributes to the development of spontaneous insulin resistance in type 2 diabetes mellitus.

Therefore, we designed our current preliminary study to test the hypothesis that nonproteolytic activation of prorenin is involved to the development of spontaneous insulin resistance. Six-week-old male Otsuka Long-Evans Tokushima Fatty (OLETF) and non-diabetic control male Long-Evans Tokushima Otsuka (LETO) rats (Otsuka Pharmaceutical, Tokushima, Japan) were maintained under a controlled temperature (24 ± 2°C) and humidity (55 ± 5%), with a 12-h/12-h light/dark cycle. Throughout the experimental period, the rats had free access to laboratory rat chow and tap water. OLETF rats exhibit a prediabetic stage characterized by postprandial hyperglycemia and insulin resistance from 10 to 20 weeks of age (25). Therefore, we harvested the tissues at 15 weeks of age. The OGTT and hyperinsulinemic-euglycemic clamp study were performed after overnight fasting to evaluate the

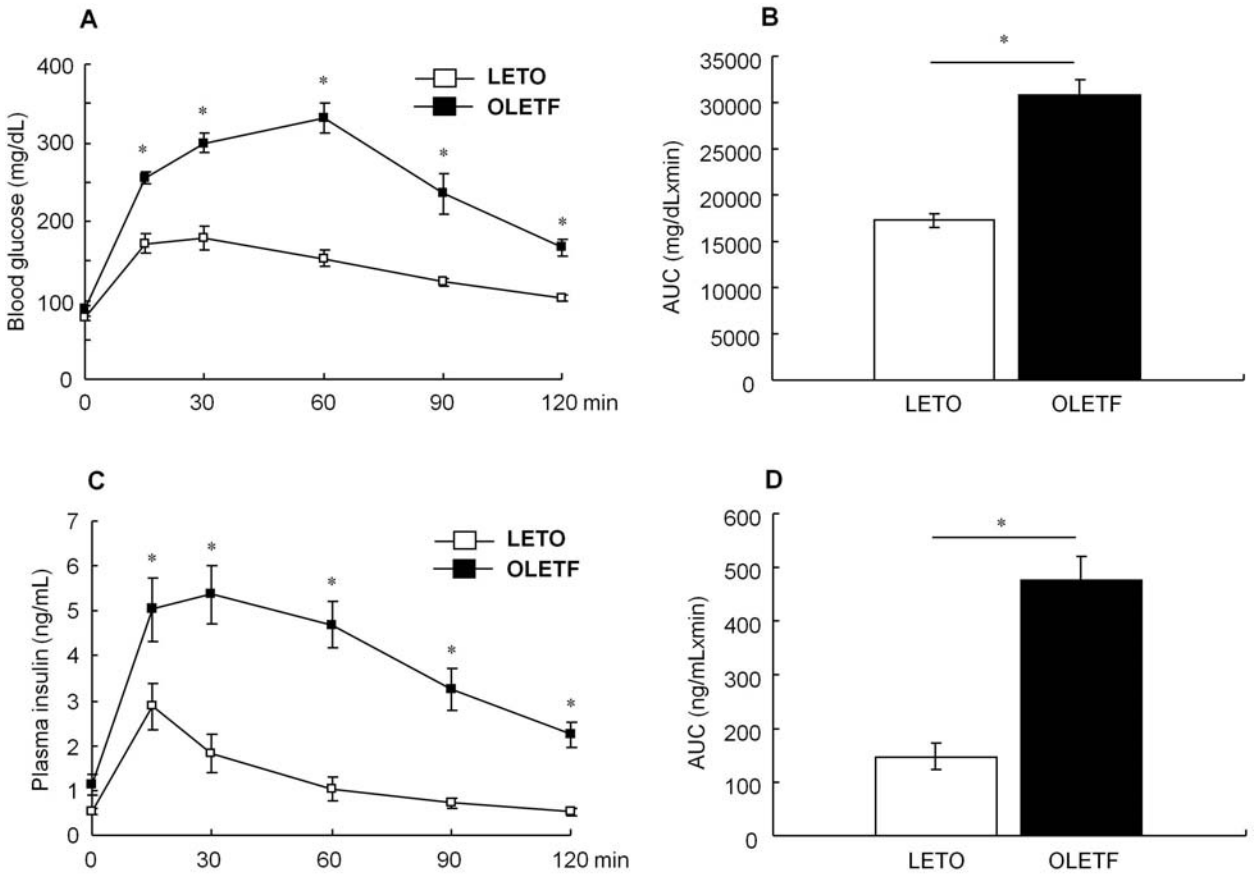

Figure 1. Glucose metabolism. Oral glucose tolerance test were performed in OLETF and LETO rats at 15 weeks of age. After overnight fasting, rats were gavaged with glucose (2 g/kg). Blood samples were collected at 0, 30, 60, 90, 120 min, and blood glucose level (A) and its area under curve (AUC) (B), plasma insulin levels (C) and its AUC (D) were measured. Data are expressed as means ± SEM of n=8 per group. **P*< 0.05 vs. LETO rats.

insulin sensitivity, as previously described (13). Immunohistochemical staining with an anti-rat prorenin gate region antibody for activated prorenin was performed as previously described (13). Ang II contents in the soleus muscle and adipose tissues were measured by a radioimmunoassay, as previously described (26). In this preliminary study, we found that 15-week-old OLETF rats exhibited glucose intolerance as assessed by the OGTT. OLETF rats showed marked increases in the blood glucose level and area under the curve in response to oral glucose loading during the OGTT (Figure 1). OLETF rats also showed a marked increase in the plasma insulin level compared with age-matched LETO rats (Figure 1). Furthermore, the whole body insulin sensitivity was assessed by the hyperinsulinemic-euglycemic clamp study. OLETF rats showed a significantly lower glucose infusion rate than LETO rats (0.90 ± 0.15 vs. 1.41 ± 0.09 mg/kg/hour, $P<0.05$, $n=4$ for each). Interestingly, OLETF rats showed nonproteolytic activation of prorenin in the soleus muscle and adipose tissues (Figure 2) as assessed by immunohistochemical staining of the gate region of prorenin, which is not accessible by its specific antibodies until it is loosened from the active site cleft, representing the phenomenon called nonproteolytic activation of prorenin (11). In contrast, the mRNA expression level of the (pro)renin receptor were similar in OLETF and LETO rats (Figure 2). OLETF rats showed augmented Ang II contents in the soleus muscle and adipose tissues compared with LETO rats (Figure 3). These findings indicate that nonproteolytic activation of prorenin participates in the development of spontaneous insulin resistance in type 2 diabetic rats through local (skeletal muscle and adipose tissues) RAS activation, at least in part (Figure 4). Further studies are needed to clarify the precise molecular mechanism responsible for the prorenin-induced insulin resistance via the (pro)renin receptor in type 2 diabetic rats.

5. CLINICAL STUDIES

Emerging clinical evidence indicates that ACE inhibitors and ARBs reduce cardiovascular and renal complications in diabetes and new onset of diabetes (4, 15), and these agents are now considered as a first-line therapies for the treatment of hypertensive patients with type 2 diabetes mellitus (27-29). These effects of ACE inhibitors and ARBs have been explained by their hemodynamic effects, such as improved delivery of insulin and glucose to peripheral skeletal muscle, and nonhemodynamic effects,

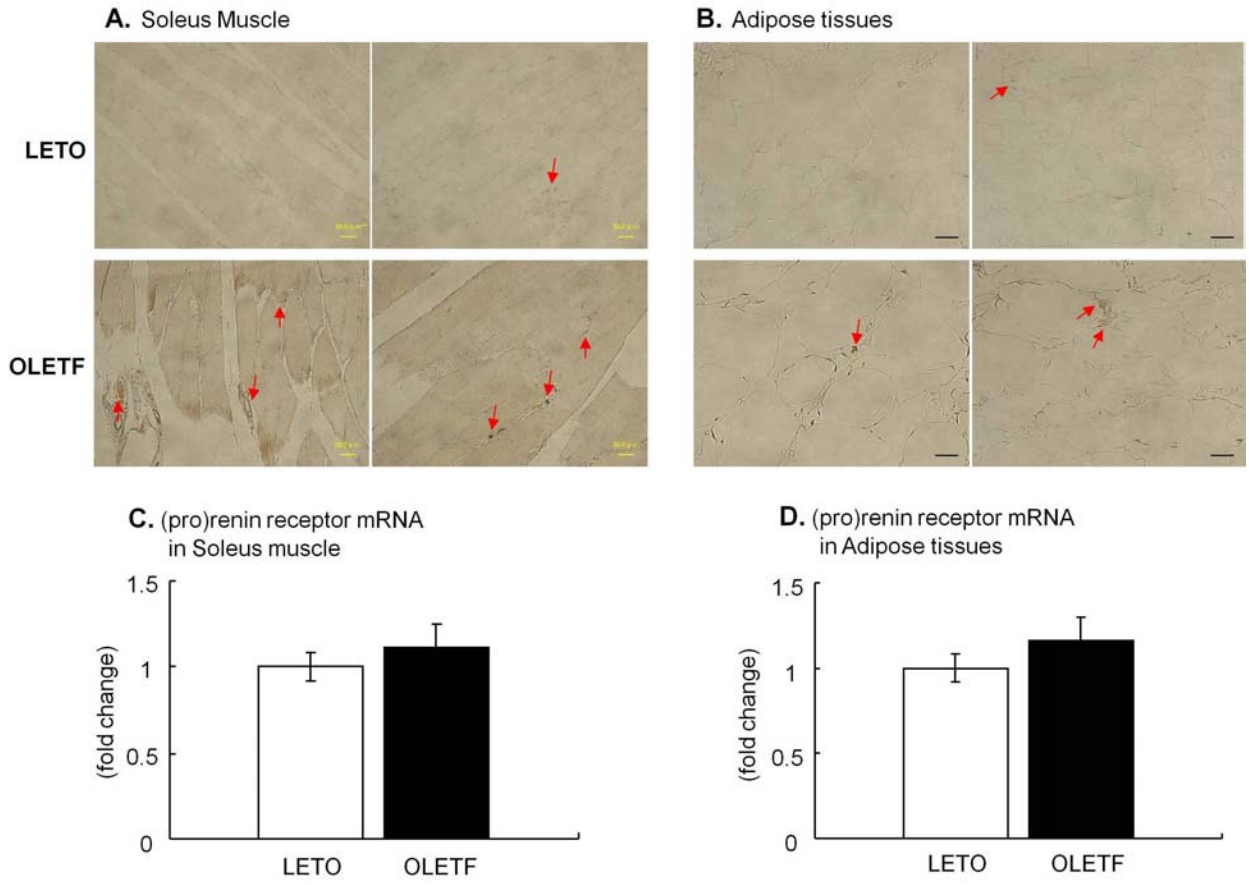

Figure 2. Activated prorenin and expression of (pro)renin receptor in soleus muscle and adipose tissue. Immunohistochemistry for activated prorenin (gate-region antibody, arrow marked in the picture) (A) in the soleus muscle and (B) in adipose tissue in OLETF and LETO rats. Scale bar represent 500 μm. (Pro)renin receptor gene expression in soleus muscle (C) and in adipose tissue (D). Data from RT-PCR are expressed as fold changes compared with LETO after normalization to the expression of glyseraldehyde-3-phosphatedehydrogenase. Data are expressed as means ± SEM of n=8 per group.

such as direct effects on glucose transport and insulin signaling pathways, all of which decrease insulin resistance (30, 31). Indeed, clinical studies showed that treatment with ARBs or ACE inhibitors improves insulin resistance in hypertensive patients (32).

Aliskiren is a novel orally effective DRI, and its RAS-blocking pharmacological actions are different from those of conventional RAS blockers (33). For instance, aliskiren can bind not only to the free and receptor-bound form of renin, but also to receptor bound prorenin, which displays kinetics similar to active renin, and thus inhibit their renin activity (34). Clinical studies have suggested that aliskiren not only lowers blood pressure in hypertensive patients (35) but also attenuates cardiovascular and renal injuries as well as pancreatic injuries in type 2 diabetes mellitus (36). A recent clinical study, entitled "Aliskiren in the Evaluation of Proteinuria in Diabetes (AVOID)", showed that aliskiren combined with losartan has significant anti-proteinuric effects that are independent of its blood pressure-lowering effects in patients with hypertension and diabetic nephropathy (6). These results suggest beneficial effects of RAS intervention by DRI administration on hypertensive and diabetic complications. Another recent clinical study found that women with polycystic ovarian syndrome show insulin resistance and increased serum renin levels (37). In addition, it has proposed that prorenin is a useful marker of diabetic microvascular complications (23) and retinopathy of prematurity (38). These data indicate a possible link between renin activation and insulin resistance. Further clinical studies are required to elucidate the benefits of the protective effects of the DRI on insulin resistance and diabetic complications. However, it remains unclear whether these effects of DRI are mediated through the inhibition of local Ang II generation by (pro)renin receptor-dependent system.

6. CONCLUSIONS

In this review, we have discussed the possible roles of the (pro)renin receptor-dependent system in the development of insulin resistance. Our preliminary data indicate that the (pro)renin receptor-dependent system may be involved, at least in part, in the development of insulin

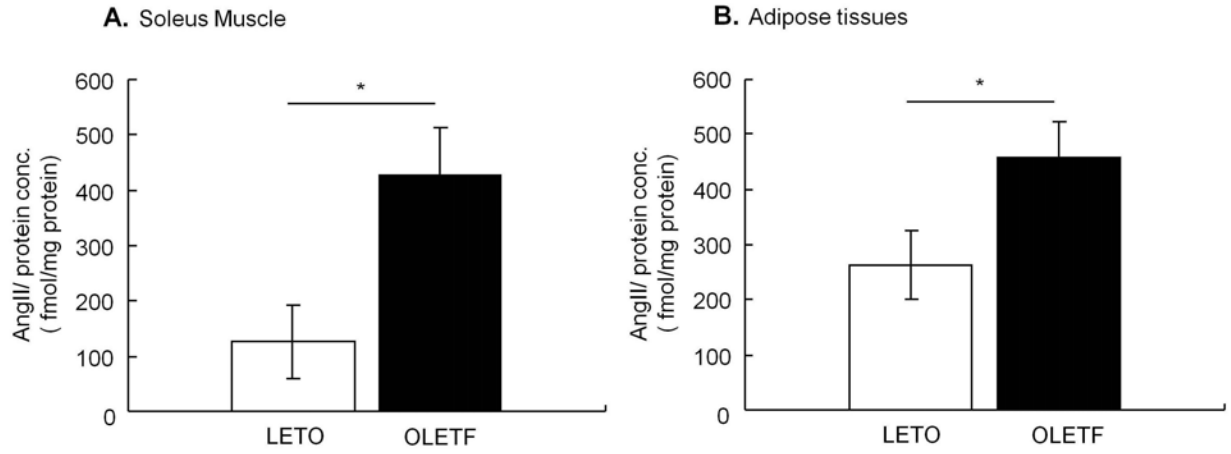

Figure 3. Ang II contents in soleus muscle and adipose tissue. Data are expressed as Ang II concentration (fmol/g tissue) per protein concentration (mg/g tissue). All data are expressed as means ± SEM of n=8 per group. **P*< 0.05 vs. LETO rats.

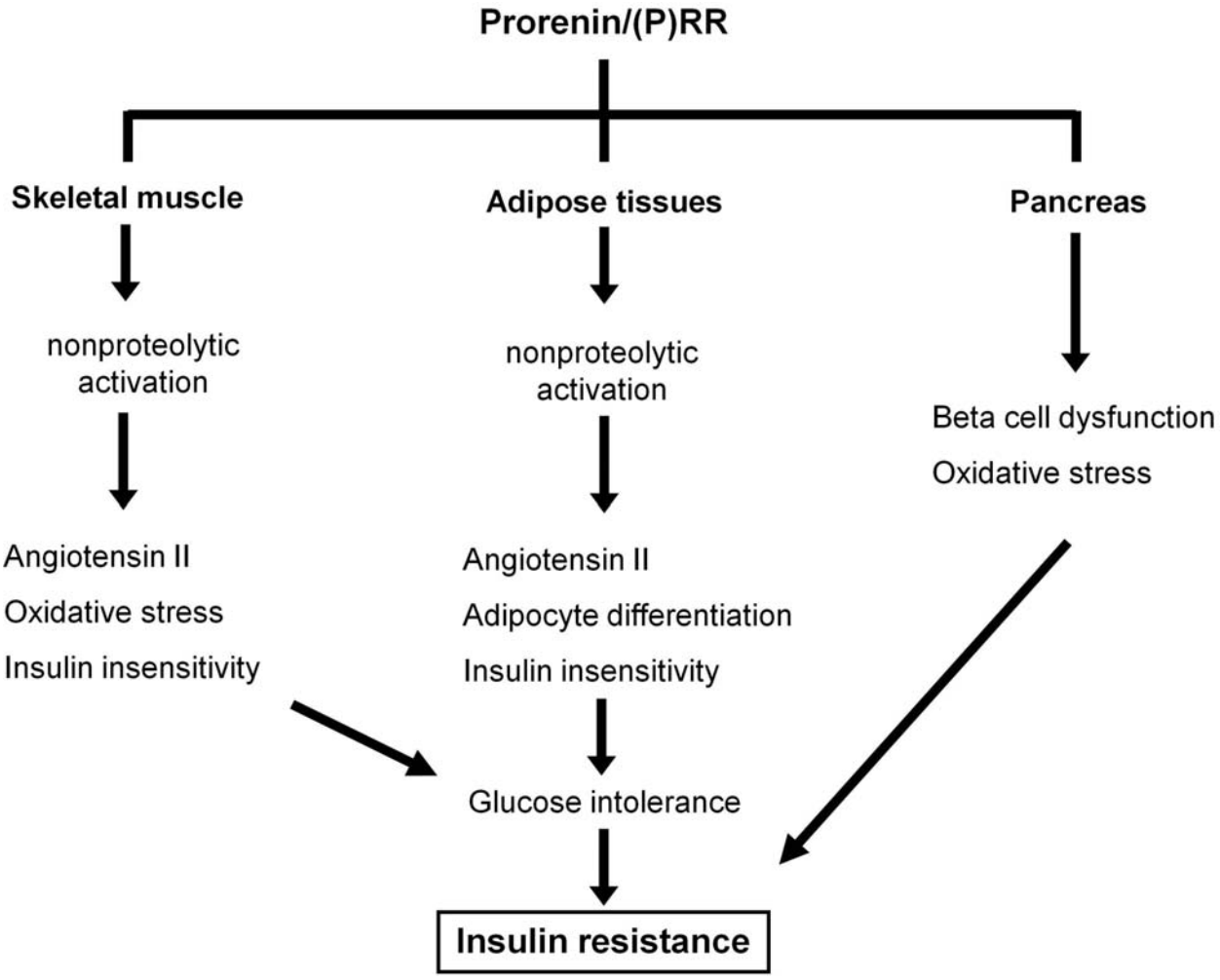

Figure 4. Schematic diagram for possible mechanisms. Schematic diagram shown the possible mechanisms in the involvement of (pro)renin receptor-dependent system to the development of insulin resistance.

resistance through local production of Ang II in type 2 diabetes mellitus.

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