Partial Peroxisome Proliferator-Activated Receptor Agonist Angiotensin Receptor Blockers

Potential Multipronged Strategy in Stroke Prevention

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\textbf{Key Words}
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\textbf{Abstract}

\textbf{Background and Purpose:} Although their primary mechanism of action is blood pressure lowering, emerging data suggest that select angiotensin receptor blockers (ARBs), which partially activate the peroxisome proliferator-activated receptor \(\gamma\) (PPAR-\(\gamma\)), may effectively treat insulin resistance and dyslipidemia without the toxicity sometimes associated with full PPAR-\(\gamma\) agonists. Since up to 50\% of the patients with ischemic stroke and transient ischemic attack harbor insulin resistance, drugs that simultaneously control hypertension and insulin resistance could be particularly useful for stroke prevention. \textbf{Summary of Review:} This review presents the experimental and preliminary clinical evidence supporting a promising role for partial PPAR-\(\gamma\) agonist ARBs in treating insulin resistance and the metabolic syndrome in patients with ischemic cerebrovascular disease. \textbf{Conclusion:} Partial PPAR-\(\gamma\) agonist ARBs by virtue of their multiple beneficial mechanisms of action could provide a single multipronged strategy for reducing future vascular events in persons with, or at risk for, stroke.

\section*{Introduction}

Over 70\% of strokes could be prevented by better control of modifiable risk factors \cite{1}. Many vascular risk factors cluster in high-risk individuals. For instance, hypertension occurs twice as often in diabetic patients than nondiabetic controls, and diabetes is more likely to afflict hypertensive than normotensive individuals \cite{2, 3}. Indeed a group of abnormalities, including visceral obesity, insulin resistance, dyslipidemia and elevated blood pressure, collectively termed the metabolic syndrome, has been associated with prothrombotic, proatherogenic and inflammatory risk factors that predispose to atherosclerotic vascular disease, including stroke \cite{4, 5}. Since the growing obesity epidemic is expected to result in substantially more individuals being diagnosed as having metabolic syndrome \cite{6}, identifying therapeutic strategies for treating components of the metabolic syndrome, thereby preventing its dreaded complications, may be...
come a public health need. This review explores the potential for one such strategy, that of using angiotensin receptor blockers (ARBs) with partial peroxisome proliferator-activated receptor γ (PPAR-γ) activity, to simultaneously treat blood pressure, dyslipidemia and insulin resistance, with a goal of reducing vascular events in prediabetic persons with, or at risk for, stroke.

**Obesity, Insulin Resistance, Metabolic Syndrome and Stroke Risk**

Metabolic syndrome, a constellation of highly interrelated risk factors that promote the development of atherosclerotic cardiovascular disease, type 2 diabetes mellitus and stroke [7–9], has a high prevalence in the USA, with as many as 35% of the adult population displaying the syndrome [10–13]. The syndrome consists primarily of atherogenic dyslipidemia (an aggregation of lipoprotein abnormalities, including elevated triglyceride and apoB, increased small LDL particles and reduced HDL-C), hypertension and hyperglycemia. Individuals with metabolic syndrome often display both a prothrombotic and a proinflammatory state.

The most significant underlying risk factors for metabolic syndrome are insulin resistance and abdominal obesity [7]. Insulin resistance, a metabolic disorder caused by impaired intracellular signaling in muscle tissue, leads to defective glycogen synthesis, resulting in a state in which a normal amount of insulin produces a subnormal physiological response [14]. Epidemiologic evidence links insulin resistance to risk for coronary heart disease, carotid disease and stroke [14, 15]; clinical trials in diabetic patients suggest that reducing insulin resistance may prevent carotid atherosclerosis and stroke [16–18]. Abdominal obesity correlates with insulin resistance and metabolic syndrome more strongly than lower-body obesity [19].

Several lines of evidence support the correlation between metabolic syndrome and cerebrovascular disease. First, metabolic syndrome is associated with leukoaraiosis, white matter periventricular hyperintensities visible on CT and MRI, which have been related to an increased risk of first and recurrent stroke [20]. Second, individuals with metabolic syndrome have an increased prevalence of carotid intima-media thickness and asymptomatic carotid atherosclerotic plaques [21, 22]. Finally, metabolic syndrome is independently associated with intracranial atherosclerosis and is present in about half of the individuals with symptomatic intracranial atherosclerotic disease [23, 24].

**Table 1. Postulated pleiotropic properties of ARBs**

<table>
<thead>
<tr>
<th>Property</th>
<th>ARB Function</th>
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<tbody>
<tr>
<td>– Influencing angiotensin II type 1 receptor function</td>
<td>– Reducing arginine-vasopressin release</td>
</tr>
<tr>
<td>– Improving insulin sensitivity</td>
<td>– Inhibiting angiogenesis</td>
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<tr>
<td>– Reversing left ventricular hypertrophy</td>
<td>– Promoting vasodilatation</td>
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<tr>
<td>– Instituting vascular remodeling</td>
<td>– Facilitating premolding</td>
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<td>– Enhancing prodifferentiation</td>
<td>– Reducing proliferation</td>
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<td>– Reducing angiotensin type 2 receptor function</td>
<td>– Inhibiting arginine-vasopressin release</td>
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<tr>
<td>– Enhancing prodifferentiation</td>
<td>– Enhancing prodifferentiation</td>
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<td>– Instituting vascular remodeling</td>
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**Overview of the Renin-Angiotensin System**

The renin-angiotensin system (RAS) has a variety of functions, the most important of which are blood pressure and intravascular volume regulation (fig. 1). The key hormone in the RAS, angiotensin II, mediates its effects via 2 receptors, AT1 and AT2. While the AT1 receptor is distributed ubiquitously in the vasculature, kidney, adrenal gland, heart, liver and brain [25], the AT2 receptor is only expressed in the adrenal medulla, uterus, ovary, vascular endothelium and distinct brain areas of adults [26]. The AT2 receptor is upregulated in pathophysiologic conditions such as cardiac failure, myocardial infarct, cerebral ischemia, and skin and nervous system lesions [27–30].

The RAS can be inhibited via angiotensin-converting enzyme (ACE) inhibitors and ARBs (fig. 1). ARBs, known as sartans, preferentially inhibit AT1. Beyond their primary blood-pressure-reducing actions, ARBs have several pleiotropic functions (table 1). ARBs have several therapeutic advantages over ACE inhibitors. First, angiotensin II can be formed by non-ACE enzymes; therefore, inhibition of ACE does not completely obliterate angiotensin II production. Second, ACE has multiple potential substrates, including bradykinin and tachykinin. Therefore, ACE inhibition can have undesirable effects. Third, ARBs preferentially block the AT1 receptor and leave the AT2 receptor unopposed. This is particularly relevant in stroke patients, since the AT2 receptor is overexpressed in cerebral ischemia and AT2 activation can lead to increased neuronal resistance to ischemia and enhanced collateral circulation recruitment [30]. Selective blockers of AT1 have generally proven to be safe and effective in the treatment of both hypertension and cardiovascular disease.
The RAS has complex interactions with insulin signaling. Both hyperglycemia and insulin activate the RAS by increasing the expression of angiotensinogen, angiotensin II and the AT1 receptor, thus contributing to the development of hypertension in insulin-resistant patients [31, 32]. In addition, angiotensin II modulates the actions of insulin [33]. The association between the RAS and insulin resistance has led to the investigation of the therapeutic role of RAS inhibition in metabolic syndrome [34]. Clinical trials have demonstrated that ACE inhibition improves insulin sensitivity and glycemic control in diabetic patients and reduces the incidence of new-onset type 2 diabetes mellitus [35–38]. Available clinical trial evidence also indicates that ARBs can improve insulin sensitivity and decrease the incidence of type 2 diabetes [39–42].
Overview of the PPAR System

The PPARs – PPAR-γ, PPAR-α and PPAR-δ – are ligand-dependent nuclear transcription factors that modulate gene expression in a variety of processes, including lipid and glucose metabolism, atherosclerotic plaque formation, vascular tone, angiogenesis, inflammation, cellular differentiation, myelogenesis, glial cell maturation and fertility [43]. PPAR-γ, expressed predominantly in adipose tissue, has a multitude of roles, including adipocyte differentiation, expression of mitochondrial uncoupling proteins, downregulation of leptin and interaction with multiple genes that control insulin sensitivity [43].

Synthetic PPAR ligands are useful in improving insulin sensitivity and lowering cholesterol levels. The fibrates, used to treat atherogenic dyslipidemia, are PPAR-α ligands; more selective and highly potent PPAR-α agonists are under investigation for the treatment of atherogenic dyslipidemia and hypercholesterolemia [43, 44]. Thiazolidinediones (TZD) antidiabetic agents, such as pioglitazone and rosiglitazone, are full PPAR-γ agonists that have insulin-sensitizing properties in patients with type 2 diabetes or impaired glucose tolerance [43, 45]. In addition to their ability to lower insulin levels, TZDs increase HDL levels, decrease serum fatty acid and triglyceride concentrations, minimally reduce blood pressure, enhance fibrinolysis, improve endothelial cell function, decrease vascular inflammation and reduce vascular smooth-muscle cell proliferation [46, 47]. PPAR-γ ligands may also have a role in stabilizing acutely ruptured plaques [48].

Clinical trial evidence supports the potential impact of PPAR-γ activation in limiting vascular risk. The Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) randomized 5,238 patients with type 2 diabetes and a history of macrovascular disease to the TZD, pioglitazone or placebo, in addition to current diabetes and cardiovascular medications [49]. In 984 patients with a history of stroke, pioglitazone significantly reduced fatal or nonfatal stroke and cardiovascular death [50]. Of particular relevance is the ongoing Insulin Resistance Intervention After Stroke (IRIS) trial, which randomizes nondiabetic patients with insulin resistance and a history of recent stroke or transient ischemic attack to the TZD, pioglitazone or placebo [51].

Despite the beneficial effects of full PPAR-γ agonists like the TZDs, recent evidence suggests that full PPAR-γ agonists are less than optimal agents in patients with metabolic syndrome. First, TZDs promote adipogenesis and fluid retention, causing weight gain [52–54]. Second, a meta-analysis of 42 trials comparing rosiglitazone to placebo suggested that patients treated with rosiglitazone had a higher odds ratio for myocardial infarction (odds ratio = 1.43; 95% confidence interval = 1.03–1.98; p = 0.03) and death from cardiovascular causes (odds ratio = 1.64; 95% confidence interval = 0.98–2.74; p = 0.06) [55].

The adverse effects of full PPAR-γ agonists like the TZDs have reinforced the need to identify additional therapies with insulin-sensitizing properties. Two classes of medications that show promise in this regard include PPAR-γ modulators (SPPARMs) that function as partial PPAR-γ agonists and PPAR-pan agonists that activate all 3 PPAR receptors [56]. SPPARMs differ from full PPAR-γ agonists because they influence some but not all of the target genes regulated by conventional PPAR-γ agonists. SPPARMs have an advantage over full PPAR-γ agonists because they exhibit less potential for undesirable side effects such as weight gain [47, 57, 58].

Experimental Studies of Partial PPAR-γ ARBs in Insulin Resistance

Two ARBs, telmisartan and irbesartan, are SPPARMs/partial PPAR-γ agonists that improve insulin sensitivity and treat hyperlipidemia in addition to lowering blood pressure. Both can induce PPAR-γ independent of angiotensin II receptor blockade [59]. Irbesartan and telmisartan enhance adiponectin protein expression, resulting in insulin sensitization [60]. In cellular PPAR-γ transactivation studies, telmisartan activates PPAR-γ at concentrations achieved in plasma following doses for treating hypertension [61] and influences the expression of PPAR-γ target genes involved in carbohydrate and lipid metabolism [57]. Irbesartan, on the other hand, acts as a PPAR-γ agonist only at high concentrations [59]. In human visceral adipocytes, telmisartan enhances the expression of genes responsible for glyceroneogenesis and fatty acid re-esterification, thus lowering fatty acid levels [57]. In addition, telmisartan increases glucose uptake and GLUT4 glucose transporter expression in preadipocytes [62]. In rats fed a high-fat, high-carbohydrate diet, telmisartan reduces serum insulin, glucose and triglyceride concentrations and significantly attenuates weight gain compared with either losartan or controls [57]. The administration of irbesartan to obese rats improves insulin sensitivity and attenuates adiponectin serum depletion [60].

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Clinical Evidence for Partial PPAR-γ ARBs in Hyperlipidemia and Insulin Resistance

Several lines of clinical evidence support the use of the partial PPAR-γ agonist, telmisartan, in treating hyperlipidemia and insulin resistance. First, a case report of a 52-year-old man with metabolic syndrome taking telmisartan showed that after 8 weeks of treatment, his triglyceride, glucose and insulin levels fell to within normal limits [63]. Just 6 weeks after switching the patient to valsartan, his triglyceride, insulin and glucose levels again increased. The levels were restored to normal by returning the patient to telmisartan therapy. Second, an open-label observational study of hypertensive patients taking telmisartan showed that patients with type 2 diabetes mellitus had reduced glucose and triglyceride concentrations compared with baseline values [64]. Third, a study of nondiabetic patients with essential hypertension randomized to telmisartan or the calcium channel blocker nisoldipine, found that high-dose treatment with telmisartan but not nisoldipine reduced serum insulin levels [65]. Finally, 2 prospective, double-blind placebo-controlled studies have shown the beneficial metabolic effects of telmisartan. In the first study, 119 patients with mild hypertension and type 2 diabetes mellitus were randomized to telmisartan, eprosartan or placebo [66]. At 12 months, telmisartan, but not eprosartan, significantly lowered total cholesterol, LDL and triglyceride levels. In the second study, patients were randomized to telmisartan or losartan. After 3 months, the telmisartan group had significantly lower fasting glucose, insulin resistance, hemoglobin A1c and insulin levels compared to baseline, whereas the losartan group had no significant changes [67]. It is noteworthy that the potential insulin-sensitizing benefit and relatively safer side effect profile of partial PPAR-γ ARBs is currently being tested in a group of heart failure patients who would otherwise not receive full PPAR-γ agonists given their risk of fluid retention [68].

Clinical Trials of Partial PPAR-γ ARBs in Stroke ONTARGET, TRANSCEND and PROFESS Trials

Several trials of SPPARMs for stroke prevention are ongoing and results should be available shortly. In the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET), subjects with increased risk for cardiovascular events were randomized to receive telmisartan, ramipril, or a combination of telmisartan and ramipril, while in the companion Telmisartan Randomized Assessment Study in ACE-In intolerant Subjects with Cardiovascular Disease (TRANSCEND) trial, subjects intolerant to ACE inhibitors were randomized to telmisartan or placebo [69, 70]. The Prevention Regimen for Effectively Avoiding Second Strokes (PROFESS) trial randomized 20,333 patients with a history of stroke to the combination of aspirin and extended-release dipyridamole versus clopidogrel in conjunction with telmisartan or placebo, in the presence of background blood pressure therapy.

Conclusions

Given the growing obesity epidemic, molecules that can simultaneously block the angiotensin II receptor and partially activate PPAR-γ have the potential to treat both hemodynamic and biochemical features of insulin resistance and could provide unique opportunities for the prevention of stroke in high-risk populations. Since hypertension frequently occurs together with insulin resistance and dyslipidemia, the availability of such multifunctional molecules that treat more than just elevated blood pressure or the associated metabolic disturbances could be of immense clinical value. The identification of ARBs with selective PPAR-γ-modulating abilities is promising for the development of third-generation ARBs and PPAR-γ partial agonists aimed at treating hypertension, insulin resistance and hyperlipidemia, and ultimately mitigating the burden of cardiovascular and cerebrovascular disease. Finally, it may be helpful to conduct a clinical trial to confirm or refute the potential dual effect of partial PPAR-γ agonist ARBs upon insulin resistance and vascular outcomes in persons at high risk for stroke.

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