Endothelin-1 Mediates the Systemic and Renal Hemodynamic Effects of GPR81 Activation


Abstract—GPR81 (G-protein-coupled receptor 81) is highly expressed in adipocytes, and activation by the endogenous ligand lactate inhibits lipolysis. GPR81 is also expressed in the heart, liver, and kidney, but roles in nonadipose tissues are poorly defined. GPR81 agonists, developed to improve blood lipid profile, might also provide insights into GPR81 physiology. Here, we assessed the blood pressure and renal hemodynamic responses to the GPR81 agonist, AZ5538. In male wild-type mice, intravenous AZ5538 infusion caused a rapid and sustained increase in systolic and diastolic blood pressure. Renal artery blood flow, intrarenal tissue perfusion, and glomerular filtration rate were all significantly reduced. AZ5538 had no effect on blood pressure or renal hemodynamics in Gpr81−/− mice. Gpr81 mRNA was expressed in renal artery vascular smooth muscle, in the afferent arteriole, in glomerular and medullary perivascular cells, and in pericyte-like cells isolated from kidney. Intravenous AZ5538 increased plasma ET-1 (endothelin 1), and pretreatment with BQ123 (endothelin-A receptor antagonist) prevented the pressor effects of GPR81 activation, whereas BQ788 (endothelin-B receptor antagonist) did not. Renal ischemia-reperfusion injury, which increases renal extracellular lactate, increased the renal expression of genes encoding ET-1, KIM-1 (Kidney Injury Molecule 1), collagen type 1-α1, TNF-α (tumor necrosis factor-α), and F4/80 in wild-type mice but not in Gpr81−/− mice. In summary, activation of GPR81 in vascular smooth muscle and perivascular cells regulates renal hemodynamics, mediated by release of the potent vasoconstrictor ET-1. This suggests that lactate may be a paracrine regulator of renal blood flow, particularly relevant when extracellular lactate is high as occurs during ischemic renal disease. (Hypertension. 2020;75:00-00. DOI: 10.1161/HYPERTENSIONAHA.119.14308.) • Data Supplement

Key Words: blood pressure • hypoxia • ischemia-reperfusion-injury • pericytes • renal blood flow

GPR81 (G-protein-coupled receptor 81), GPR109a, and GPR109b form the hydroxycarboxylic acid receptor subfamily. Encoded by the HCAR1 gene, GPR81 is predominantly expressed in brown and white adipose tissue. L-lactate is the endogenous ligand with an EC50 of ≈5 mmol/L. Lactate, formed from pyruvate during anaerobic glycolysis, has a physiological plasma concentration of 0.5 to 2 mmol/L, rising from 10 to 30 mmol/L during intense exercise or prolonged hypoxia. This suggests that GPR81 is either physiologically quiescent basally or that it is primarily responsive to the local, rather than circulating, concentration of lactate. In adipocytes, activation of GPR81 by L-lactate prevents lipid breakdown and promotes storage of energy-rich metabolites in adipocytes. Synthetic GPR81 agonists are potential therapies for dyslipidemia and inhibit lipolysis in cultured adipocytes and in vivo.

GPR81 is also expressed in brain, kidney, liver, skeletal muscle, and immune cells, but the function in nonadipose tissue is poorly defined and the limited data is somewhat contradictory. In mouse macrophages and human monocytes, GPR81 activation suppresses Toll-like receptor pathways, preventing NLRP3 (NACHT, LRR and PYD domains-containing protein 3) inflammasome activation and cell death. This mechanism appears protective, with receptor activation reducing tissue injury in models of hepatitis, pancreatitis, and colitis. GPR81 inhibition/knockdown has also been shown to be protective, enhancing neuron survival in cerebral ischemia and slowing cancer growth, partly due to effects on the vasculature. For example, GPR81 knockdown in a breast cancer cell line suppressed VEGF (vascular endothelial growth factor) and amphiregulin, retarding angiogenesis. Similarly, in the sensorimotor cortex of GPR81

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knockout mice (Gpr81−/−), the induction of VEGF-A and increased capillary density by either treadmill exercise or subcutaneous lactate injections was absent. Ex vivo lactate infusion in the rat retina decreases capillary lumen diameter, suggesting vasomotor effects of GPR81 activation. Indeed, a small molecule GPR81 agonist, AZ2 (aka AZ’ 5538), which suppressed in vivo free fatty acid levels, also increased blood pressure (BP) when infused intravenously. Nonselective α-adrenoceptor antagonism and endothelin receptor blockade separately reduced this pressor effect.

The concept that lactate could influence blood pressure (BP) through activation of GPR81 is relevant to human health. In the current study, we used AZ’ 5538 and Gpr81−/− mice to resolve the effects of GPR81 activation on BP and renal hemodynamics in mice and further demonstrated that genetic deletion of the receptor conferred protection against renal ischemia-reperfusion injury.

Methods
See the Data Supplement for detailed methods. The data that support the findings of this study are published in the University of Edinburgh data storage and available from the corresponding author upon reasonable request.

Experiments were performed on adult male C57Bl/6JCrI (Charles River, Paris, France) or adult male Gpr81−/− (wild-type) and Gpr81−/− (knockout) mice on a C57BL/6OlaHsd background. Experiments were performed under a UK Home Office Licence following ethical review by the University of Edinburgh.

In Vivo Measurement of BP and Renal Function
In anesthetized mice, either AZ’ 5538 (1 μmol/kg bw/min) or 5% mannitol vehicle was infused intravenously for 15 minutes. BP was measured via a carotid cannula and renal hemodynamics measured via a Doppler transit time probe, and Doppler flux probes were inserted into the cortex and medulla. Separately, renal artery blood flow (RBF) was measured noninvasively by Pulse-wave Doppler (Veo670 and 707B 30 MHz ultrasound probe; VisualSonics, Canada). Glomerular filtration rate (GFR) was measured by Fluorescein isothiocyanate-inulin clearance before and after administration of AZ’ 5538.

In Vivo Blockade of Endothelin Receptors
Anesthetized C57Bl/6JCrI mice had separate intravenous infusion of AZ’ 5538 and endothelin receptor antagonists or their corresponding vehicles. Bosentan, a mixed endothelin receptor antagonist, was used at 20 and 40 mg/kg; BQ123 (endothelin-A receptor antagonist) and BQ788 (endothelin-B receptor antagonist) were used at 1 and 2 mg/kg.

Ischemia-Reperfusion Injury (IRI)
Male Gpr81−/− and wild-type littermates were subject to 27 minutes of renal pedicle clamping (reperfusion was confirmed visually) followed by nephrectomy of the nonclamped kidney. After 6 days, mice were killed by cervical dislocation and the kidney taken for mRNA extraction and analysis.

RNA Analysis
Polymerase chain reaction (PCR) was used to determine if Gpr81 was expressed in arteries. Subsequently, RNAseq in situ hybridization was used to localize Gpr81 in artery and kidney sections. For quantitative PCR, RNA was extracted from quarter kidneys (RNeasy Mini Kit, Qiagen) and used to assess mRNA abundance by real-time quantitative PCR (Universal Probe Library; Sigma Aldrich). To assess Gpr81 expression in defined populations of renal cells, kidneys from male mice were dissociated into a single-cell suspension and incubated with the following rat anti-mouse antibodies: PDGFRβ (Platelet Derived Growth Factor Receptor Beta), CD31 (cluster of differentiation 31), LITL (Lotus tetragonalobus lectin), and F4/80. Fluorescence-activated cell sorting was performed using the fluorescence-activated cell sorting Aria II (BD Biosciences) using 4,6-diamidino-2-phenylindole to determine live cells. Cells were sorted into lysis buffer and RNA extracted using RNase microkit (Qiagen), quality checked by Agilent Bioanlyser (RNA integrity number >8), and amplified cDNA made from the RNA using Ovation RNA-Seq System V2 (NuGen).

Endothelin-1
ET-1 (endothelin-1) was measured by ELISA (R&D Systems, United Kingdom). ET-1 protein concentrations were normalized to total protein (Pierce BCA assay; Thermo Fisher, United Kingdom).

Statistics
All data are mean±SD. After confirming normal distribution, statistical comparisons (Graphpad Prism 6, La Jolla, CA) were made by using 1-sample t test (comparing against a value of 0), unpaired t test, and 1- or 2-way ANOVA. For 2-way ANOVA, the main effects of the genotype/treatment and time were assessed, and the interaction between them. Planned comparisons were made using Holm-Sidak with a family P value fixed at 0.05.

Results
Activation of GPR81 Increases BP and Decreases RBF
In anesthetized male C57Bl/6J mice, baseline systolic BP (SBP) was 86±9 mm Hg, diastolic BP (DBP) was 69±11 mm Hg, and heart rate was 284±38 bpm. AZ’ 5538 increased SBP (Figure 1A; ANOVA effect of treatment P<0.0013; effect of time and interaction P<0.0001) and DBP (Figure 1B; ANOVA effect of treatment P=0.0094; effect of time and interaction P<0.0001). The peak BP increases were 13±4 mm Hg and 1±3 mm Hg for SBP and DBP, respectively (Figure 1C). Heart rate fell with infusion of AZ’ 5538 compared with 5% mannitol vehicle (Figure 1D). All mice received a second infusion of AZ’ 5538, 35 minutes after the first administration. The pressor response to the second administration was attenuated, particularly in DBP (Figure S1 in the Data Supplement).

RBF was measured in 2 different groups of mice by direct Doppler ultrasound with a probe around the right renal artery (baseline RBF =0.60±0.23 mL/min) and by pulse-wave Doppler (baseline velocity =275±21 mm/s). AZ’ 5538 infusion significantly decreased RBF, by ≈50% measured by flow probe (Figure 1E; ANOVA effect of treatment P=0.027; effect of time and interaction P<0.0001) and by ≈30% by pulse-wave Doppler (Figure S2; peak decrease of −186±26 mm/s; ANOVA drug treatment P=0.0002, time and interaction P<0.0001). In another experiment, GFR was measured, and the mice were then randomized to receive continued intravenous vehicle (n=8) or AZ’ 5538 (n=8). There was no significant change in GFR with vehicle but AZ’ 5538 infusion caused GFR to fall significantly (Figure 1F).

The Cardiovascular Effects of AZ’ 5538 Are Mediated Via Gpr81
BP and heart rate were comparable in Gpr81−/− mice and wild-type littermates (Table S3). In wild types, AZ’ 5538 significantly increased SBP (Figure 2A; P<0.0001 for main effects of genotype and time and interaction) and DBP (Figure 2B; P<0.0001 for main effects of genotype and
time and for interaction) and decreased heart rate (Figure S3; ANOVA genotype $P=0.025$, time $P=0.003$, and interaction $P<0.0001$), consistent with our data in C57BL/6J mice. AZ’5538 did not increase BP in *Gpr81*−/− mice.

RBF decreased significantly with AZ’5538 infusion in wild-type mice but remained unchanged in *Gpr81*−/− mice (Figure 2C; ANOVA genotype $P=0.008$ interaction and time $P<0.0001$). Renal vascular resistance did not differ between genotypes, although the interaction was significantly different (Figure 2D; ANOVA genotype $P=0.151$, time $P=0.022$, and interaction $P=0.0002$). AZ’5538 reduced renal cortical perfusion but only in wild-type mice (Figure 2E; genotype $P=0.0003$ and time interaction $P<0.0001$). Medullary flux also fell in wild-type mice but not in the *Gpr81*−/− (Figure 2F; genotype $P=0.070$, time and interaction $P<0.0001$). Baseline GFR was not different between genotype. AZ’5538 reduced GFR in wild-type mice (Figure 2G; $\Delta$GFR=$-125\pm48$ µL/min;
Expression of Gpr81 in Arteries and Kidney

Gpr81 was expressed in aorta, renal, and mesenteric arteries (Figure 3A). Separately, quantitative PCR was used to assess Gpr81 expression in fluorescence-activated cell sorting–isolated renal cell populations (Figure 3B; n=4 mice). Gpr81 mRNA was highly expressed in PDGFRβ+ cells (pericytes) from all 4 samples, identified in only one of 4 samples of CD31+ cells (endothelial) and was undetectable in LTL (renal tubules) and F4/80 (macrophage) cell populations. Using in situ hybridization on whole kidney sections, Gpr81 was localized in the cortex and medulla of wild-type but not Gpr81−/− mice (Figures 4A through 4D). The staining in the cortex was localized mainly to the glomeruli (Figure 4A and Figure S4), particularly at the vascular pole, consistent with localization in arterioles. Gpr81 was also expressed in the medulla (Figure 4C) and did not co-localize with the nuclear stain. We examined Gpr81 expression in aorta and renal artery (Figure 4E and 4F), observing positive staining in the medial layer, indicating localization to vascular smooth muscle cells. No staining was visible in arteries from Gpr81−/− mice (Figure S5).

Cardiorenal Effects of GPR81 Activation Are Endothelin-1 Dependent

AZ′5538 infusion significantly increased plasma ET-1 concentration (Figure 5A) without changing the amount in aorta or whole kidney homogenates (Figure S6); renal expression of Edn1 was lower in mice that had received a 15-minute infusion of AZ′5538 (Figure S6). To assess functional crosstalk between GPR81 and the endothelin system, wild-type mice were pretreated with bosentan, before infusion of AZ′5538. Bosentan pretreatment at 40 mg/kg did not change the peak pressor response to AZ′5538 but significantly blunted the sustained effect on BP (Figure 5B; treatment P=0.024, time P<0.0001, and interaction P=0.064); similar actions were also observed at the 20 mg/kg bosentan. Next, we used pretreatment with BQ123 and, separately, BQ788. Baseline BP was...
B Q123 at 2 mg/kg largely prevented the pressor effect of GPR81 activation, and there was no sustained BP rise in this group (Figure 5C and Figure S8; BQ123 treatment \(P=0.044\), time \(P<0.0001\), and interaction \(P=0.988\). BQ788 did not change the BP response to AZ5538 (Figure 5D and Figure S8).

**Gpr81**−/− Mice Are Protected From Renal Ischemia-Reperfusion Injury

In wild-type mice, renal ischemia significantly increased the mRNA expression of the tubule injury marker KIM-1 (Kidney Injury Molecule 1) (Figure 6A), the fibrosis marker collagen 1α1 (Figure 6B), the inflammatory cytokines TNF-α (Tumor necrosis factor alpha; Figure 6C), MCP-1 (monocyte chemotactic protein 1; Figure 6D), CXCL-1 (C-X-C Motif Chemokine Ligand-1; Figure 6E), CXCL-10 (C-X-C Motif Chemokine Ligand-10; Figure S9A), and the pan-macrophage marker F4/80 (Figure S9B). ET-1, assessed by renal expression of Edn1 mRNA, was also increased by injury (Figure 6F).

The transcriptional response to IRI was significantly blunted in **Gpr81**−/− mice. Injury did not affect endothelin-A receptor expression in either genotype (Figure S9C); endothelin-B receptor expression was reduced in both genotypes by IRI (Figure S9D).

**Discussion**

A decade ago, the orphan receptor GPR81 was shown to be activated with low affinity by L-lactate and α- and γ-hydroxybutyrate. GPR81 mRNA was enriched in mouse and human adipocytes and receptor activation by lactate inhibited lipolysis. GPR81 mRNA expression was also found in nonadipose tissue, with expression in the highly vascularized tissues of heart, skeletal muscle, and kidney being ∼10% of that in adipocytes. Here, we detected **Gpr81** mRNA in whole kidney homogenates. In each of 3 artery types examined, **Gpr81** localized to the smooth muscle layer. Transgenic fluorescent-reporter mice show **Gpr81** expression in the vessel wall of pial arteries. Single-cell RNA sequencing detected **Gpr81** in cerebral and lung vascular smooth muscle cells. **Gpr81** has been identified in cultured human umbilical vein endothelial cells, but we suggest this is not a major expression site, finding discernable levels in only 1 of 4 isolated renal endothelial cell samples and no in situ endothelial **Gpr81** mRNA expression in large arteries. Similarly, **Gpr81** does not co-localize with endothelial cell markers in the cerebral vasculature. Within the kidney, **Gpr81** was additionally expressed in glomerular arterioles, with a previous study reporting afferent arteriolar localization in dog and mouse. We detected **Gpr81** in perivascular cells, particularly, in the renal medulla and in isolated PDGFRβ+ cells. **Gpr81** also colocalizes with PDGFRβ+ expressing cells and leptomeningeal cells in the cerebral microcirculation.

This expression profile suggests that GPR81 is intimately involved in vascular/microvascular function, as described for other metabolic GPCRs. For example, activation of GPR109a by niacin reduces reactive oxygen production in arterial endothelial cells and promotes vasodilation by stimulating prostaglandin production. Succinate, which activates GPR91, acutely increases circulating Ang II (angiotensin II) and BP in rats. Like GPR81, GPR91 is also coupled to \(G_i\), and
succinate has direct effects on arterial contractility.\textsuperscript{23} For lactate/GPR81, however, functional data are limited. Increasing lactate concentration in the brain, either through exercise or by exogenous administration, promotes angiogenesis.\textsuperscript{16} This effect is GPR81-dependent since lactate-induced angiogenesis does not occur in \textit{Gpr81}\textsuperscript{−/−} mice. Lactate also constricts retinal microvessels, but it is not known whether this is GPR81-mediated.\textsuperscript{17} Infusion of very high concentrations of lactate increases BP in rats,\textsuperscript{24} most likely reflecting panic-induced sympathoexcitation, rather than activation of GPR81.

The recent development of potent GPR81 agonists to treat dyslipidemia\textsuperscript{8,9,25} provides tools to probe the cardiovascular physiology of GPR81. One study has examined this, finding that structurally distinct GPR81 agonists increased SBP by \textasciitilde{15} mm Hg in rats and dogs when given intravenously and by \textasciitilde{5} mm Hg in mice when given orally.\textsuperscript{9} Our studies confirm and extend this work, unequivocally demonstrating that one of these compounds, AZ\textsuperscript{′}5538, increases BP dependent on the expression of GPR81. We further show that GPR81 activation reduces renal artery flow, cortical and medullary perfusion, and GFR. The rapid increase in BP makes it difficult to unambiguously interpret these renal hemodynamic effects of AZ\textsuperscript{′}5538. However, RBF and cortical perfusion normally autoregulate when BP increases\textsuperscript{26,27} and our data most likely reflect direct vasoconstriction of the renal artery and preferential constriction of the afferent over efferent arteriole, accounting for the GFR reduction. Furthermore, expression of GPR81 in renal PDGFR\textsuperscript{β} cells is consistent with localization in pericytes, contractile cells which regulate vasa recta blood flow,\textsuperscript{28} independent of changes in total or cortical blood flow.\textsuperscript{29} Thus, pericyte constriction may contribute to reduced intrarenal perfusion following GPR81 activation, but this was not demonstrated directly.

The cellular mechanism underpinning GPR81-mediated vasoconstriction is not fully known. In adipocytes, GPR81 couples to \textit{G}_{\text{i}}, downregulating cAMP production and protein
kinase A signaling. Activation of G\textsubscript{i} pathways in vascular smooth muscle cells, by GPCR kinase 5, for example, lowers intracellular cAMP (Cyclic adenosine monophosphate), enhances vasoconstriction, and causes sustained hypertension. Similarly, activation of A\textsubscript{1} receptors by adenosine constricts the renal afferent arteriole by a G\textsubscript{i}-mediated cascade involving activation of phospholipase C. Reciprocally, agents that increase cAMP promote arterial vasorelaxation. However, our data do not support a direct vasomotor effect of GPR81 activation and instead indicate dependency on ET-1 release and subsequent endothelin-A receptor activation. Notably, ET-1 is synthesized by arterial myocytes, a cell that expresses GPR81. Further, a reduction in cAMP stimulates the production of ET-1 by myocytes, as does vascular disease and injury. The hemodynamic response to AZ\textsuperscript{5538} is also consistent with this sequence: ET-1, via endothelin-A receptors, induces a stronger constriction of the afferent than efferent arteriole and also causes pericyte contraction, reducing vasa recta blood flow, both of which were found in our study.

In the final series of experiments, renal IRI was induced as this is known to increase intrarenal extracellular lactate. We selected a panel of transcriptional markers to capture cardinal features of IRI, tubular injury (KIM-1), increased matrix deposition (collagen 1a1), enhanced intrarenal cytokine production (TNF-\textalpha, CXCL-1, CXCL-10), and increased monocyte/macrophage infiltration (F4/80). In wild-type mice, ischemia-reperfusion increased expression of these markers, as anticipated. In contrast, this transcriptional response to ischemia-reperfusion was absent or blunted in Gpr81\textsuperscript{−/−} mice. Similar outcomes are reported in cerebral ischemic injury: 3-hydroxy-butyrate, which antagonizes GPR81, prevents lactate-induced injury in primary cultured neurons and is neuroprotective in mice exposed to cerebral artery occlusion. In contrast, overexpression of GPR81 amplifies sensitivity to hypoxic injury in a neuronal cell line.

We cannot unequivocally establish the mechanism of renoprotection in Gpr81\textsuperscript{−/−} mice, but these animals did not display the sustained post-ischemic increase in renal ET-1 expression that occurred in wild-type mice. This is likely to be important for at least 2 reasons. First, endothelin-A receptor–dependent vasoconstriction may contribute to progressive renal injury, which has a strong hemodynamic component. Second, ET-1, via endothelin-B receptors, can drive epithelial-mesenchymal transition and promote renal fibrosis. Gpr81\textsuperscript{−/−} mice did not respond to ischemia-reperfusion with an increase in TNF-\textalpha or collagen 1a1 production, and the disconnection between extracellular lactate and ET-1 may account for this.

A limitation of our work is that all of the studies were performed on male mice. Although recent studies show that sex does not influence afferent arteriolar reactivity to ET-1, other literature indicates sex differences in the renal actions of ET-1, which might be particularly relevant in an injury context.
For example, post ischemia-reperfusion, male rats display an exaggerated early increase in renal vascular resistance and then a more pronounced decline in renal function and lower survival rate than do female rats. Furthermore, IRI increased ET-1 expression in male rats and prophylactic endothelin-A receptor blockade improved survival. In marked contrast, endothelin-A receptor blockade in females was detrimental, worsening post-ischemic survival rates, suggesting a protective role of ET-1/endothelin-A receptors activation. Overall, these data indicate that female Gpr81−/− may not show the post-ischemic renoprotection of male animals identified by the current study.

**Perspectives**

In summary, our study indicates that GPR81 activation regulates macro- and microvascular perfusion within the kidney, dependent on ET-1 signaling. The physiological requirement for a system that would lead to vasoconstriction of regions with high anaerobic cellular metabolism is not readily apparent, given the injurious effect of hypoxia. However, earlier work in skeletal muscle associated exercise-induced accumulation of extracellular lactate with the release of ET-1 and proposed that constraining vasodilation of the skeletal vasculature would help maintain systemic BP during exercise. It may be that GPR81 activation similarly constrains the propensity to increase flow into relatively ischemic areas of the kidney and thereby mitigates against hyperemic damage. Additionally, the ET-1 release may contribute to vascular remodeling with sustained hypoxia. Overall, our data suggest that blockade of the GPR81/ET-1 system could offer beneficial vascular support in the post-injury phase.
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40. What isrelevant? The endogenous ligand for GPR81 is lactate. Our results suggest that lactate, via activation of GPR81, may contribute to the physiological regulation of blood pressure and renal hemodynamics.


43. What is new? Activation of GPR81 (G-protein-coupled receptor 81) increases blood pressure, induces renal vascular and microvascular constriction, and reduces glomerular filtration rate.

What Is Relevant?

- The systemic and renal hemodynamic effects are mediated by release of ET-1 (endothelin-1) and activation of the endothelin-A receptor.
- GPR81 is localized to arterial vascular smooth muscle, to the arterioles, and in pericytes that influence capillary blood flow.
- Genetic deletion of Gpr81 in mice protects against renal ischemic injury.

What Is New?

- GPR81 antagonists may offer a route for vascular support in renal ischemia, the most common cause of acute kidney injury in humans.

Summary

In male mice, activation of GPR81 increased blood pressure and reduced renal artery blood flow, renal capillary perfusion, and glomerular filtration rate. GPR81 activation rapidly increased plasma ET-1: the pressor effects were prevented by selective endothelin-A receptor antagonism. In male wild-type mice, ischemia-reperfusion increased renal expression of ET-1 and genes associated with injury, fibrosis, and inflammation. Gpr81-/- did not show this post-ischemic injury response.