Commentary

Glucocorticoid Receptor Antagonism as a New “Remedy” for Insulin Resistance—Not There Yet!

Elena V. Varlamov, Jonathan Q. Purnell, and Maria Fleseriu

1Departments of Medicine, Division of Endocrinology, Diabetes and Clinical Nutrition, Oregon Health & Science University, Portland, OR, USA; 2Department of Neurological Surgery, Oregon Health & Science University, Portland, OR, USA; 3Pituitary Center, Oregon Health & Science University, Portland, OR, USA; and 4Knight Cardiovascular Institute, Oregon Health & Science University, Portland, OR, USA

ORCID number: 0000-0001-9264-6289 (M. Fleseriu).

Received: 17 February 2021; Editorial Decision: 21 February 2021; First Published Online: 28 February 2021; Corrected and Typeset: 17 April 2021.

Key Words: mifepristone, insulin sensitivity, glucose intolerance, adipose

Insulin resistance (IR) remains an enigma even after many decades of research (1–3). Low-grade inflammation, lipotoxicity, mitochondrial dysfunction, hypoxia, as well as cortisol and glucocorticoid (GC) receptors (GR) all have roles to play in glucose metabolism and IR. Cortisol stimulates hepatic gluconeogenesis, suppresses pancreatic insulin release, and increases IR in both skeletal muscle and adipose tissue (1–3). Glucocorticoids also play a pivotal role in stress response modulation and in the tight synchronization of central and peripheral clocks. Loss of cortisol circadian rhythm and flattened secretion pattern(s) induce GC-mediated effects on appetite, obesity, and metabolic disturbances including IR, hyperglycemia, and type 2 diabetes mellitus (DM2), dyslipidemia, osteopenia and osteoporosis, and hypertension (4). In patients with adrenal incidentalomas, even those deemed nonfunctioning, adrenalectomy improves cardiovascular parameters, suggesting a cortisol “continuum” between “normal” and “abnormal” (2). Higher cortisol production rates and free cortisol are associated with increased visceral fat and impaired insulin sensitivity in men, suggesting that enhanced cortisol signaling across a range of values considered “normal” could influence visceral fat accumulation, which may in turn impact IR (5).

In addition to dysregulated cortisol secretion and increased physiologic GC exposure contributing to expression of metabolic syndrome (MS), altered GC tissue metabolism and GR activation have likewise been implicated in metabolic dysfunction (1). Eucortisolemic patients with obesity and/or MS, exhibit increased 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) levels, leading to elevated “tissue” cortisol concentrations and 11β-HSD1 inhibitors can improve glycemia and weight in DM2 (3). Moreover, increased GR levels, activity, and gene polymorphisms have been shown to play a role in expression of obesity and MS (1).

Thus, GR antagonism to reverse GC-related metabolic alterations has drawn specific interest (3). Specifically, in patients with Cushing’s syndrome (CS), the majority of whom exhibit abnormal metabolic changes, GR-blockade has been studied as a potential treatment target. Encouragingly, in a phase III clinical trial with mifepristone, a GR and progesterone-receptor
blocker showed significant improvements in glycemia, IR, and weight in CS patients regardless of etiology (6).

How Do These Metabolic Improvements in Patients With CS Translate to Patients Without Known Hypercortisolism?

Multiple animal studies have demonstrated antidiabetic effects of GR-blockade in obese rodents without hypercortisolism. An excellent study by Gubbi et al has explored this effect in humans (3). In their randomized, placebo-controlled, double-blinded study, 16 eucortisolemic patients who were overweight or obese with prediabetes or DM2 were treated with mifepristone at 50 mg every 6 h for 9 days (3). Overall, insulin sensitivity indices as assessed by frequently sampled intravenous glucose tolerance test (the study’s primary outcome) or oral glucose tolerance test (OGTT) were not different between treatment groups. However, adipose tissue insulin sensitivity did improve, and a tendency toward improvement in hepatic insulin sensitivity-indices was found. Improvements in fasting plasma glucose (100.4 mg/dL vs 107.8 mg/dL, \(P < 0.001\)) and insulin levels (95.6 pmol/L vs 142.8 pmol/L, \(P < 0.01\)) rather than dynamic parameters derived from frequently sampled intravenous glucose tolerance and OGTTs suggested a potentially greater role of GC blockade in the liver than in muscle or islet cells.

These results support the concept of GR-blockade to improve IR in humans. However, the short study duration and the relatively low mifepristone dose may have precluded more significant observations. For comparison, a double-blind, randomized, placebo-controlled trial of mifepristone in healthy postmenopausal women used a mifepristone dose of 600 mg/day for 6 weeks (7). In this study, fasting insulin levels and homeostatic model assessment for insulin resistance (HOMA-IR) improved without a change in fasting glucose. In another study of patients with subclinical hypercortisolism and an adrenal adenoma, mifepristone dose was 400 mg/day for 4 weeks, and improved insulin levels, HOMA-IR, and Matsuda index without a change in fasting glucose levels were found (2). In patients with overt CS and DM2 or impaired glucose tolerance receiving a mean mifepristone dose of 732 ± 366 mg/day, improvement in insulin levels, fasting plasma glucose levels, and HOMA-IR were observed as early as 6 weeks and continued to improve through week 24 (2). In the study by Gubbi et al, mifepristone (200 mg/day) improved adipose tissue sensitivity without significant change in whole-body insulin sensitivity indices (3). Importantly, this suggests a possible dose-dependent effect in different tissues.

While either longer duration or a higher mifepristone dose might produce more pronounced changes in the assessed parameters, adverse effects (AEs) associated with GR-blockade and mineralocorticoid receptor (MR) activation by elevated cortisol could become more apparent. Gubbi et al, did not report any AEs during the 9 days of treatment, although blood pressure was slightly increased and potassium levels were slightly decreased while remaining in the normal range (3). No adrenal insufficiency was reported (3). In healthy postmenopausal women, 6 weeks of mifepristone at 600 mg/day led to AEs potentially related to adrenal insufficiency and mineralocorticoid effects in 20% of subjects (7), compared to patients with CS, where 50% experienced nausea and fatigue at various doses (6). Hypertension, peripheral edema, and hypokalemia were also frequent, with many patients requiring MR antagonists (6). Moreover, endometrial thickening and abnormal vaginal bleeding related to progesterone receptor blockade were observed in some patients (6).

In addition, activation of the hypothalamic-pituitary-adrenal axis with significant adrenocorticotropic hormone and cortisol elevation occurs even with mild GR-blockade (3). One could speculate that eventually this activation could overcome the GR-blockade and negate effects in the long run. Moreover, MR activation could also counteract the positive effects of GR-blockade as MR has been also shown to play a role in inflammation, IR, and adipogenesis (8). In patients with IR and DM2, long-term effects and safety of GR-blockade are unknown. Additionally, most patients with obesity, MS, and DM2 require multimodal treatment, and mifepristone has many known drug-drug interactions including, but not limited to, some statins, antidepressants, and aspirin. As the magnitude of the effects is small relative to other agents and relative to cost, further applicability of any cortisol modulators (GR-blockers, including new generation selective agents, 11\(\beta\)-HSD1 inhibitors, or steroidogenesis inhibitors) for a primary therapeutic indication of DM2 remains to be further explored in future studies.

Acknowledgments

The authors thank Shirley McCartney, PhD, Oregon Health & Science University, for editorial assistance.

Additional Information

Correspondence: Maria Fleseriu, MD, Oregon Health & Science University, Mail Code CH8N, 3303 South Bond Avenue, Portland, Oregon 97239, USA. E-mail: fleseriu@ohsu.edu.

Disclosures: MF has received research support to university from Novartis/Recordati, and Strongbridge has been an occasional scien-
Scientific consultant to Novo Nordisk, Recordati, Sparrow Pharmaceuticals, and Strongbridge. JQP has received consulting fees for Novo Nordisk. EV has no conflicts to report.

Data Availability: Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

References
1. Akalestou E, Genser L, Rutter GA. Glucocorticoid metabolism in obesity and following weight loss. Front Endocrinol (Lausanne). 2020;11:59.
2. Debono M, Chadarevian R, Eastell R, Ross RJ, Newell-Price J. Mifepristone reduces insulin resistance in patient volunteers with adrenal incidentalomas that secrete low levels of cortisol: a pilot study. PLoS One. 2013;8(4):e60984.
3. Gubbi S, Muniyappa R, Sharma ST, Grewal S, McGlotten R, Nieman LK. Mifepristone improves adipose tissue insulin sensitivity in insulin resistant individuals. J Clin Endocrinol Metab. Published online 2021. doi:10.1210/clinem/dgab046
4. Oster H, Challet E, Ott V, et al. The functional and clinical significance of the 24-hour rhythm of circulating glucocorticoids. Endocr Rev. 2017;38(1):3-45.
5. Purnell JQ, Kahn SE, Samuels MH, Brandon D, Loriaux DL, Brunzell JD. Enhanced cortisol production rates, free cortisol, and 11beta-HSD-1 expression correlate with visceral fat and insulin resistance in men: effect of weight loss. Am J Physiol Endocrinol Metab. 2009;296(2):E351-E357.
6. Fleseriu M, Biller BM, Findling JW, Molitch ME, Schteingart DE, Gross C; SEISMIC Study Investigators. Mifepristone, a glucocorticoid receptor antagonist, produces clinical and metabolic benefits in patients with Cushing’s syndrome. J Clin Endocrinol Metab. 2012;97(6):2039-2049.
7. Page ST, Krauss RM, Gross C, et al. Impact of mifepristone, a glucocorticoid/progesterone antagonist, on HDL cholesterol, HDL particle concentration, and HDL function. J Clin Endocrinol Metab. 2012;97(5):1598-1605.
8. Thuzar M, Stowasser M. The mineralocorticoid receptor—an emerging player in metabolic syndrome? J Hum Hypertens. 2021;35(2):117-123.