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Miniperspective

Blockade of Glucocorticoid Excess at the Tissue Level: Inhibitors of 11β-Hydroxysteroid Dehydrogenase Type 1 as a Therapy for Type 2 Diabetes

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Introduction

Glucocorticoids are stress hormones with regulatory effects on carbohydrate, protein, and lipid metabolism. There are two forms of glucocorticoids in humans: the active cortisol (corticosterone in rodents) and inactive cortisone (11-dehydrocorticosterone in rodents). The physiological actions of glucocorticoids are mediated by glucocorticoid receptor (GR[a]) which, upon binding to its natural ligand cortisol, is activated and regulates diverse physiological events. GR is a nuclear receptor ubiquitously expressed in tissues and triggers biological effects through transcriptional activation or suppression of target genes (Figure 1). Cortisol is synthesized in the adrenal glands as part of adrenal steroidogenesis that also involves the production of mineralocorticoids and androgens.[1] Cortisol is secreted in a relatively high level at 10−20 mg/day.[1] Cortisol biosynthesis is tightly controlled by adrenocorticotropic hormone (ACTH), a peptide hormone secreted from the anterior pituitary and is itself regulated by the hypothalamic peptide corticotrophin-releasing hormone (CRH).[2] Circulating cortisol regulates its own biosynthesis by sending negative feedback signals to the pituitary and hypothalamus.[2] Together, this neuroendocrine feedback circuit constitutes the hypothalamic−pituitary−adrenal (HPA) axis. The HPA activity is stimulated by physical or psychological stress and varies throughout the 24 h cycle. As a result, the circulating cortisol undergoes circadian rhythm, reaching its peak concentration of ∼800 nmol/L in the morning and nadir of ∼200 nmol/L at midnight in humans.[3] About 96% of the circulating cortisol is protein-bound with 6% to albumin and 90% to corticosteroid binding globulin (CBG).[4] Circulating CBG levels are approximately 700 nmol/L and regulated by estrogens and disease conditions.[1] Free cortisol dictates glucocorticoid action. It is thought that CBG may serve to restrict access of cortisol to target tissues and regulate its bioavailability and metabolic clearance. CBG may also serve as a carrier for cortisol facilitating transport of cortisol in blood to certain tissues. In contrast, the inactive cortisone is in a free unbound form and its plasma concentration remains steady at approximately 100 nmol/L throughout the day.[3] The metabolism of both cortisol and cortisone occurs in liver involving the A-ring reductases and several other enzymes, and the principal metabolites are tetrahydrocortisone (THE) and 5α- and 5β-tetrahydrocortisol (5α- and 5β-THF)[5] (Figure 2). Another aspect of the regulation of glucocorticoid production involves two 11β-hydroxysteroid dehydrogenase (11β-HSD) isozymes that interconvert cortisone and cortisol (Figure 2). 11β-HSD1 is a reductase in vivo converting cortisone to cortisol and amplifies glucocorticoid action in a tissue-specific manner. In contrast, its isozyme 11β-HSD2 acts as a dehydrogenase and catalyzes the opposite reaction, converting cortisol to cortisone. 11β-HSD1 is predominantly expressed in liver, adipose, placenta, and brain.[5] 11β-HSD2 is primarily expressed in kidney and functions as the main source of cortisone production.[5] Together, glucocorticoid homeostasis is maintained by the HPA axis and the activities of the 11β-HSD enzymes.

The metabolic syndrome is a cluster of metabolic abnormalities including central obesity, insulin resistance, atherogenic

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[a] Abbreviations: 11β-HSD1 or -2, 11β-hydroxysteroid dehydrogenase type 1 or 2; CBG, corticosteroid binding globulin; CBX, carbenoxolone; CRH, corticotrophin-releasing hormone; GA, glycyrrhetinic acid; GR, glucocorticoid receptor; HPA axis, the hypothalamic−pituitary−adrenal axis; THE, tetrahydrocortisone; THF, tetrahydrocortisol.

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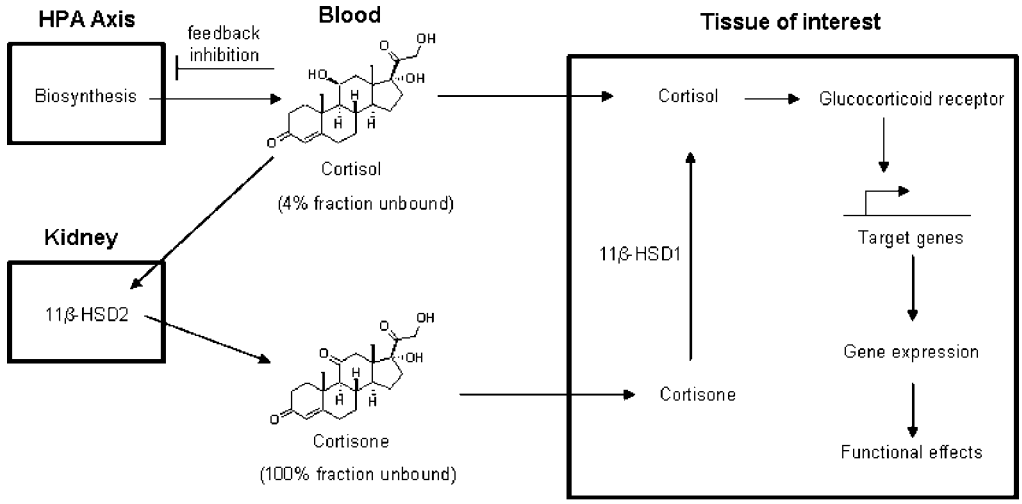


Figure 1. Schematic representation of glucocorticoid metabolism and action.

dyslipidemia, hyperglycemia, and hypertension.[6] Although it is not recognized as a therapeutic indication from the regulatory perspective, the syndrome has been increasingly recognized as a major risk factor for cardiovascular diseases and type 2 diabetes.[6] Targeting multiple components of the syndrome with novel therapies is an important strategy to reduce cardiovascular risks and complications. Although many distinct molecular mechanisms have been proposed, the etiology of the metabolic syndrome is still unclear. The link of glucocorticoid excess to the metabolic syndrome is implicated in Cushing's syndrome, where patients have increased glucocorticoid exposure and exhibit similar metabolic disorders such as central obesity, insulin resistance, and hypertension.[7] These clinical manifestations are consistent with glucocorticoid action at the molecular level ranging from induction of insulin resistance, lipogenesis, and central adiposity to augmentation of hepatic glucose production. These mechanisms could contribute to the metabolic defects in type 2 diabetes and the metabolic syndrome. Like the metabolic syndrome, glucocorticoid excess either in Cushing's syndrome or from prescription use is associated with increased cardiovascular risks.[8,9] More importantly, glucocorticoid excess was observed in some type 2 diabetic patients,[10–12] and there was a good correlation of salivary cortisol level with components of the metabolic syndrome.[11] In addition, tissue-specific glucocorticoid excess reflected by elevated 11β-HSD1 expression was observed in the adipose tissue of obese subjects.[13] These data suggest that glucocorticoid action could be involved in the development of the metabolic syndrome or at least contribute in some way to disease progression. However, there is no direct evidence that glucocorticoid excess is the main cause of the metabolic syndrome. Nonetheless, correction of glucocorticoid excess in Cushing's syndrome normalized certain metabolic parameters.[14] Likewise, treatment of Cushing's patients with a GR antagonist (11β,17β)-11-(4-(dimethylamino)phenyl)-17-hydroxy-17-(1-propyn-1-yl)estra-4,9-dien-3-one (RU 486) improved several metabolic functions.[15,16] These findings strongly suggest that blockade of glucocorticoid excess in the metabolic syndrome and type 2 diabetes could be a viable therapy. However, GR antagonism is not clinically desirable because it is associated with increased risk of HPA axis activation.[17] An alternative strategy is to inhibit 11β-HSD1 activity to suppress glucocorticoid action in 11β-HSD1 expressing tissues such as liver and adipose.

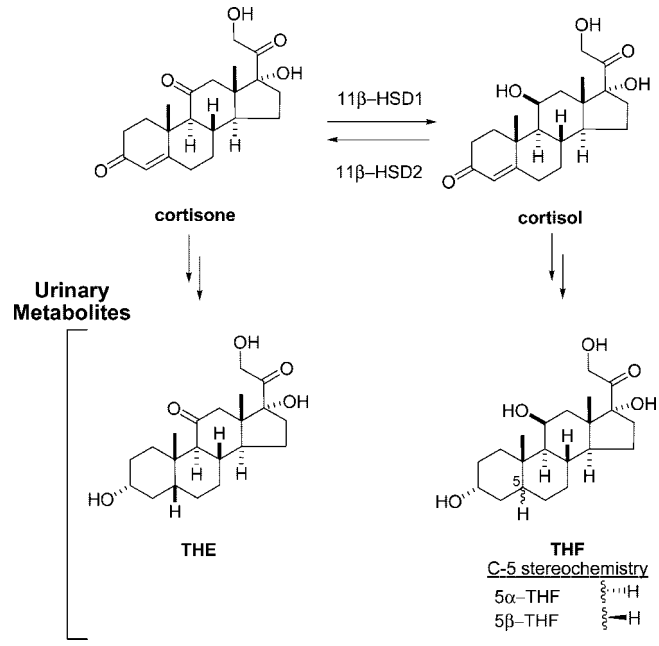
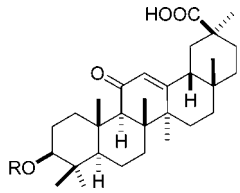


Figure 2. Interconversion of cortisone and cortisol and their principal metabolites.

Role of 11β-HSD1 in Obesity and Insulin Resistance

In humans, the expression of 11β-HSD1 in adipose tissue is positively correlated with the degree of obesity.[13,18] Furthermore, the adipose 11β-HSD1 expression was investigated in young adult monozygotic twins, one of which was obese and the other was lean. 11β-HSD1 expression was elevated in obese twins relative to their lean counterparts,[19] suggesting that the association of adipose 11β-HSD1 overexpression with obesity is acquired independent of genetic factors. These findings demonstrate that there is glucocorticoid excess in the adipose tissue of obese subjects. To ascertain if this is sufficient to cause metabolic disturbances, mice with 11β-HSD1 overexpression in adipose tissue were generated.[20] These animals had increased corticosterone in fat tissues and elevated serum free fatty acids and triglycerides.[20] They also developed central obesity, impaired glucose and insulin tolerance, and other features of the metabolic syndrome.[20] These data suggest that glucocorticoid excess in the adipose tissue of obese subjects could contribute to the development of obesity and insulin resistance. In addition, disruption of 11β-HSD1 expression in mice improved glucose



R = H, Glycyrrhetinic acid (GA)
R = C(O)CH_2CH_2C(O)OH, Carbenoxolone (CBX)

Figure 3. Licorice derived nonselective 11β-HSD1 inhibitors.

tolerance,[21] indicating that inhibition of 11β-HSD1 activity may lead to beneficial metabolic effects. To suppress glucocorticoid action in the adipose tissue specifically, 11β-HSD2 was overexpressed in the adipose tissue of mice.[22] These animals were protected against diet-induced obesity and insulin resistance.[22] Taken together, these data suggest that 11β-HSD1 inhibitors are potential therapeutics for obesity and type 2 diabetes. More specifically, since the adipose 11β-HSD1 expression is elevated in human obesity, inhibition of the adipose glucocorticoid action alone may be sufficient to improve insulin sensitivity.

Development of 11β-HSD1 Inhibitors

Years ago the extract from licorice root was used to treat aliments such as malaria, peptidic ulcers, and snake bites.[23] More recently, it was discovered that an active ingredient in licorice root that provided a therapeutic effect was glycyrrhetinic acid (GA) (Figure 3), an inhibitor of both 11β-HSD types 1 and 2.[24] The pharmacological effects of its synthetically derived analogue, carbenoxolone (CBX) (Figure 3), have been studied in both preclinical species and humans.[25,26] In hyperlipidemic mice, CBX lowered fasting insulin levels, lowered plasma lipids, and reduced atherosclerotic lesions.[25] In humans, CBX was shown to improve hepatic insulin sensitivity in both healthy volunteers[26]and diabetic subjects;[27] however, the therapeutic potential of CBX may be limited. Besides inhibiting 11β-HSD1, CBX also inhibits 11β-HSD2, which may cause hypokalemia and hypertension.[28] CBX was also reported to have limited ability to penetrate adipose tissue,[29] the target tissue where 11β-HSD1 inhibition is thought to be important for mitigating insulin resistance.

Since the discovery of GA and CBX, several pharmaceutical companies have identified nonsteroidal inhibitors that are potent and selective for 11β-HSD1.[30–36] Representative compounds are summarized in Table 1. These compounds evolved from the hits identified in high-throughput screening of internal compound collections using isolated human 11β-HSD1 enzyme. Several of the most potent inhibitors from these efforts have been assessed in rodent pharmacodynamic (PD) models measuring the conversion of cortisone to cortisol in a tissue explant (ex vivo). Compounds reported by Merck[35] and Amgen[33] inhibited the conversion of cortisone to cortisol in adipose tissue ex vivo after oral administration in mice. In addition to adipose tissue, similar assays were carried out in tissue explants from mouse liver[37] and brain.[35] Besides measuring the ex vivo inhibition of 11β-HSD1 using the cortisone to cortisol conversion assay, several research groups measured the in vivo inhibition of 11β-HSD1 by monitoring the conversion of exogenously administered prednisone to prednisolone. Amgen demonstrated that with their compound 2922, the turnover of prednisone to prednisolone was inhibited in mice.[37] Pfizer used a similar assay to measure the inhibitory effects of PF-915275 in cynomolgus monkeys (see Table 1).[36]

While several groups have identified potent 11β-HSD1 inhibitors with in vivo PD effects, there are fewer examples of 11β-HSD1 inhibitors with in vivo efficacy in preclinical models of diabetes. One of the first reports of efficacy in a disease model with a selective 11β-HSD1 inhibitor was reported by Biovitrum.[30] Their 11β-HSD1 inhibitor BVT-2733 significantly reduced blood glucose in hyperglycemic KKAy mice, a rodent model for diabetes. Biovitrum concluded that lower hepatic glucose production contributed to the reduced blood glucose, since a significant reduction in the expression of genes that regulate gluconeogenesis was observed, i.e., phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase). BVT-2733 was not advanced for further development, since it was ~35-fold less potent in the human 11β-HSD1 assay than in the mouse assay.[30] Changes to the structure of BVT-2733 led to BVT-14225, a compound that was more potent in the human 11β-HSD1 assay than in the mouse assay.[30] Differences between mouse and human 11β-HSD1 potencies have also been observed for other chemotypes,[33,36] which might be explained by the differences in amino acid sequence between mouse and human 11β-HSD1 (sequence homology between the two enzymes is 79%). This amino acid sequence difference results in slightly different substrate binding pockets as revealed by the X-ray crystal structures of mouse and human 11β-HSD1.[38,39]

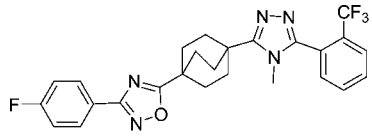
Additional studies with 11β-HSD1 inhibitors in animal models have been reported by both Pfizer[36] and Merck.[35] The Pfizer inhibitor, PF-915275, significantly reduced plasma insulin levels in nondiabetic cynomolgus monkeys after a single oral dose.[36] However, plasma glucose and lipid levels did not change.[36] Compound 544, an 11β-HSD1 inhibitor from Merck, improved the metabolic profile in high fat fed and streptozotocin treated (HF/STZ) mice after twice daily oral administration for 11 days.[35] The mice treated with compound 544 had decreased fasting glucose and improved insulin sensitivity.[35] In addition to the preclinical diabetes model, researchers at Merck showed that compound 544 reduced serum lipids and lowered aortic cholesterol levels in apoE deficient mice, a rodent model for atherosclerosis.[35] Recently, we showed that the time of the day for 11β-HSD1 inhibition in a diabetes model is a critical factor in targeting this pathway to improve glucose homeostasis.[40]

Clinical Trials with 11β-HSD1 Inhibitors

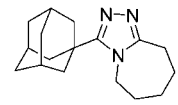
Despite the lack of selectivity, CBX was used as an 11β-HSD1 inhibitor in a clinical study with type 2 diabetic patients.[27] Although CBX showed no effect on the rate of glucose disposal or the suppression of free fatty acids during hyperinsulinemia, it significantly reduced glucose production during hyperglucagonemia in lean male type 2 diabetic patients.[27] Since CBX did not affect gluconeogenesis, this effect is mediated by decreased glycogenolysis.[27] This study suggests that 11β-HSD1 inhibition may lead to beneficial metabolic effects. This notion is further supported by a separate study in healthy volunteers where CBX suppressed lipolysis.[41] Further, CBX improved cognitive function in healthy elderly men and type 2 diabetics,[42] suggesting that 11β-HSD1 inhibitors may have expanded therapeutic use beyond type 2 diabetes. However, because of the nonselective nature of CBX, these clinical findings should be interpreted with caution and remain to be validated with selective 11β-HSD1 inhibitors.

The first selective 11β-HSD1 inhibitor that was tested in clinical trials was BVT-3498 (AMG-331).[43] The compound was in phase II clinical development by Amgen under license from Biovitrum and later terminated.[43] Recently, Incyte Corporation reported that their 11β-HSD1 inhibitor INCB13739 was well tolerated in healthy volunteers.[44] After 9 days of repeated dosing,

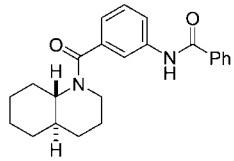
Table 1. Representative Selective 11β-HSD1 Inhibitors



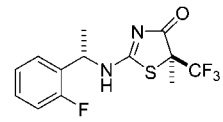
Merck[Ref. 34]
11β-HSD1 IC_{50} = 2.2 nM
11β-HSD2 IC_{50} > 1 μM



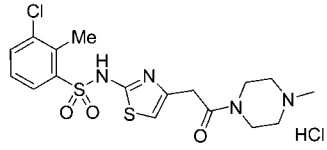
Merck 544[Ref. 35]
11β-HSD1 IC_{50} = 7.5 nM
11β-HSD2 IC_{50} > 3.3 μM



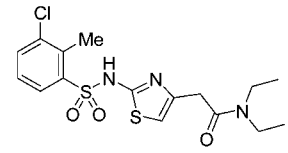
Novartis[Ref. 31]
11β-HSD1 IC_{50} = 14 nM
11β-HSD2 12% inhibition @ 10 μM



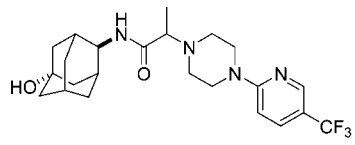
Amgen 2922[Ref. 33]
11β-HSD1 K_i = 22 nM
11β-HSD2 IC_{50} >10 μM



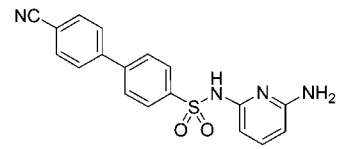
Biovitrum BVT-2733[Ref. 30]
hu 11β-HSD1 IC_{50} = 3341 nM
mouse 11β-HSD1 IC_{50} = 96 nM
hu 11β-HSD2 IC_{50} >10 μM



Biovitrum BVT-14225[Ref. 30]
hu 11β-HSD1 IC_{50} = 52 nM
mouse 11β-HSD1 IC_{50} = 284 nM
hu 11β-HSD2 IC_{50} >10 μM



Abbott[Ref. 32]
11β-HSD1 K_i = 5 nM
11β-HSD2 IC_{50} >100 μM



Pfizer PF-915275[Ref. 36]
11β-HSD1 K_i = 2.3 nM
11β-HSD2 1.5% inhibition @ 10 μM

the ratio of the urinary metabolites of cortisol and cortisone (5α-THF + 5β-THF/THE) was suppressed but no change in 24 h plasma cortisol profile was noted,[44] indicating that 11β-HSD1 was inhibited but the HPA axis was not activated in the treated subjects. Furthermore, the inhibition of adipose and liver 11β-HSD1 was also demonstrated.[44] INCB13739 exhibited a trend of lowering fasting glucose and reduced LDL cholesterol in a 28-day phase IIa study in type 2 diabetic patients.[45] This compound also showed trends of reducing glucose production and improving glucose utilization in the same patients, although no statistical significance was observed.[46] Pfizer tested their 11β-HSD1 inhibitor, PF-915275, in 60 healthy adult volunteers in a phase I study.[47] This compound inhibited the endogenous prednisone to prednisolone conversion,[47] demonstrating that 11β-HSD1 was inhibited after dosing in these subjects. In addition, the decrease in the 5α-THF + 5β-THF/THE ratio in treated subjects confirms 11β-HSD1 inhibition.[47] The plasma ACTH and androgen levels in these subjects did not increase,[47] suggesting that the HPA axis was not activated. These clinical studies with different classes of 11β-HSD1 inhibitors represent encouraging progress with this pathway as a therapeutic target, which holds promise for further clinical proof-of-concept as a therapy for type 2 diabetes.

Opportunities and Challenges for the Future

It is widely recognized that elevated 11β-HSD1 activity in adipose tissue may contribute to the etiology of the metabolic syndrome, and thus, its inhibitors have been sought after as therapies of type 2 diabetes. The first sign of clinical efficacy with 11β-HSD1 inhibition is the marginal effect of CBX on insulin sensitivity in type 2 diabetics.[27] However, CBX is not selective for 11β-HSD1. With the large research efforts in the pharmaceutical industry, potent and selective 11β-HSD1 inhibitors have been identified, among which are the molecules currently in clinical trials.[45–47] The positive trend observed with Incyte's compound INCB13739 in reducing fasting glucose and glucose production and increasing glucose disposal is encouraging.[45,46] However, a clinical trial with a larger patient population and a longer treatment period is needed to see if this compound can positively modify other biomarkers of diabetes (e.g., glycosylated hemoglobin or HbA1c). In fact, INCB13739 is reported to be under investigation in a larger phase IIb clinical trial.[46] Studies in animals and with human

tissues suggest that there may be multiple mechanisms under which 11β-HSD1 inhibitors may be effective in treating type 2 diabetes. In addition to suppressing the adipose glucocorticoid action to improve insulin sensitivity as demonstrated in mouse studies, 11β-HSD1 inhibitors may improve glucose-dependent insulin secretion (GSIS) because 11β-HSD1 expression is elevated in diabetic islets.[48] 11β-HSD1 is also expressed in skeletal muscle and its expression in type 2 diabetes is elevated,[49] which could contribute to the development of insulin resistance in skeletal muscle in type 2 diabetics. The therapeutic opportunities with 11β-HSD1 inhibitors go beyond the treatment of type 2 diabetes. A large body of evidence from several decades of research indicates that glucocorticoids mediate deleterious effects on neurons, and thus, antiglucocorticoids may be useful in treating neurological disorders. The improvement of cognitive function in healthy elderly men and type 2 diabetics by CBX supports this notion.[42]

The development of 11β-HSD1 inhibitors still faces challenges ahead. Although Incyte observed a positive efficacy trend with INCB13739 in type 2 diabetics in their phase IIa trial,[45,46] clinical efficacy with 11β-HSD1 inhibitors is still unproven. Moreover, it is known that GR blockade leads to HPA axis activation, which triggers deleterious effects. 11β-HSD1 is also expressed in brain, and its inhibition may have a similar effect on the HPA axis. In fact, 11β-HSD1 knockout mice displayed HPA axis activation, adding to the concern of potential clinical adverse effects. However, Pfizer's 11β-HSD1 inhibitor PF-915275 did not activate the HPA axis after 14-day repeated oral administration in healthy volunteers at doses with adequate enzyme inhibtion,[47] suggesting that there may be a therapeutic window within which the enzyme is inhibited but the HPA axis is not activated.

Conclusion

Glucocorticoid action has been linked to several metabolic effects such as augmentation of hepatic gluconeogenesis and induction of peripheral insulin resistance. The beneficial metabolic effects of glucocorticoid blockade have been demonstrated in diabetic animal models using GR antagonists. Unfortunately, the HPA axis activation caused by GR blockade has limited its use. Since 11β-HSD1 is responsible for the regeneration of cortisol from cortisone in a tissue-specific manner, it contributes to tissue cortisol levels but not circulating cortisol levels. Inhibition of 11β-HSD1 is therefore an alternative antiglucocorticoid strategy. Two key questions about this approach should be considered: (1) the relevance of 11β-HSD1 activity in the development of obesity and insulin resistance and (2) potential HPA axis activation that may be triggered by 11β-HSD1 inhibitors. The role of 11β-HSD1 in the development and treatment of the metabolic syndrome has been implicated in both preclinical studies and humans. First, 11β-HSD1 expression in the adipose tissue of obese subjects is elevated. Second, overexpression of 11β-HSD1 in adipose tissue of mice led to obesity, insulin resistance, and other metabolic disorders. Further, inhibition of 11β-HSD1 in diabetic animal models mitigated these metabolic parameters. These data support the use of 11β-HSD1 inhibitors as antidiabetic therapies. The potential HPA axis activation by 11β-HSD1 inhibitors remains a major concern; although it has been first demonstrated by Pfizer that in healthy human volunteers, the enzyme can be sufficiently inhibited at doses that did not cause HPA axis activation. On the basis of these findings, 11β-HSD1 inhibitors are attractive therapies for type 2 diabetes. However, this premise remains to be validated in clinical trials involving type 2 diabetic patients with definitive biomarkers such as HbA1c.

Biographies

Christopher Fotsch received his Ph.D. degree in Organic Chemistry from the University of California, Irvine in 1992 under the direction of Professor A. Richard Chamberlin. Following an NIH postdoctoral fellowship at The Scripps Research Institute with Professor Chi-Huey Wong, he joined Sandoz Pharmaceuticals in 1994. In 1997 he joined the Chemistry Research & Discovery group at Amgen Inc. where he has led the medicinal chemistry efforts for several programs in the metabolic disorders therapeutic area. His scientific interests include structure-based drug design, enzyme mediated synthesis of metabolites, and targeting of proteins through allosteric modulation. He has coauthored over 31 publications and is co-inventor on 19 U.S. patents.

Minghan Wang is Scientific Director and Head of the In Vitro Diabetes/Dyslipidemia group on the Thousand Oaks site at Amgen. Prior to joining Amgen in 2003, he championed drug discovery programs in cardiovascular and metabolic diseases at Pharmacia. Dr. Wang started his industry career in 1996 at Parke-Davis/Pfizer, where he worked on the mechanisms of actions of Resulin (troglitazone), Neurontin (gabapentin), and Gemcabene. Dr. Wang received his Ph.D. in Biochemistry and Molecular Biology from the Medical College of Ohio and had postdoctoral training at the University of Michigan with Dr. Jack Dixon. His scientific interests include insulin resistance, obesity, dyslipidemia, atherosclerosis, and drug discovery approaches guided by integrated physiology. He has over 31 publications and is a frequent speaker on drug discovery topics.

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