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Review

REVIEW

Effect of Glucocorticoid and 11β-Hydroxysteroid-Dehydrogenase Type 1 (11β-HSD1) in Neurological and Psychiatric Disorders

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Abstract

11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) activity is implicated as a moderator of the progression of multiple diseases and disorders in medicine and is actively subject to investigation as a therapeutic target. Here we summarize the mechanisms of the enzyme and detail the novel agents under investigation. Such agents modulate peripheral cortisol and cortisone levels in hypertension, type 2 diabetes, metabolic disorders, and Alzheimer's disease models, but there is mixed evidence for transduction into symptom management. There is inchoate evidence that 11β-HSD1 modulators may be useful pharmacotherapies for clinical improvement in psychiatry and neurology; however, more research is required.

Keywords: 11β-HSD1 inhibitors, clinical translation, glucocorticoids, neurological, psychiatric

11β-HSD1: ROLE AND DISTRIBUTION

The enzyme 11β-HSD1 is expressed in vertebrate species within many body regions, including cells of the liver, adipose tissue, islet cells of the pancreas, skeletal and heart muscle, gonads, inflammatory cells, and brain as well as in placenta and fetus (Chapman et al., 2013). Rodent brain studies have demonstrated that 11β-HSD1 is mainly expressed in the cerebellum, hippocampus, cortex, and pituitary, although it is present at detectable levels in other brain regions (Seckl, 1997). 11β-HSD1 is a nicotinamide adenine dinucleotide phosphate–dependent enzyme, and 11β-HSD2 is a nicotinamide adenine dinucleotide

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HIGHLIGHTS

11β-HSD1 inhibitors show some efficacy in mitigating peripheral glucocorticoid levels, but clinical translation in disease models beyond hypertension has not been demonstrated. However, there is now emerging evidence that 11β-HSD1 inhibitors may have a therapeutic role in neurological and psychiatric disorders. Examination of in neurological and psychiatry is nascent, with a small number of clinical trials examining psychiatric symptoms, cognitive performance, or mood dysfunction in samples of psychiatric disorder. Alzheimer's disease is a notable inclusion, but efficacy has not been demonstrated.

11β-HSD1 inhibitors have demonstrable desirable effects on biological markers for metabolic syndrome, hypertension, obesity, and diabetes type II, but are not known to attenuate the stress response and their impact on anxiety is uncertain. Genetic polymorphism on glucocorticoid receptors is responsible for substantial variation in major depressive disorder progression and medication response, and the evidence suggests that cognitive performance measurements follow an inverted U-shaped in response to HPA activation.

(NAD$^+$)-dependent enzyme. Besides, 11β-HSD1 can also convert 7-ketocholesterol to 7β-hydroxycholesterol as well as catalyze other 7-oxygenated sterols and steroids.

11β-HSD1 and 11β-HSD2 catalyze the interconversion of cortisol and cortisone, with 11β-HSD1 catalyzing the reduction of cortisone into cortisol and 11β-HSD2 catalyzing the oxidation of cortisol into cortisone (Figure 1). In intact cells, 11β-HSD1 functions as a reductase due to the presence of coenzyme hexose-6-phosphate dehydrogenase, which potentiates reduced nicotinamide adenine dinucleotide phosphate (NADPH) in the endoplasmic reticulum (Zhang et al., 2009). In intact cells, 11β-HSD2 functions as an oxidase, as the enzyme kinetics of the oxidation reaction has a much greater rate constant than the reduction reaction. However, under some conditions, such as in tissue homogenates, 11β-HSD1 can catalyze the reverse reaction of cortisol into cortisone (Chapman et al., 2013). 11β-HSD1 and 11β-HSD2 are not collocated within the organism, with 11β-HSD1 predominantly in the liver and 11β-HSD2 in the kidney (Chapman et al., 2013).

PHYSIOLOGY AND FUNCTION OF GLUCOCORTICOIDS

Glucocorticoids are lipophilic and pass through the cell membrane to bind with glucocorticoid receptors in the cytoplasm. Activated glucocorticoid receptors can translocate to the cell nucleus, where they act as transcription factors activating or inhibiting genes and modulating the function of other transcription factors (Timmermans et al., 2019). The principal role of glucocorticoids is to maintain cellular homeostasis through the upregulation of anti-inflammatory proteins while also downregulating proinflammatory protein expression. Glucocorticoids function through 2 receptors: the glucocorticoid receptors (GR), which are ubiquitous throughout the CNS and periphery, and the mineralocorticoid receptors (MR). Most GR activity is in the nucleus; however, some non-nuclear activity of glucocorticoid receptors is part of a trans-repressive mechanism in the cytosol (Rhen and Cidlowski, 2005; Pascual and Glass, 2006).

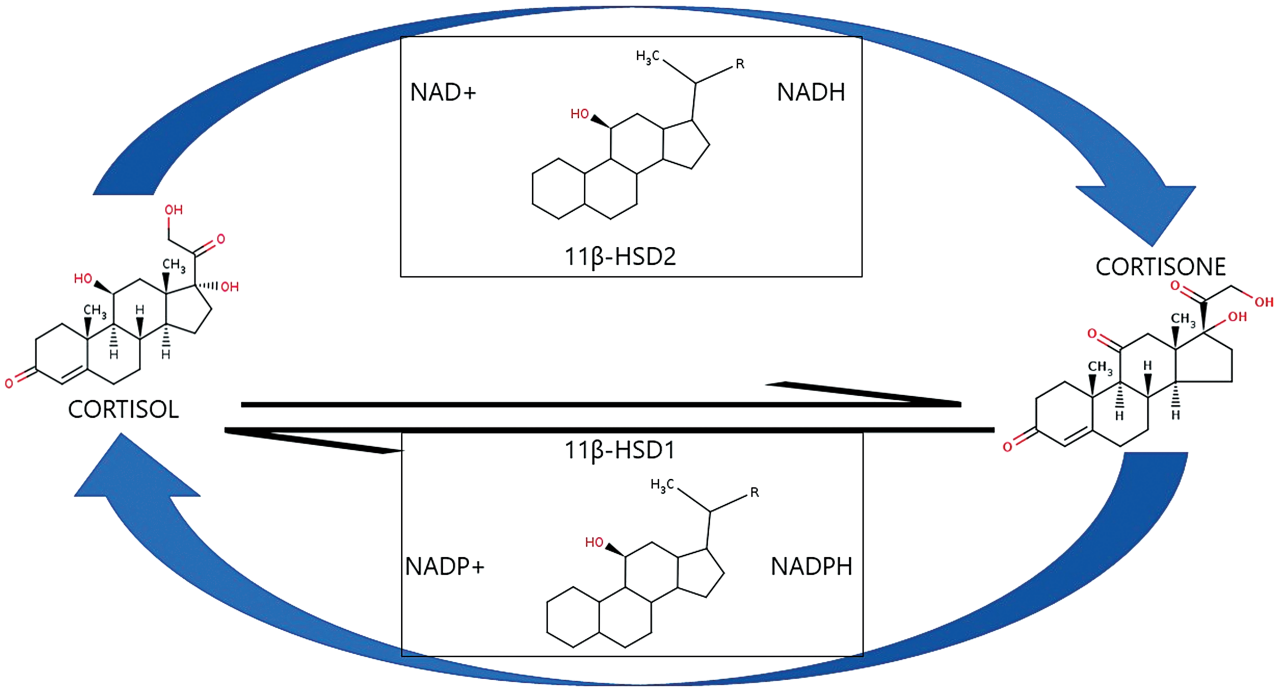

Figure 1. Cortisol-cortisone interconversion via 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD).

Glucocorticoids have many roles in human physiology. Besides major metabolic and immunological functions, glucocorticoids influence fetal development and body fluid homeostasis. Glucocorticoids also contribute to arousal states and vigilance and modulate memory formation. Cortisol and the inert form, cortisone, are the primary glucocorticoid in humans and are synthesized in the zona fasciculate of the adrenal glands. Governed by the hypothalamic-pituitary-adrenal (HPA) axis, cortisol is synthesized and released in a circadian pattern to promote daytime arousal and respond to stress and other cues (Ramamoorthy and Cidlowski, 2016). The upregulation of cortisol forms part of a cyclical response that triggers hepatic gluconeogenesis and reduces insulin sensitivity (Adam et al., 2010), inhibits inflammatory immune response (Adam et al., 2017), and adjusts electrolyte homeostasis via the mitigation of hyperkalemia and hyponatremia (Dineen et al., 2019). In electrolyte rebalancing, the presence of glucocorticoids stimulates the renal endothelial sodium channel alpha subunits and upregulates sodium channels, facilitating a sodium-potassium ion exchange (Sayegh et al., 1999; Taves et al., 2011). As such, dysregulation of the interconversion between cortisol and cortisone is considered a therapeutic target.

GLUCOCORTICOID DYSREGULATION CONTRIBUTES TO DISEASE AND DISABILITY

Glucocorticoids function in concert with the HPA axis, glucocorticoid receptors, and a range of interconnecting biological pathways. Consequently, disease and abnormality can result from dysregulation anywhere within these interconnecting systems. Dysregulation of 11β-HSD1 itself or supply of the nicotinamide adenine dinucleotide hydrogen (NADH+) cofactor, called cortisone reductase deficiency, is a genetic abnormality responsible for increased cortisol clearance and androgen excess linked to pseudo-puberty in males and hirsutism, oligomenorrhea, and infertility in females. Cortisone reductase deficiency results in low levels of circulating cortisol, which through a negative feedback loop in the HPA axis signals to the adrenal gland to produce more cortisol, and, through concomitant stimulation of co-located steroid synthesis pathways, releases androgens. In some patients, heterozygous mutations in the HSD11B1 gene have been identified as a cause of cortisone reductase deficiency (Lawson et al., 2011). Whatever the cause, the detrimental effect of chronic stimulation of GRs is observed clinically through the long-term use of endogenous glucocorticoids and in the rare condition of Cushing's disease, where cortisol production is autonomous. Classic features of Cushing's syndrome, caused by hypercortisolism, include proximal muscle weakness, wide purple striae, hypertension, weight gain, glucose dysregulation, and osteoporosis. Cognitive and psychiatric symptoms are commonly described, including short-term memory impairment, impaired mental calculation, insomnia, depression, or euphoria and worsening or onset of pre-existing psychiatric conditions (Nieman, 2015). Similarities exist with the much more prevalent metabolic syndrome, and clinical studies have provided substantial evidence of altered cortisol metabolism in obesity and type 2 diabetes mellitus. Increased 11βHSD1 activity is observed in adipose tissue of obese men and women (Rask et al., 2001, 2002). With no net increase in circulating cortisol associated with obesity, increased glucocorticoid metabolism has been observed by measuring urinary glucocorticoid metabolites (Stewart et al., 1999). Using deuterated tracers, cortisol metabolism by 11βHSD1 has been estimated at a tissue level; such studies have identified the liver as a critical site in developing glucose dysregulation in type 2 diabetes mellitus (Stimson et al., 2011). Crucially, while metabolic syndrome and type 2 diabetes mellitus models have also routinely confirmed the mediating role of 11β-HSD1 dysfunction, the clinical utility of 11β-HSD1 inhibition for symptom management is not well established (White, 2018). Correspondingly, 11βHSD1 is a potential target for developing novel therapeutic agents to treat metabolic syndrome and type 2 diabetes mellitus.

STRESS AND SUBSEQUENT GLUCOCORTICOID RESPONSE HAS PROFOUND IMPLICATIONS FOR PSYCHIATRIC AND NEUROLOGICAL DISORDERS

Biologically, the stress response is governed broadly through 2 systems: the autonomic nervous system and the HPA axis. During the stress response in humans, inactive cortisone is catalyzed by 11β-HSD1 to active cortisol, which, in turn, regulates the biological stress response in the peripheral nervous system (Belda and Armario, 2009; Pruessner et al., 2017; Schifani et al., 2018). Once an environmental stressor is encountered, one of the earliest biological reactions is the activation of the hypothalamic periventricular nucleus, which releases corticotropin-releasing hormone, which in turn mediates a response from the sympathetic nervous system through the anterior pituitary gland. The anterior pituitary gland then signals the sympathetic preganglionic nerves in the spinal cord around the thoracolumbar region, activating the adrenal medullae with the release of acetylcholine. The adrenal medulla then triggers the release of the catecholamines epinephrine, norepinephrine, dopamine, and glucocorticoids into the bloodstream (Goldstein, 1987).

When acute stress is encountered, cortisol binds to limbic MRs that govern the initiation of the neurological response (the ramping up) and later bind to GR sites to facilitate recovery (De Kloet et al., 2005; Koning et al., 2019). Specific regions and structures express the cortisol response differently; hippocampal reactivity is associated with episodic memory production moderated by a host of contextual factors (Shields et al., 2017). Increased stress is considered a net negative force for cognitive function in general and memory in particular, except for stressor-relevant stimulus (Shields et al., 2017, 2019). According to the consolidation theory of stress and memory, the acute "flash" of emotional stimulus creates a "flashbulb" memory that then facilitates a conditions stress-fear response (Zorn et al., 2017; Yan et al., 2019). The timing of the stressor and the anticipation is relevant; anticipated stressors, such as the foreboding of an upcoming stressor, substantially interfere with memory encoding. By contrast, if the stress response occurs after an event, such as during an unexpected stressor, the memory function of that stressor is substantially improved (Shields et al., 2017). When context and other cues promote recognition of the stressor event, the memory and emotional response are retrieved. This dose- and timing-dependent relationship between memory function and corticoid physiology is described as having an inverse-quadratic distribution of activation and performance. More minor or short-term activation fosters long-term potentiation for learning and memory formation, but a sustained stress-response increases serotonin sensitivity and calcium channel permeability and ultimately disrupts long-term potentiation (Joëls, 2006).

The modulating effect of cortisol on memory illustrates how overstimulation of the HPA axis can contribute to neurodegeneration. In contrast to the prevalence of GR, MR are expressed more selectively but are particularly abundant within the CA1 region of the hippocampus (Joëls, 2018). Mild increases in cortisol, such as those observed within the circadian rhythm, preferentially activate MR. Still, sustained or severe fluctuations also activate GRs, and at sufficient severity, this mechanism drives neuronal loss. While MR ordinarily out-expresses GR on the CA1 hippocampal region, rodent models of post-traumatic stress disorder (PTSD) demonstrate that exposure to a single prolonged stressor not only significantly reduces expression of both receptors but appears to do so in a manner that disproportionately affects the expression of MR (Zhe et al., 2008). In other animal models, this same disproportion of MR to GR expression in the CA1 region is associated with decreased birth weight in neonates and increased 11β-HSD1 production (Ong et al., 2013). In humans, the relationship appears to be more complex; reviews suggest stimulation of MRs is beneficial for younger people but detrimental to the cognitive function in older adults, and the effect is further pronounced in the context of emotional dysregulation (Wingenfeld and Otte, 2019).

Emotionality appears crucial to the interaction of glucocorticoids and changes in neural plasticity. The upregulation of endogenous cortisol and norepinephrine in the basolateral nucleus of the amygdala strengthens neural pathways between the basolateral nucleus, the hippocampus, and medial prefrontal cortex. This consolidation of pathways is, in part, attributed to the moderated expression of α-amino-3-hydroxy-5-methyl-4-isoxazole propionate receptor subunits in the limbic system. Sustained exposure to cortisol promotes changes in the expression of the GluR2-lacking subunit of α-amino-3-hydroxy-5-methyl-4-isoxazole propionate receptor. Consequent disruption to Ca^{2+} permeability renders neurons vulnerable to excitotoxicity (Joëls et al., 2011). However, the cognitive effect of moderated functional connectivity appears to be both context and domain specific. Increased hippocampal connectivity with the prefrontal cortex improves immediate visual encoding, whereas increased connectivity between the hippocampus and the inferior lateral occipital cortex predicts poorer retrieval (Hakamata et al., 2019). Neuroimaging research finds conflicting evidence for the mediation of specific pathways (Sazma et al., 2019; Shields et al., 2019). The memory-enhancing effect of cortisol through neuroplasticity also appears decidedly nonlinear, with regular oscillations and brief spikes in response to threat-eliciting neurotrophic factors (Begni et al., 2017). However, severe or sustained spikes downregulate the expression of glucocorticoid receptors, in turn dampening future neurotrophic responses (McEwen and Stellar, 1993; McEwen, 2007). The CA1 region of the hippocampus is particularly vulnerable to a delayed influx of Ca^{2+} and subsequent apoptosis (Joëls, 2006; Frodl and O'Keane, 2013). Crucially, however, the exhaustion of available MR and subsequent activation of GRs is detrimental to structural integrity in the brain regardless of the organs implicated. The activation of GRs in the prefrontal cortex is known to inhibit executive function and reduce executive function overall grey matter (Ouanes and Popp, 2019).

Hippocampal and prefrontal vulnerability to chronic overactivation of the glucocorticoid system is strongly implicated in various neuropsychiatric disorders, and the role of cortisol as a negative feedback system for HPA axis activation can create a vicious feed-forward cascade. For example, hippocampal atrophy has severe implications across several autonomic systems and is associated with psychopathology and cognitive dysfunction. Hippocampal atrophy is implicated in the diminished cortisol awakening response characteristic in schizophrenia (Berger et al., 2016), which potentiates further cognitive deficits. This dysregulation of cortisol levels exacerbates ventral tegmental and prefrontal cortex dopamine release that would ordinarily be attenuated via signaling from the hippocampus (Schifani et al., 2018), and this intensified upregulation of dopamine mediates disordered psychiatric symptomology, including psychosis and cognitive deficits (Green et al., 2014; Grace, 2016; Murri et al., 2016). As such, neuronal damage caused by overactivation of the HPA axis can contribute to a continuing cascade of other cognitive symptoms, subsequent stress hormone activation, and increased symptom severity in a feedback loop.

The exacerbating mechanisms of neuropsychiatric disorder attributable to glucocorticoid dysfunction or dysregulation also vary between diagnoses. For example, the conversion of peripheral cortisone to cortisol is expedited in major depression (Poór et al., 2004). However, both glucocorticoids appear to be elevated in major depression (Weber et al., 2000), and genetic polymorphisms on glucocorticoid receptors may regulate stress response to depression and antidepressant medication (Figaro-Drumond et al., 2020). For example, the single-nucleotide polymorphism rs11119328 is a common genotypical variant associated with not only increased nighttime cortisol production but also increased risk of suicide attempt in incident depression generally (Dekker et al., 2012) and cognitive impairment (Ragnarsson et al., 2014). By contrast, the variant rs11811440 has recently been demonstrated to enhance symptom response to antidepressant treatment (Figaro-Drumond et al., 2020) but is also associated with reduced bone mineral density in elderly patients (Siggelkow et al., 2014). Moderated responses to depression during elevated cortisol are likely further exacerbated by increasing dose-dependent 1α-serotonin sensitivity to and reductions in β-adrenoreceptors response as GR are progressively activated (Joëls, 2006). In Alzheimer's disease, the overactivation of the HPA axis also further contributes to oxidative stress and, in turn, the increased vulnerability to β-amyloid and tau entanglements (Ouanes and Popp, 2019). In common with other disease models, the ensuing production of oxidative species, such as interleukin-β and interleukin-6, can perpetuate the cyclic response to HPA activation in Alzheimer's disease. Further, the mediating effect of cortisol on oxidative biomarkers is not only consistent with modeling of cognitive performance under stress in humans; sustained elevated cortisol response not only produced the expected oxidative damage to RNA and DNA, but mild exposure to cortisol was protective (Aschbacher et al., 2013).

11β-HSD1 AS A DRUG TARGET IN MEDICINE

Despite the abundance of evidence implicating cortisol as a psychiatric provocateur, we stress that 11β-HSD1 inhibitors are not known to attenuate the stress response and have even been reported as anxiogenic rather than anxiolytic (see Table 1). There are established mechanisms for manipulating the glucocorticoid system, such as administering synthetic or natural glucocorticoids. 11β-HSD1 inhibitors regulate the conversion of cortisone into cortisol, whereas stress is alleged to kindle mental illness through allostatic processes (Kapczinski et al., 2008). Although cortisol is a stress hormone, among other roles, the mechanistic explanation of the benefit of 11β-HSD1 inhibitors in psychiatry is not adequately explained by acute stress, and further research is required.

Nevertheless, there is a need for novel therapies with better efficacy or greater specificity for symptoms not targeted by

current agents. 11β-HSD1 is a potential drug target for many indications and may play a role in treating diverse elements, including inflammation, metabolic dysregulation, hypertension, stress and arousal, and related conditions. Numerous selective and non-selective 11β-HSD1 inhibitors have been reported over the last 2 decades, with a substantial number of published reports of agents used for in vitro and rodent studies. In human studies, a current (November 2021) search of the clinical trials registry clinicaltrials.gov identified five 11β-HSD1 inhibitors (AZD4017, BI135585, MK0736, MK0916, UE2343) under investigation in healthy human subjects and conditions, including hypertension, type 2 diabetes mellitus, metabolic syndrome, Cushing's disease, and Alzheimer's type dementia. A further search of PubMed identified additional 11β-HSD1 inhibitors developed for type 2 diabetes mellitus and metabolic syndrome (RO5093151, RO5027383, MK-0916, and INCB13739), non-alcoholic fatty liver disease (RO5093151), hypertension, obesity (MK0736 and AMG 221), and Alzheimer's disease (ABT384) (Bellaire et al., 2019). The PubMed search also identified the selective 11β-HSD1 inhibitor ASP3662, registered in clinicaltrials.gov for a randomized controlled trial to treat painful diabetic peripheral neuropathy. Additionally, adamantyltriazoles, arylsulfonamidothiazoles, anilinothiazolones, BVT2733, and INCB-13739 were also reported as 11β-HSD1 inhibitors under investigation for weight reduction, dyslipidemia, and related disorders (Anagnostis et al., 2013). The novel agents under examination are presented in Table 1.

Table 1. Current 11β-HSD1 Inhibitory Investigatory Targets

Trade name/ identifier	Structure	Target condition	Clinical safety and efficacy data	Evidence of positive clinical findings (biomarkers/outcomes)
ABT384	C25H34F3N5O2 (1s,4r)-4-(2-methyl-2-{4-[5-(trifluoromethyl) pyridin-2-yl]piperazin-1-yl}propanamido) adamantane-1-carboxamide	Alzheimer's disease	Daily doses of 1 mg significantly reduced urine biomarkers for 11β-HSD1 but only reduced serum levels of cortisol with doses of at least 8 mg after 24 h; nonsignificant increases detected after 7 d in healthy adults and elderly adults (n = 103) even in 100-mg doses (Liu et al., 2013b). In a 12-wk clinical study, neither 10 nor 50 mg daily of ABT384 demonstrated any significant effect of Alzheimer's symptoms or cognitive measures (Marek et al., 2014). Most common adverse reactions in healthy adults (diarrhoea, dizziness, or headache) were minor to moderate. In Alzheimer's patients (n = 267), anxiety was most common adverse event followed by cough and headache, but rates were equal across all treatment groups, including placebo and donepezil comparators.	Yes/no
AMG221	C14H22N2OS (5S)-2-[[(1S,2S,4R)-2-bicyclo[2.2.1]heptanyl] imino]-5-methyl-5-propan-2-yl-1,3-thiazolidin-4-one	Type 2 diabetes, obesity	Healthy, obese participants administered single dose of 3, 30, or 100 mg of oral AMG 221 (n = 44) or placebo (n = 11) that significantly inhibited levels of 11β-HSD1 in ex vivo adipose tissue in approximate dose-dependent fashion (Gibbs et al., 2011).	Yes/NA
ASP3662	C19H16ClF3N4O2 4-{5-[2-(4-chloro-2,6-difluorophenoxy) propan-2-yl]-4-methyl-4H-1,2,4-triazol-3-yl}-3-fluorobenzamide	Diabetic peripheral neuropathy	Preclinical evidence suggests that ASP3662 at concentrations up to 30 μM, inhibited human 11β-HSD1 but not 11β-HSD2 nor any other observed enzyme, transporter, or receptor targets (Kiso et al., 2018). In single-dose 50 mg (n = 48) and multiple ascending dose analyses of 60 mg (n = 62), ASP3662 was well-tolerated and demonstrated that significant 11β-HSD1 inhibition was observed with doses as low as 2 mg over 14 d. No significant changes to mood states detected within the cohort or between treatment groups; a phase II study examining pain (n = 115; NCT02372578) was abandoned in 2016 after futility analyses (Bellaire et al., 2019).	Yes/NO

Table 1. Continued

Trade name/ identifier	Structure	Target condition	Clinical safety and efficacy data	Evidence of positive clinical findings (biomarkers/outcomes)
AZD4017	C22H33N3O3S (3R)-1-[(3-butyl-2-ethylsulfonylimidazol-4-yl)methyl]-3-phenylmethoxypiperidine	Idiopathic intracranial hypertension, type 2 diabetes.	A small, double-blinded RCT with n = 31 women and twice-daily 400-mg doses of AZD4017 or placebo over 12 wk demonstrated significant within-group decrease in lumbar puncture pressure for intervention but not placebo group. However, no significant group*time interaction present. Inhibition of 11β-HSD1 significantly correlated with reduction in lumbar puncture pressure; adverse events were few and mild in intervention group (Markey et al., 2020). A phase II RCT for AZD4017 in type 2 diabetes was recently completed; publication of results forthcoming (ISRCTN74621291).	Yes/no
BI135585	C28H32N2O4 (S)-6-(2-hydroxy-2-methylpropyl)-3-((S)-1-(4-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl) phenyl)ethyl)-6-phenyl-1,3-oxazinan-2-one	Type 2 diabetes	Phase I ex vivo analysis of human adipose tissue revealed that BI135585 significantly inhibited 11β-HSD1 but not 11β-HSD2 (Hamilton et al., 2015). In a 14-d open-label study of adults with type 2 diabetes (n = 72), treatment with 5–200 mg BI 135585 inhibited hepatic 11β-HSD1. However, inhibition was substantially reduced compared with healthy participants on comparable treatment regimens (Freude et al., 2016).	Yes/NA
BVT2733	C17H21ClN4O3S2 3-chloro-2-methyl-N-[4-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-1,3-thiazol-2-yl]benzenesulfonamide	Type 2 diabetes, obesity, metabolic syndrome, rheumatoid arthritis.	While no clinical data available, preclinical mouse and rat models suggest inhibition of 11β-HSD1 through administration of BVT2733 is efficacious at reducing levels of serum insulin and blood glucose while increasing expression of brown adipocytes (Wu et al., 2013; Liu et al., 2013a).	NA/NA
Carbenoxolone	C34H50O7 (3β)-3-[(3-Carboxypropanoyl) oxy]-11-oxoolean-12-en-30-oic acid	Type 2 diabetes, obesity.	Carbenoxolone evaluated in a small number of clinical trials related to obesity and type 2 diabetes. While carbenoxolone administration appears efficacious in inhibiting 11β-HSD1, comparatively few effects observed for glucose disposal, cholesterol, or lipid production beyond reduced glucose production rate during hyperglucagonemia in diabetic patients after 7 d of 100 mg/d compared with placebo (Andrews et al., 2003). In comparing obese and non-obese men, 100 mg carbenoxolone every 8 h significantly reduced serum levels of 11β-HSD1 in non-obese participants. Still, no effect observed for glucose or insulin concentrations, glucose infusion rate in steady-state, or glucose disposal and production rates in obese participants.	Yes/NA

Table 1. Continued

Trade name/ identifier	Structure	Target condition	Clinical safety and efficacy data	Evidence of positive clinical findings (biomarkers/outcomes)
INCB13739	N/A	Type 2 diabetes	Three clinical trials concluded as of 2016 and data from 1 phase II RCT for type 2 diabetes was published (Rosenstock et al., 2010). A total 302 participants were randomized to either 5, 15, 50, 100, or 200 mg/d INCB13739 or placebo plus their usual metformin administration for 12 wk. Results revealed a dose-dependent statistically significant reduction in glycated hemoglobin, plasma glucose, and insulin resistance throughout trial for intervention groups compared with controls. Adrenocorticotropic hormone (ACTH) and Dehydroepiandrosterone sulfate (DHEAS) levels increased significantly within intervention groups until plateau at approximately wk 4, though authors suggest this was likely a compensatory response. Adverse events uncommon, with headache most reported in placebo and lowest-dose intervention groups and nausea at 200 mg.	Yes/NA
MK0736	C23H30F3N3O2S 3-{4-[3-(ethanesulfonyl) propyl]bicyclo[2.2.2] octan-1-yl}-4-methyl-5-[2-(trifluoromethyl)phenyl]-4H-1,2,4-triazole	Hypertension	One phase II clinical RCT evaluated MK0736 and MK0916 for hypertension, administering doses of 2, 6, or 7 mg once daily for 12 wk compared with placebo (n = 249) (Shah et al., 2011) At 12 wk, trough sitting diastolic blood pressure significantly reduced compared with placebo for 2 mg MK0916 and 6 mg but not 7 mg MK0736. However, 24-h average diastolic blood pressure was significantly reduced in all treatment conditions compared with placebo as was 24-h systolic blood pressure in all treatment conditions except for 2 mg MK07366. Treatment with 7 mg MK-0736 and 6 mg MK-0916 increased plasma levels of Dehydroepiandrosterone (DHEA) and DHEAS, and androstenedione compared with placebo; otherwise all treatments well-tolerated and few safety concerns were reported.	Yes/NA
MK0916	C18H19ClFN3 3-[trans-1-(4-Chlorophenyl)-3-fluorocyclobutyl]-4,5-dicyclopropyl-4H-1,2,4-triazole	Hypertension	As above, though authors observed MK0916 appeared to induce CYP3A4 when administered in therapeutic doses.	Yes/NA

Table 1. Continued

Trade name/ identifier	Structure	Target condition	Clinical safety and efficacy data	Evidence of positive clinical findings (biomarkers/outcomes)
RO5027383	N/A	Type 2 diabetes	One phase II clinical RCT evaluated both ROS502383 and ROS5093151 compared with placebo for type 2 diabetes, administering RO5093151 5 mg twice daily, RO5093151 200 mg twice daily, RO5027383 50 mg 4 times daily, or RO5027383 200 mg 4 times daily orally for d (N = 110) (Heise et al., 2014). While 11β-HSD1 was significantly inhibited after treatment and encouraging trends observed on several parameters, including HbA1c, plasma glucose, insulin, or C-peptide levels, neither compound able to demonstrate statistical significance for any treatment condition.	Yes/NA
RO5093151	C23H27ClN2O2 (3S)-1'-Benzyl-3-phenyl-3,4'-bipiperidine-2,6-dione hydrochloride (1:1)	Type 2 diabetes	As above	Yes/NA
UE2343 "Xanamem"	C19H19N5O2S 5-(1H-pyrazol-4-yl) thiophen-3-yl)((1R,3r,5S)-3-hydroxy-3-(pyrimidin-2-yl)-8-azabicyclo[3.2.1] octan-8-yl)methanone	Alzheimer's disease	One phase I clinical trial in healthy adults identified examining UE2343 using single ascending dose (n = 36) and multiple ascending doses (n = 24) (Webster et al., 2017). Participants randomly allocated to either placebo or 10, 18, 25, or 35 mg in single ascending dose or placebo or 10, 25, or 25 mg in multiple ascending doses. Plasma ACTH levels significantly elevated 23 h after quantities of 10, 25, and 35 mg but not 18 mg or placebo, but this effect not sustained over 2 wk. Cortisol and DHEAS significantly elevated at d 10 for 20-mg treatment compared with placebo; 4-androstenedione elevated from baseline at 10 and 20 mg compared with placebo. A phase II clinical trial for Alzheimer's disease was completed in 2019 (NCT02727699). Results of phase II trial were reported on clinical trials registry in May 2021, but no significant effects, cognitive or otherwise, observed.	Yes/no

EFFICACY AND SAFETY FOR NOVEL ADJUNCTIVE 11β-HSD1 INHIBITORS IN MEDICINE

Current support for the use of adjunctive 11β-HSD1 inhibitors in medicine is, at best, inconsistent, though some promising signs are evident. While most treatment regimens and compounds demonstrated significant inhibition of urine and serum markers of 11β-HSD1, the clinical translation of this inhibition was mixed. For example, biomarker reduction of 11β-HSD1 was observed with both ABT384 and UE2343, but neither compound demonstrated a clinical change in other outcome variables, such as cognitive decline or symptom severity. In contrast, the use of 11β-HSD1 inhibitors for biomarker management in type 2 diabetes appeared to have more robust pre-clinical and early-phase clinical support. Still, null results were reported for the phase II clinical trials for compounds carbenoxolone, INCB13739, and RO5027383. However, pharmacokinetic and other parameters are not published for many novel 11β-HSD1 inhibitors, and pertinent to neurology and psychiatry, many of these agents may not cross the blood-brain barrier.

Despite a lack of convincing evidence among broader medical conditions, some of the 11β-HSD1 inhibitors may have promise for use in neurology and psychiatry. For example, carbenoxolone has been used in routine clinical practice to treat gastric and peptic ulcers, and investigations into the off-label use of the compound have demonstrated pro-cognitive effects. Treatment for 4 wk with carbenoxolone, a non-selective inhibitor of both 11β-HSD2 and

11β-HSD1, improved verbal fluency in 10 healthy older men and enhanced verbal memory after 6 wk in 12 patients with type 2 diabetes (Sandeep et al., 2004). Elsewhere, carbenoxolone reduced both baseline and excessive drinking of alcohol in rats and mice (Sanna et al., 2016), the selective 11β-HSD1 inhibitor A-918446 improved memory consolidation and recall in inhibitory avoidance, and A-801195 significantly improved short-term memory in rat social recognition (Mohler et al., 2011). Taken together, these results are encouraging if indicative of the difficulties in the translation of preclinical to clinical efficacy.

At least 2 other 11β-HSD1 inhibitors have been investigated for indications associated with mental health. ABT384 was evaluated in a multicenter phase II trial conducted at 30 sites in 4 countries to test the hypothesis that elevated cortisol levels in the brain contribute to cognitive impairment. The study compared 10 and 50 mg of ABT384 once daily, donepezil 10 mg once daily, or placebo for 12 wk in people with mild to moderate Alzheimer's disease. The primary efficacy endpoint was the change from baseline to final evaluation on the Alzheimer's Disease Assessment Scale-Cognitive subscale total score. After randomizing 267 participants, the study was stopped for futility. Neither dose of ABT384 affected cognitive performance, whereas the active comparator donepezil significantly improved cognition and functional endpoints. The study group stated that the dose amount of ABT384 was sufficient to achieve total inhibition of 11β-HSD1 in the brain (Marek et al., 2014).

Elsewhere, the 11β-HSD1 inhibitor UE2343 is being tested as a pharmacotherapy for cognitive impairment in Alzheimer's disease. In humans, UE2343 was shown to have acceptable pharmacokinetic properties and crossed the blood-brain barrier at a sufficient concentration for 11β-HSD1 inhibition; there were no significant safety or tolerability concerns (Webster et al., 2017). Listed on clinicltrials.gov, a phase II, randomized, double-blind study to assess the safety, tolerability, and efficacy of 10 mg daily oral UE2343 or placebo for 12 wk in adults with mild dementia due to Alzheimer's disease was completed in March 2019. Study sites were in 3 countries (Australia, United Kingdom, and the United States), and 186 participants were enrolled. The trial results have not yet been published in the peer-reviewed literature. However, the study sponsors have updated the clinical trials registry with the cognitive outcomes reporting that results were negative and produced no statistically significant distinction between 10-mg doses and placebo. Further, the study sponsors reported that the results of an earlier phase I study (NCT03830762) suggested that cognitive protection was associated with a 20-mg daily dose in healthy adults, though the results have yet to be published. The announcement also suggested that higher doses and a longer duration of treatment were worth pursuing (Actinogen Medical Limited Trading as Actinogen Medical ACN, 2019a, 2019b).

Crucially, where the safety and tolerability of 11β-HSD1 inhibitors have been reported, the results are encouraging, even at high doses with ASP3662 (Bellaire et al., 2019). While the reporting of specific safety and tolerability data to particular agents varied, severe reactions or adverse events were rare, and the majority of reported adverse events and reactions appear to be relatively mild—the most commonly reported include headache and nausea (common non-specific adverse events with diverse agents; Dodd et al., 2019).

CONCLUDING REMARKS

11β-HSD1 inhibitors are being developed as a novel drug target for multiple medical, neurological, and psychiatric indications, with selective inhibition as the preferred mechanism. Currently, there are no 11β-HSD1 inhibitors approved for mental health or neurological treatment, although there are efforts underway to develop 11β-HSD1 inhibitors for obesity and metabolic disorder, diabetes, and cognitive functioning. Safety and tolerability concerns do not appear to be problematic for any agents that progressed through to human trials. Agents seem to be effective for reducing levels of peripherally circulating cortisol, and several agents have demonstrated efficacy in rodent models. However, preliminary phase II trials have either been ineffective for the test condition or of limited effectiveness, suggesting difficulties translating basic research into the clinical environment. For some lead drug candidates, such as UE2343, fundamental questions remain regarding adequate dose and selecting which condition to target for treatment. Other 11β-HSD1 inhibitors should also be adequately investigated, although many already appear to have fallen along the wayside. In disease models where the reversal of pathology is unrealistic, such as in Alzheimer's disease, it is hoped that continued and sustained administration can attenuate a functional decline compared with treatment as usual, though this has yet to be demonstrated. It is also possible that there is greater potential for disorders where cortisone-mediated stress response acts as a precipitating factor, especially where irreversible structural damage has not yet occurred. Thus, 11β-HSD1 inhibitors merit further investigation as treatments for psychiatric and neurologic disorders.

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Interest Statement

The authors declare no conflicts of interest.

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