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11β-Hydroxysteroid dehydrogenase and the brain: Not (yet) lost in translation

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11-beta-hydroxysteroid dehydrogenases (11β-HSDs) catalyse the conversion of active 11-hydroxy glucocorticoids (cortisol, corticosterone) and their inert 11-keto forms (cortisone, 11-dehydrocorticosterone). They were first reported in the body and brain 70 years ago, but only recently have they become of interest. 11β-HSD2 is a dehydrogenase, potently inactivating glucocorticoids. In the kidney, 11β-HSD2 generates the aldosterone-specificity of intrinsically non-selective mineralocorticoid receptors. 11β-HSD2 also protects the developing foetal brain and body from premature glucocorticoid exposure, which otherwise engenders the programming of neuropsychiatric and cardio-metabolic disease risks. In the adult CNS, 11β-HSD2 is confined to a part of the brain stem where it generates aldosterone-specific central control of salt appetite and perhaps blood pressure. 11β-HSD1 is a reductase, amplifying active glucocorticoid levels within brain cells, notably in the cortex, hippocampus and amygdala, paralleling its metabolic functions in peripheral tissues. 11β-HSD1 is elevated in the ageing rodent and, less certainly, human forebrain. Transgenic models show this rise contributes to age-related cognitive decline, at least in mice. 11β-HSD1 inhibition robustly improves memory in healthy and pathological ageing rodent models and is showing initial promising results in phase II studies of healthy elderly people. Larger trials are needed to confirm and clarify the magnitude of effect and define target populations. The next decade will be crucial in determining how this tale ends – in new treatments or disappointment.

Keywords: 11β-hydroxysteroid dehydrogenase, ageing, cognition, glucocorticoid, mineralocorticoid

1953

1953 was a momentous year. The Korean War ended, Queen Elizabeth II was crowned, Stalin died, Eisenhower became US president and Mount Everest was conquered. In science, Crick and Watson published the structure of DNA, Howard and Pelc reported the cell cycle and Salk announced his polio vaccine.

Also in 1953, following the 1950 Nobel Prize to Kendall and Reichstein for identifying and synthesizing 'compound E' (cortisone) and Hench for discovering its astonishing therapeutic impact in rheumatoid arthritis [1], Burton discovered that cortisone administered to humans in vivo was converted to cortisol (hydrocortisone, 'compound F') [2], and Amelung showed this reaction occurred in rats in vivo and in liver extracts in vitro [3]. These were the first descriptions of 11β-hydroxysteroid dehydrogenase (11β-HSD). Following clinical evidence in arthritis, it emerged that cortisone is inert, and cortisol (hydrocortisone) is the active glucocorticoid [4].

A potted 70-year history of 11β-HSD

The history of 11β-HSD has been reviewed [5]. After its discovery, 11β-HSD-like activity was shown to be microsomal, highest in the liver and kidney and present elsewhere – including the brain [6]. Thereafter, for three decades, 11β-HSD remained an obscure backwater of steroid biology.

There are two intracellular receptors for corticosteroids: the lower affinity glucocorticoid receptor (GR) [7] and a higher affinity mineralocorticoid receptor (MR) [8]. GR cDNA [9] expressed in

vitro yields sites binding physiological (cortisol, corticosterone) and synthetic (prednisolone, dexamethasone, triamcinolone) glucocorticoids. However, MR cDNA expressed in cells [10] surprisingly bound corticosterone and cortisol with similarly high affinity as aldosterone. Yet in vivo MR in the kidney solely binds aldosterone despite 100–1000 circulating excess of glucocorticoids. Structurally identical MR in the hippocampus [11, 12] are occupied by glucocorticoids [13].

The solution to this MR conundrum lies in the 'syndrome of apparent mineralocorticoid excess (AME)', a rare, fatal childhood hypertensive disorder with hypokalaemia, hypernatraemia and metabolic alkalosis. In AME, mineralocorticoids (aldosterone, 11-deoxycorticosterone) are suppressed, hence 'apparent'. Cortisol levels are normal. However, 11β-dehydrogenase is deficient, revealed by markedly elevated cortisol:cortisone metabolites in urine [14]. Stewart et al. in Edinburgh investigated a unique adult AME patient [15] and showed that cortisol caused the mineralocorticoid excess. Dexamethasone-suppression of endogenous cortisol reversed AME, while concurrent cortisol replacement recapitulated AME in the patient, not in controls.

AME resembles the adverse effects of liquorice (confections, herbal medicines) [16, 17], which potently inhibit 11β-HSD (Ki low nanomolar) [18]. Building on this, teams in Edinburgh [19, 20] and Melbourne [21] showed that selectivity of renal MR resides in 11β-HSD. In the kidney, this catalyses the rapid inactivation of cortisol to inert cortisone, which cannot bind MR. The non-substrate aldosterone bypasses 11β-HSD and activates MR. 11β-HSD inhibition by liquorice or deficiency in AME allows cortisol illicitly to activate renal MR.

Glucocorticoid inactivation by 11β-HSD in the kidney exemplifies *intracrinology* – pre-receptor metabolism determining steroid access to receptors. Analogous biology occurs for oestrogen receptors and aromatase, androgen receptors and 5α-reductase type 2 and thyroid hormone receptors and mono-deiodinases [22].

11β-HSD up to date

Rat liver 11β-HSD, the only known enzyme in the 1980s, was curiously not expressed in the distal nephron where MR are located, nor was its gene (*HSD11B1)* mutated in AME patients. This drove the characterization [23, 24] and cloning of a second, distantly related enzyme – 11β-HSD type 2 – from the kidney [25] and placenta [26]. The original liver enzyme is called 11β-HSD1, the renal/placental isoform is 11β-HSD2 (Fig. 1. Table 1 lists their characteristics.

11β-HSD2

11β-HSD2 is an NAD-dependent, potent 11β-dehydrogenase located in aldosterone-specific mineralocorticoid target tissues in distal nephron, colon, salivary and sweat glands [26]. Its gene (*HSD11B2*) is mutated in AME. 11β-HSD2 is also highly expressed in the placenta and foetus, where it minimizes access of high maternal cortisol to maintain a low glucocorticoid foetal environment. Bypass, inhibition or knockout of feto-placental 11β-HSD2 alters developmental trajectories, engendering life-long 'programming' of cardiometabolic and neuro-behavioural pathophysiology [27].

11β-HSD1

11β-HSD1 uses NADP/NADPH as a co-substrate. It is widely expressed, highest in the liver and plentiful in adipose, vasculature, muscle and inflammatory cells; gonads; and the brain [5]. Initially, 11β-HSD1 was believed to be bidirectional or a dehydrogenase. However, the transfection of 11β-HSD1 cDNA into amphibian mineralocorticoid-responsive or mammalian kidney-derived cells unexpectedly encodes an exclusive 11β-reductase, regenerating cortisol from inert cortisone [28, 29]. 11β-reduction also predominates in primary hepatocytes [30].

11β-reduction is not an intrinsic property of 11β-HSD1 but is driven by its colocation in the endoplasmic reticulum with hexose-6-phosphate dehydrogenase (H6PDH), a powerful NADPH generator. In omental pre-adipocytes where H6PDH is limiting, 11β-dehydrogenase emerges [31]. 11β-reduction potently amplifies local tissue glucocorticoid action. A patient with cortisone reductase deficiency and coincidental Cushing's disease resisted morphological and pathological manifestations despite marked circulating cortisol excess [32].

11β-HSD1 as a cardio-metabolic disease target

Although cortisol levels are not elevated in uncomplicated metabolic syndrome, 11β-HSD1 is

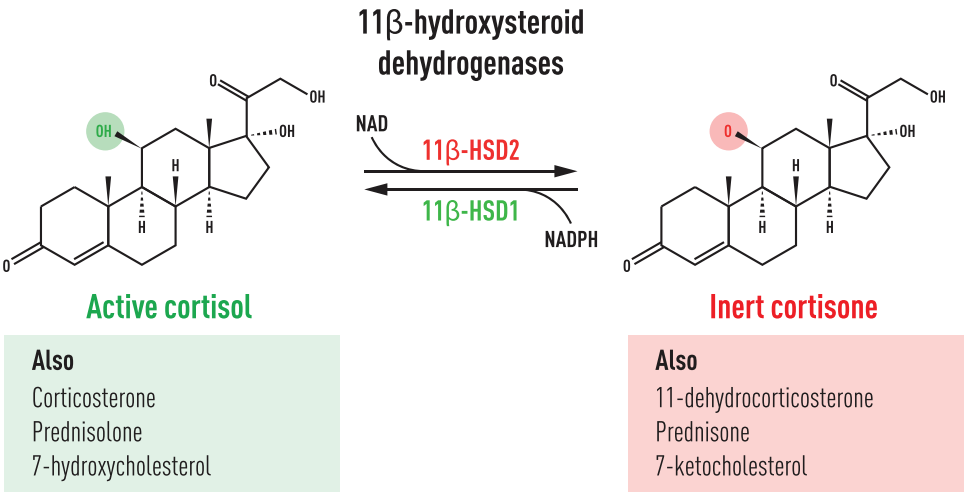


Fig. 1 *11β-Hydroxysteroid dehydrogenases (11β-HSDs) catalyse the interconversion of active cortisol and corticosterone to inert cortisone and 11-dehydrocorticosterone, respectively. 11β-HSD2 is a dehydrogenase which drives the inactivation of glucocorticoids in kidney, colon, salivary gland and other aldosterone-selective mineralocorticoid target cells. This includes the nucleus of the solitary tract in the brain stem where aldosterone selectively stimulates salt appetite. 11β-HSD2 also acts as a barrier to active glucocorticoids in placenta and foetal tissues. 11β-HSD1 is a reductase that catalyses the reactivation of inert cortisone to active cortisol. It functions as an amplifier of glucocorticoid action in liver, adipose and other peripheral tissues as well as key regions of the brain (hippocampus, cortex, amygdala, cerebellum). 7-keto and 7-hydroxy-cholesterols are also substrates for 11β-HSD (the 7-position mirrors inversely the 11-position). Both oxysterols accumulate in Alzheimer's disease brain, but any function of this reaction remains obscure.*

selectively increased in visceral adipose tissue in obese rodents [33] and humans [34, 35]. Could metabolic syndrome be 'Cushing's of the omentum'? [36]. Transgenic overexpression of 11β-HSD1 in adipose tissue in mice reproduces metabolic syndrome, with hyperglycaemia, hyperinsulinaemia, obesity, hyperlipidaemia, hypertension and adipose inflammation [37, 38]. Conversely, 11β-HSD1 null mice resist metabolic consequences of high-fat feeding [39, 40] and get less atherosclerosis and plaque inflammation [41]. Thus, 11β-HSD1 inhibition was proposed as a therapeutic target [42].

Selective 11β-HSD1 inhibitors have been generated (recent review [43]). In preclinical models, these have similar effects to 11β-HSD1 knockout [44–46]. Human phase II trials showed modestly lower glucose/glycated haemoglobin, insulin, blood pressure, lipids, liver enzymes and bodyweight [47–51], though some agents were ineffective [48, 52]. To date, the magnitude of benefits has been insufficient to support progression [53]. Some failures may be due to tachyphylaxis [54] or target-mediated drug disposition [55], and perhaps the metabolic target is lower in humans. Nonetheless, a drug which even modestly improves many of the features of metabolic syndrome may have utility.

11β-HSD1 inhibitors have been explored in other glucocorticoid-associated disorders. Encouraging outcomes have been reported in early phase trials in osteoporosis, benign intracranial hypertension and myopathy [50], Cushing's disease [56], non-alcoholic fatty liver disease/hepatic steatosis [49], cutaneous wound healing [57] and prednisolone side-effect reduction [58]. But what about the brain?

11β-HSDs in the brain (Fig. 2)

11β-HSD2

11β-HSD2 is highly expressed in the foetal CNS and transiently in early postnatal-maturing regions, notably the cerebellum [59, 60]. The complex, cell-specific shut off of 11β-HSD2 expression appears to parallel brain regions entering terminal differentiation [60]. Indeed, 11β-HSD2 null mice exhibit increased sensitivity of the developing CNS to exogenous corticosterone [61].

Although whole foetal and placental 11β-HSD2 knockout mice as adults show 'programming' of

Table 1. *The characteristics of the 2 isozymes of 11β-hydroxysteroid dehydrogenase (11β-HSD).*

Characteristic	11β-HSD1	11β-HSD2
Gene	*HSD11B1*	*HSD11B2*
Chromosome	1q32.2	16q22.1
Mutations cause	AME	Cortisone reductase deficiency
Molecular weight	34 kDa	44 kDa
Amino acid residues	292	405
Cellular location	Inner leaflet ER	Outer facing (cytoplasmic) ER
Reaction in vitro	Reversible	Dehydrogenase
Reaction in vivo	Reductase	Dehydrogenase
Co-substrate	NADP(H)	NAD
Major substrates	Cortisone, 11-dehydrocorticosterone, prednisone, 7-ketocholesterol, 7-OH-DHEA, 7-OH-pregnenolone, 7-oxo-lithocholic acid	Cortisol, corticosterone, prednisolone
distribution	Liver, adipose, muscle, gonad, vasculature, immune, brain	Kidney, colon, salivary and sweat glands, placenta, foetus
Location in adult CNS	Widespread, neurons and glia	NTS, sub-commissural organ

Abbreviations: AME, Apparent mineralocorticoid excess; DHEA, dehydroepiandrosterone; ER, endoplasmic reticulum.

anxiety and depressive-like behaviours, reduced cognitive function and hypothalamic–pituitary–adrenal (HPA) axis hyperactivity, foetal brain-specific knockout engenders a partial phenotype with reduced cognition and depression-like behaviours but without anxiety or HPA axis activation [62], illustrating the complexity. The children of Finnish women who electively consumed substantial amounts of liquorice during pregnancy show a 7–10 point decrease in IQ aged 8 and 12, a 1.5–3-fold increase in attention disorders, and elevated cortisol and sleep disturbances, implying feto-placental 11β-HSD2 inhibition also programmes human brain function [63–66].

In the adult rodent CNS, substantial 11β-HSD2 expression is confined to hindbrain regions associated with aldosterone-specific MR-mediated actions on salt appetite and blood pressure [67], notably in the nucleus tractus solitarius (mice, rats) and sub-commissural organ (rats) [68]. Selective knockout of 11β-HSD2 in the mouse brain causes a striking threefold increase in salt appetite, consequent hypertension and the development of salt sensitivity in a salt-resistant strain. The effects are reversed by MR antagonism or suppression of endogenous corticosterone [69]. Intriguingly, a longer *HSD11B2* intronic CA repeat linked to modestly reduced enzyme activity associates with higher salt intake without changes in renal glucocorticoid metabolism [70], implying brain 11β-HSD2 influences salt appetite in humans. There is an opportunity for elegant human experimental medicine studies.

11β-HSD1

11β-HSD1 mRNA, immunoreactivity and NADPH-driven activity are present in the adult CNS in rodents [71–74] and humans. Higher levels occur in the cerebellum, hippocampus and cortex, particularly the cerebellar Purkinje and granule cells, CA3 hippocampal pyramidal cells and neocortical layer V neurons [72], but lower levels of 11β-HSD1 are observed throughout the brain and spinal cord. This includes the hypothalamic paraventricular nucleus (PVN) [74, 75] and pituitary [73] (in corticotrophs in humans [76]) loci mediating HPA axis glucocorticoid negative feedback.

Primary cultures of rat hippocampal neurons express 11β-HSD1, which is an exclusive 11β-reductase. It is functional because 11-dehydrocorticosterone and corticosterone are equipotent in glucocorticoid-potentiation of excitatory amino-acid neurotoxicity unless 11β-reductase is inhibited [77]. What might 11β-HSD1 do in vivo?

A first study used glycyrrhetinic acid – a non-selective, liquorice-derived 11β-HSD inhibitor – to examine cerebral 2-deoxy-glucose uptake as

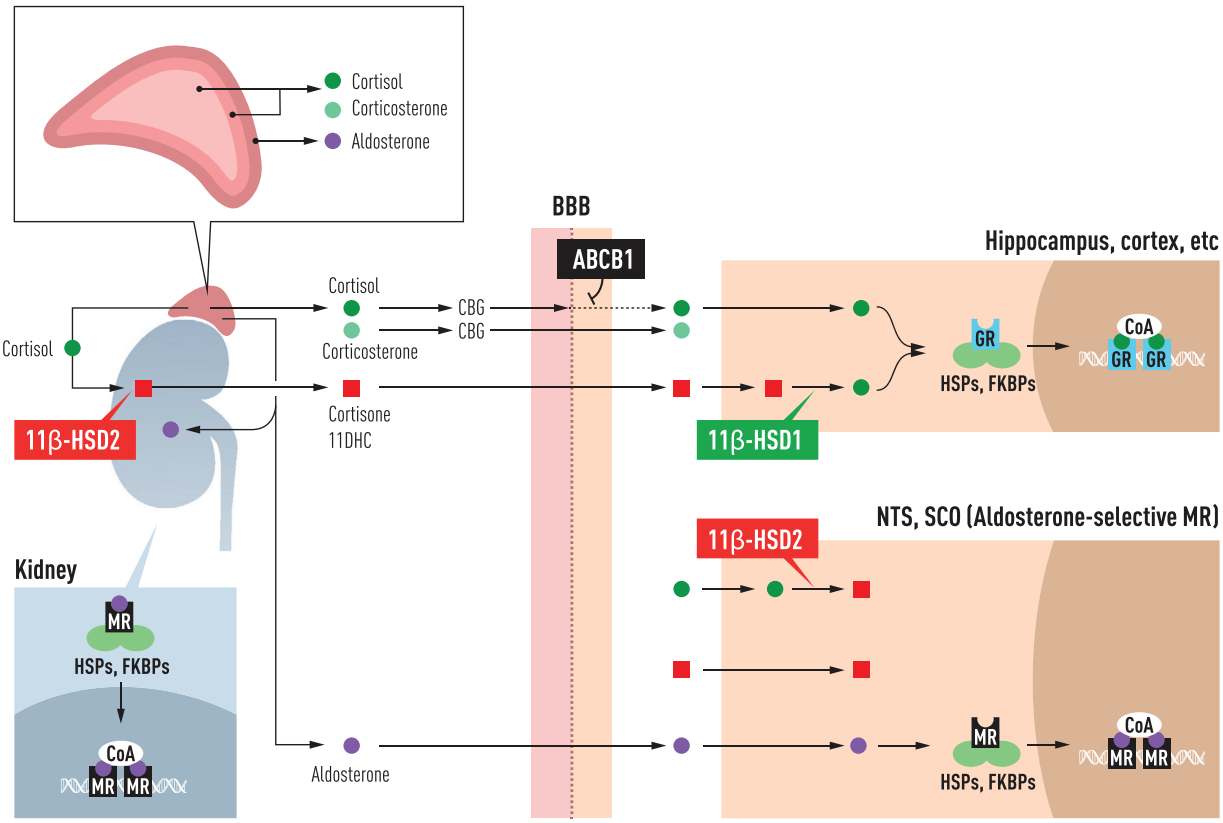


Fig. 2 *The inner zones of the adrenal cortex synthesize active glucocorticoids, cortisol and corticosterone. In vitro, these bind to both glucocorticoid receptors (GR) and mineralocorticoid receptors (MR). The outer adrenal zone makes the exclusive MR agonist aldosterone. Renal 11β-hydroxysteroid dehydrogenase 2 (11β-HSD2) rapidly converts active cortisol to inert cortisone which circulates at substantial concentrations. These steroids cross into the brain, although the ABCB1 pump on the blood–brain barrier attenuates access specifically of cortisol. In most of the brain, MR and GR bind cortisol and corticosterone; aldosterone concentrations are too low to impact on MR. In specific sub-regions such as hippocampus, high levels of 11β-HSD1 approximately double intracellular levels of active glucocorticoids by regenerating these from inert cortisone and 11-dehydrocorticosterone (11DHC), thus amplifying intracellular glucocorticoid signalling. In the nucleus of the solitary tract (NTS) and the subcommissural organ (SCO), 11β-HSD2 catalyses the inactivation of cortisol to inert cortisone, thus allowing only aldosterone to access MR, where it drives salt appetite and elevates blood pressure.*

a proxy for regional brain activation. Increased uptake occurred in the hypothalamus (PVN, lateral and arcuate nuclei); hippocampus; neocortex; zona incerta; and subthalamus, broadly paralleling high 11β-HSD1 mRNA expression [78].

At a cellular level, 11β-HSD1 is expressed in both neurons and glia [74]. Microglia [79] have high levels of 11β-HSD1 which are further increased when these innate immune cells are activated. This parallels control in peripheral macrophages [80, 81], implicating 11β-HSD1 in modulating neuroinflammation. In humans, microglial 11β-HSD1 levels are increased in multiple sclerosis. Any function remains moot but is worthy of investigation [82].

11β-HSD1 and the HPA axis

The presence of 11β-HSD1 in anterior pituitary, PVN, and supra-hypothalamic sites of HPA axis control – notably the hippocampus – suggests it may contribute to feedback regulation. An early in vivo study suggested glycyrrhetinic acid altered glucocorticoid feedback at the PVN, increasing vasopressin but unexpectedly decreasing corticotropin-releasing hormone secretion into pituitary portal blood [75]. This inhomogeneity of

changes in hypothalamic stimulants of adrenocorticotropin (ACTH) release may appear surprising, but acute adrenalectomy (reducing glucocorticoid feedback, analogous to inhibiting 11β-reductase) has similar divergent effects [83], perhaps reflecting a short timescale or the invasive portal sampling technique employed.

The original 11β-HSD1 knockout mouse on the 129/MF1 strain background [39] had elevated basal and post-stress corticosterone levels [84]. This encouraged those seeking to inhibit 11β-HSD1 in the human periphery (liver, adipose) to develop molecules that do not penetrate the brain to avoid hypercortisolaemia, which might antagonize the benefits of lowering intracellular cortisol. However, further studies showed that HPA axis over-activity is a feature of 129 mice. 11β-HSD1 null mice on other strain backgrounds have unaltered basal corticosterone levels, plausibly because they show a 'compensatory' rise in GR expression in the PVN and hippocampus, increasing feedback sensitivity. Mice of the 129 strain lack this plasticity and are relatively resistant to glucocorticoid negative feedback [85]. In humans, most studies with selective 11β-HSD inhibitors – including brain-accessing compounds – report no changes in plasma cortisol [47]. However, the mouse findings suggest inter-individual differences might occur.

11β-HSD1 or H6PDH knockout mice show a rise in plasma ACTH levels with increased adrenal weight [39, 86]. Similarly, in humans, selective 11β-HSD1 inhibitors produce a modest (25%–50%) rise in plasma ACTH and its non-glucocorticoid adrenocortical products such as the androgen precursor dehydroepiandrosterone (DHEA) [47–49, 87, 88]. This is an anticipated effect of enzyme deficiency/inhibition. 11β-HSD1 reductase – particularly in liver and splanchnic bed organs – contributes substantially to glucocorticoid regeneration [89]. Its inhibition shortens steroid half-life. To maintain circulating glucocorticoids, there is compensatory HPA activation with an elevation of ACTH. Confirmation that this follows increased peripheral clearance of glucocorticoids was shown by the transgenic rescue of 11ß-HSD1 selectively in the liver in 129 background null mice. This reversed elevated corticosterone and adrenal weight [90]. Indeed, elevated ACTH and DHEA are useful biomarkers of effective 11β-HSD1 inhibition in humans [47, 87].

Glucocorticoids and cognition

Myriad human studies associate *long-term* elevation of physiological glucocorticoids with cognitive decrements. Cortisol excess correlates with memory decline in Cushing's disease [91, 92], hydrocortisone therapy, severe depression and Alzheimer's disease [93], reviewed [94]. Even mild cortisol excess in autonomous adrenal secretion links to cognitive deficits [95].

Suggesting causality, prospective studies in rodents [96] and humans [97–99] link naturally occurring high or rising glucocorticoid levels with subsequent memory decline, hippocampal volume loss and the onset of memory deficits. Successful treatment of Cushing's disease associates with partial reversal of hippocampal volume loss and cognitive deficits [100]. In humans, declarative and spatial memory formations are attenuated by cortisol administration [101].

What of mechanism? In animal models and in vitro, chronic glucocorticoid excess has deleterious impacts on hippocampal neuronal dendritic complexity, synaptic plasticity, metabolism, neurotransmission, episodic/declarative and working memory, neurogenesis and sometimes neuronal viability [93]. Glucocorticoids stimulate synthesis of beta-amyloid and tau [102], hallmarks of Alzheimer's disease, implying a possible role in neuropathogenesis (Table 2).

Confusingly, contemporaneous *acute* elevation of glucocorticoids – interacting with noradrenaline – is required to develop memory of traumatic events (fear, severe emotion) [103]. Glucocorticoids evolved to enhance survival during stress. When the challenge is substantial (predation, major trauma), glucocorticoids inhibit detailed episodic (factual, spatial, moderate emotional) learning in the hippocampus and cortex but enhance fear memory hubbed in the amygdala and prefrontal cortex. This switch may represent a survival advantage. However, these circuits intersect, and the detailed molecular mechanisms require further elucidation.

The hippocampus highly expresses both MR and GR. Both exert some rapid membrane actions and slower nuclear effects [104]. For classical nuclear actions, higher affinity MR is already substantially occupied by glucocorticoids under basal conditions and supports episodic memory formation.

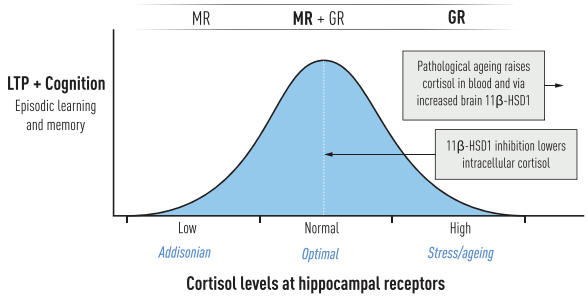


Fig. 3 *In the hippocampus, high-affinity mineralocorticoid receptors (MR) are occupied by basal (low) levels of cortisol and corticosterone and promote memory formation and long-term potentiation (LTP), a feature of synaptic plasticity. In Addison's disease, cortisol levels are extremely low, and cognition is attenuated as MR is unoccupied. In health, basal cortisol levels activate MR, which promotes hippocampal cognition. As cortisol levels rise further, MR are fully occupied, and there is progressive activation of lower affinity glucocorticoid receptor (GR). When GR predominate over MR, hippocampal learning and LTP are attenuated. With ageing, intra-hippocampal glucocorticoid levels rise due to elevated plasma cortisol levels and increased hippocampal 11β-hydroxysteroid dehydrogenase 1 (11β-HSD1). Inhibition of brain 11β-HSD1 reduces intra-hippocampal glucocorticoid levels by ~50%. The effect is to shift the high glucocorticoid GR-predominant stressed or aged hippocampal milieu to a lower glucocorticoid MR-predominant state, thus optimizing episodic learning and memory.*

In contrast, lower affinity GR is largely unoccupied by basal glucocorticoid levels but activated as glucocorticoids rise during stress (Fig. 3). Hippocampal GR mediates anti-cognitive effects in the hippocampus (whilst promoting fear conditioning in the amygdala, and thus indirectly in the hippocampus, illustrating the complexity). GR antagonists (mifepristone) or glucocorticoid synthesis inhibitors (metyrapone) support episodic memory formation but risk glucocorticoid deficiency (Addisonian crisis) on severe stress. Might this intriguing system be modulated with less hazard?

11β-HSD1 and cognition

As mammals age, they exhibit greater variation in cognitive function. A substantial subgroup develops cognitive deficits, notably in hippocampus-associated memory, associated with elevated plasma glucocorticoid levels. Also with ageing, 11β-HSD1 becomes variably elevated in the hippocampus and cortex in rodents and perhaps in humans, as suggested by a recent PET study [105, 106]. Indeed, glucocorticoids themselves, via GR, up-regulate hippocampal 11β-HSD1 [107], further amplifying the glucocorticoid signal. Intriguingly, hippocampal 11β-HSD1 correlates inversely with cognitive function in aged mice [108].

Addressing causation, modest forebrain-specific overexpression of 11β-HSD1 in transgenic mice – mirroring the rise seen with ageing – causes premature memory deficits in mid-life. This is not associated with changes in plasma corticosterone, suggesting mediation within the CNS [105].

11β-HSD1 knockout mice, when young, exhibit normal learning and memory. With ageing, 11β-HSD1 null mice on distinct strain backgrounds resist the cognitive impairments seen in aged wild-type litter-mates [108]. This protection appears to be due to the lack of 11β-HSD1 in the brain, as transgenic 'rescue' of 11β-HSD1 solely in the forebrain of knockout mice restores age-related cognitive deficits [109].

How much impact does 11β-HSD1 have on CNS glucocorticoid levels? Corticosterone concentrations are approximately 50% lower in hippocampus extracts from aged 11β-HSD knockout mice, despite similar plasma glucocorticoid levels [108]. Similarly, microdialysis in conscious, freely moving mice shows at least 50% lower corticosterone concentrations in the hippocampus in young or aged 11β-HSD null mice, including attenuated intra-hippocampal glucocorticoid elevations to circadian or stressful stimuli [110, 111]. Thus, 11β-HSD1 contributes substantially to active glucocorticoid levels in the hippocampus under basal and stress conditions, at least in rodents.

Such attenuation might be anticipated to off-load GR and reduce its 'deleterious' effects on episodic memory. Indeed, intracerebroventricular infusion of a GR antagonist in aged wild-type mice improves their cognitive function, whereas an MR antagonist has no effect. Conversely, in the lower intra-cellular glucocorticoid milieu of 11β-HSD1 null mice, MR antagonism causes cognitive decrements, whereas GR blockade has no effect as these receptors are largely unoccupied [112].

A problem with transgenic (including knockout) models is that lifelong deficiency may reflect developmental effects. Importantly, a brain-accessing selective 11β-HSD1 inhibitor (UE2316) – which lowers hippocampal and cortical corticosterone

levels on mass spectrometry imaging [113] or microdialysis [114] – reversibly improves age-associated cognitive deficits in mice [114, 115]. This appears to be a CNS effect, as inhibitors given in tiny doses intracerebroventricularly are equally effective. Some 11β-HSD1 inhibitors (A-918446, A-801195) have acute cognitive-enhancing effects in young animals in passive avoidance and social recognition tests [116] – though this may address more amygdala-related functions than hippocampus-associated memory, which declines with age.

An electrophysiological marker of synaptic plasticity ('learning') is long-term potentiation (LTP) in hippocampal slices. LTP is attenuated in aged mice, but aged 11β-HSD1 null mice maintain similar LTP to young animals [117]. In young mice, stress suppresses hippocampal LTP, an effect prevented by 11β-HSD1 inhibition [118]. These extensive preclinical data are consistent with the idea that 11β-HSD1 inhibition effectively lowers intrahippocampal glucocorticoid levels, thus facilitating episodic learning and memory.

Intriguingly, acute fear conditioning is attenuated by UE2316 in mouse [114, 118] and rat models [119] in keeping with the pleiotropic effects of glucocorticoids on learning and memory and indicating a distinct possible use in attenuating anxiety and post-traumatic stress disorder (PTSD). This remains to be explored in humans.

11β-HSD1 inhibition in neurodegeneration

In a transgenic mouse model (Tg2576) of Alzheimer's disease bearing the human 'Swedish' mutation in the amyloid precursor protein gene, 11β-HSD1 inhibition (UE2316) for 4 weeks improved memory and decreased cortical beta-amyloid plaques in already aged mice. Longer term (1 year) treatment of young Tg2576 mice also prevented cognitive decline but not amyloid plaques [115], suggesting 11β-HSD1 inhibition at most delays genetically driven pathology. What about in human Alzheimer's disease?

In humans, one report linked a rare *HSD11B1* polymorphism to Alzheimer's disease [120], but other studies have not replicated this, suggesting gene variants do not contribute substantially to neurodegeneration.

In a longitudinal study of over 100 elderly subjects with Alzheimer's disease, mild cognitive impairment or healthy ageing, there was little correlation between plasma cortisol levels and diagnosis or cognitive function, but a much better correlation between higher CSF cortisol levels and cognitive decline [121]. One possible explanation is that in pathological cognitive ageing, elevated 11β-HSD1 in the brain contributes more to CSF cortisol. So much for speculation based on observational studies – what about interventions?

Non-selective 11β-HSD inhibition with carbenoxolone (the hemi-succinate of glycyrrhetinic acid) plus amiloride to prevent renal mineralocorticoid excess – in two small randomized, double-blind, placebo-controlled, cross-over studies – showed significant, if modest (Cohen's d ~0.3), cognitive benefits after 4–6 weeks in healthy elderly men and male and female middle-aged subjects with type 2 diabetes [122].

Selective 11β-HSD1 inhibitors have begun to be tested in early randomized trials in Alzheimer's disease. First reported was ABT-384. Twelve-week dosing was completed in 81 subjects with mild–moderate Alzheimer's disease (mini-mental state score 10–24). Controls had placebo or the acetylcholinesterase inhibitor donepezil, which improved cognitive function. Although ABT-384 was safe (trend for more reported infections/infestations), neither dose altered cognition, and the study was terminated [123]. Two caveats occur. The approach to assessing 11β-HSD1 inhibition in the CNS involved deuterated cortisol infusion [124, 125]. This is converted first by 11β-HSD2 in the kidney to form D^4-cortisone and then by 11β-HSD1 (largely in the liver) to D^3-cortisol. Over many hours, steroids will flux in and out of the CNS. Perhaps the technique therefore measured more peripheral rather than central conversion [126]. But ABT-384 inhibited 11β-HSD1 in non-human primate CNS, so it is not unreasonable to assume there was some central impact as well. The other concern is whether moderate Alzheimer's disease is tractable by this approach.

UE2343 (Xanamem), a derivative of UE2316, was designed to access the human CNS [126]. Actinogen – the company progressing Xanamem – reports a PET study showing extensive binding of Xanamem to 11β-HSD1 in the human CNS in vivo (https://actinogen.com.au/category/corporate-presentations/). A randomized, placebo-controlled, double-blind phase II trial (NCT02727699) in patients with mild–moderate Alzheimer's disease

Table 2. *Preclinical evidence for potential mechanisms by which chronically elevated cortisol levels can damage cells in hippocampus and cortex – largely mediated via glucocorticoid receptors (GR).*

• Increased amyloid A-beta synthesis and neurotoxicity
• Reduced A-beta catabolism (BACE, IDE)
• Induction of pathogenic phosphorylated tau
• Increased excitotoxicity (glutamate [NMDA], GABA)
• Second messenger toxicity (calcium, G-proteins)
• Structural loss (synaptic and dendritic pruning)
• Reduced hippocampal neurogenesis
• Metabolic toxicity (increased glucose, insulin, lipids, local ROS generation)
• Vascular pathology (atherosclerosis, microvascular disease)
• Neuroinflammation (microglia, cytokines), exacerbating A-beta toxicity
• Endocrine (reduced 'neuroprotective' DHEA)

Abbreviation: DHEA, dehydroepiandrosterone.

showed Xanamem is safe but apparently had no overall cognitive effect (unpublished). However, subgroup analysis suggests the inhibitor slowed cognitive decline in 50% of patients with higher phospho-Tau181 who are at particular risk of progression [127]. The effect size (Cohen's $d = 0.4$) equated to doubling the rate of cognitive stability (56% drug, 28% placebo), albeit only over 12 weeks. Two subsequent small ($n = \sim 30$ treated), randomized, double-blind studies of Xanamem in 'healthy elderly' showed significant improvements in working and declarative memory parameters with effect sizes greater (Cohen's d 0.3–0.6) than reported in similar populations using carbenoxolone [122]. These data, albeit as yet unpublished, encourage the notion that age-related cognitive decline may be a valid target for 11β-HSD1 inhibition in humans. Further phase II trials addressing cognitive deficits in 'mild cognitive impairment' and depression are underway.

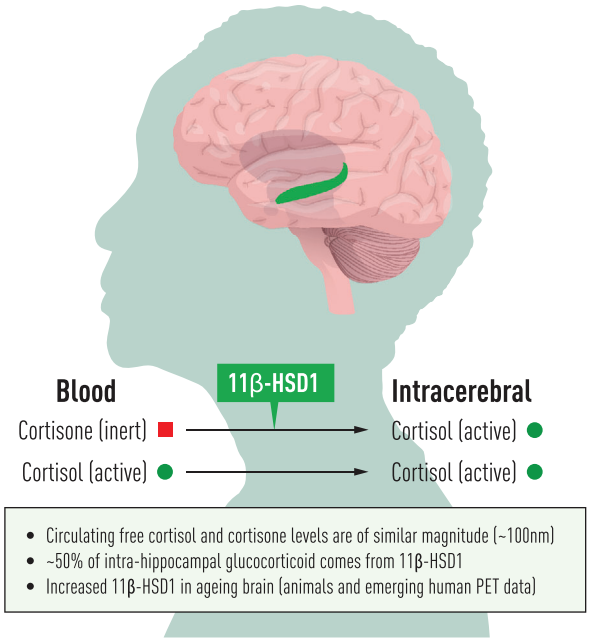
Potential mechanisms of 11β-HSD1 inhibitor cognitive enhancement (Fig. 4)

Studies addressing mechanism have been performed in rodent models. 11β-HSD1 inhibition in aged Tg2576 mice up-regulates amyloid-catabolizing insulin-degrading enzyme [115], itself down-regulated by glucocorticoids [128]. Another inhibitor, RL-118, decreases β-secretase-1 in stressed mice [129]. Alongside possible reduced glucocorticoid-driven synthesis of beta-amyloid and tau [102], such changes could delay pathogenesis.

In 4-month-old, senescence-prone SAMP8 mice – in which elevated corticosterone levels contribute to cognitive and hippocampal structural deficits [130] – 11β-HSD1 inhibition (RL-118) improves cognitive function, increases markers of synaptic function, lowers pathogenic hyperphosphorylated tau and reverses epigenetic changes of stress, reducing DNA methylation and 5-hydroxymethylation, with transcription-associated histone modifications, plausibly via lowering of DNA-methyltransferase-1 and Tet2 [129]. Moreover, in young SAMP8 mice when fed a high-fat diet, 11β-HSD1 inhibition induces FGF21 and the SIRT1/PGC1α/AMPKα nutrient sensor pathway in hippocampal cells alongside cognitive improvements [131], though extrapolation to normal senescence is unexplored. The inhibitor also reduces reactive oxygen species (ROS), with reduced Nrf2 (a key ROS transcription factor) and iNOS [129]. However, SAMP8 mice are short-lived (mean lifespan 13 months, around half 'wild-type'), have markedly elevated basal corticosterone levels, are susceptible to glucocorticoid-mediated neuronal death (most strains/species resist this) and exhibit dramatic reductions in circulating corticosterone with 11β-HSD1 inhibition, unlike most rodents and humans [131]. They may not be optimal to dissect human glucocorticoid-related ageing.

Both 11β-HSD1 gene knockout and inhibitors reduce drivers of neuroinflammation in the hippocampus – including IL-1β, IL-6, TNF-α and Cxcl2 – in response to lipopolysaccharide or chronic stress [129, 132]. Null mice also have increased hippocampal markers of aerobic glycolysis, mitochondrial oxidation, and hypoxia-induced factor-1α – targets implying metabolic protection from a range of insults, including ROS-related challenges [132].

With inhibitor A-918446, cortex CREB levels are unaltered, but pro-cognitive CREB phosphorylation increases [116] – a distinct mechanism from cholinergic cognitive modulators such as donepezil.



Effects of 11β-HSD1 deficiency and/or inhibition on the ageing brain (mainly hippocampus)

- Reduced (delayed deposition) of amyloid A-beta
- Increased A-beta catabolism (IDE) and reduced synthesis (β-secretase 1)
- Reduced hyperphosphorylated tau (in a young accelerated ageing model)
- Increased pro-cognitive CREB phosphorylation (ditto)
- Reduced epigenetic consequences of stress (less DNA methylation)
- Increased hippocampal neurogenesis (in young animals)
- Enhanced LTP in hippocampal slices from ageing and young animals
- Lower neuroinflammatory cytokines (IL1β, IL6, TNFα, Cxcl2)
- Lower brain reactive oxygen species (ROS) and iNOS
- Increased hippocampal glycolysis, mitochondrial oxidation and hypoxia-induced factor-1a, suggesting metabolic protection (e.g. from ROS)
- Increased FGF21 and nutrient sensor pathway (SIRT1/PGC1α/AMPKα) – young animals
- Attenuated peripheral cardio-metabolic contributions to neurotoxicity (reduced glucose, insulin, cholesterol, triglycerides, blood pressure)
- Reduced peripheral atherosclerosis and associated inflammation, though relevance to CNS vessels is unexplored
- Increased 'neuroprotective' DHEA (humans)
- Possible role of altered balance of 7-keto: 7-hydroxycholesterol on neuropathogenesis, including inflammation, membrane function and Apolipoprotein E isoform effects.

Fig. 4 *Chronically elevated cortisol levels (chronic stress, severe psychiatric disturbance, pharmacotherapy, Cushing's disease) damage vulnerable neurons and glia in specific CNS regions – notably the hippocampus, which has a very high density of glucocorticoid receptors (GR) and mineralocorticoid receptors (MR). There are multiple mechanisms involved, from evidence derived from preclinical models. But human observational studies, and the partial recovery of hippocampal volume loss and cognitive deficits in successfully treated Cushing's patients, suggest the same pathobiology applies to humans. Preclinical studies suggest several of these processes are attenuated with 11β-hydroxysteroid dehydrogenase 1 (11β-HSD1) deficiency (knockout) or inhibition.*

The hippocampal dentate gyrus is one of the few regions exhibiting neurogenesis in adult life. Neurogenesis is attenuated by glucocorticoids [133]. 11β-HSD1 deficiency increases neurogenesis substantially in young mice [117]. Hippocampal neurogenesis is very low in aged animals, and no effect of 11β-HSD1 deficiency was discernible. It may have relevance in pathological ageing or before senescence.

Glucocorticoids drive an excitatory (glutamate, calcium, energy depletion) pathway of neurotoxicity in hippocampal cells, spawning the 'glucocorticoid-cascade' hypothesis of brain ageing [134]. This pertains in vitro and, in some species, in vivo. Whether or not modest glucocorticoid excess kills neurons in humans is uncertain, but the effect of reducing 'glucocorticoid tone' by 11β-HSD1 inhibition may protect vulnerable cells in the ageing CNS, not least by affording energy and metabolic support [132, 135]. This notion merits dissection with 11β-HSD1 inhibitors.

Could this be mediated in the body rather than the brain? 11β-HSD1 inhibition/deficiency increases angiogenesis in peripheral arteries [136]. In the CNS, this appears somewhat unlikely given the resistance of retinal vessels to this mechanism [137], but any such action could benefit the ageing brain. Peripheral 11β-HSD1 inhibition's advantageous cardio-metabolic actions may also contribute to neuroprotection. However, cognitive improvement is seen in aged mice given a tiny dose of inhibitor (UE2316) intracerebroventricularly that is ineffective outside the brain. Thus, peripheral 11β-HSD1 inhibition seems unnecessary for cognitive effects [115].

Finally, 11β-HSD1 also catalyses the interconversion of 7-keto and 7-hydroxycholesterol, which may impact brain cells via sterol receptors and associated binders (LXR, SREBP), altering lipid homeostasis, with potential impacts on neurodegenerative pathologies. However, any functional differences between these oxysterols in the CNS

appear slight, if underexplored [138]. A caveat is that administered sterols will be interconverted by 11β-HSD1. Studies should be conducted in the presence of an inhibitor.

11β-HSD1 inhibition in other CNS disorders

Depression and anxiety: Cushing described prominent depression in his eponymous disease [139]. Carroll reported elevated, suppression-resistant cortisol in melancholic depression [140]. 11β-HSD1 is expressed in the rodent [141] and human [142] amygdala and prefrontal cortex, crucial loci for affective control. Does the enzyme have an impact on mood?

In the human post-mortem brain, 11β-HSD1 mRNA is elevated in the prefrontal cortex in major depression and bipolar disorder [143]. An *HSD11B1* single-nucleotide polymorphism (SNP; rs11119328) associates with a higher risk of depression and higher evening cortisol levels, a marker of depression [144]. In a second study, this variant was associated with suicide attempts, though not depression [145]. Another SNP (rs11811440) links with better recovery after antidepressant treatment. Further, *HSD11B1* SNPs (rs12565406, rs701950, rs10863782) associate with peri-partum depression [146], perhaps mediated via effects on neuroticism, which shares genetic variance with depression [147]. These studies are relatively small, and *HSD11B1* has not (yet) emerged in genome-wide analyses of depressive illnesses. Of course, that does not obviate its potential as a therapeutic target.

Most studies in young rodents show 11β-HSD1 deficiency or inhibition has little impact on basal anxiety-related behaviours but – as anticipated – attenuates fear conditioning [114, 118]. Chronic stress in mid-life in rodents causes anxiety, depression-like behaviours and cognitive deficits that persist for months after stress. 11β-HSD1 knockout mice resist these immediate and persisting effects [148]. 11β-HSD1 inhibition in aged mice also reduces the potency and persistence of new fear memories [114], suggesting that lowering intracerebral glucocorticoids enables resistance to stress-induced affective dysfunction.

PTSD: PET imaging in patients with PTSD shows higher 11β-HSD1 in amygdala-prefrontal limbic circuits [149], plausibly yielding additional glucocorticoid feedback and perhaps contributing to the enigma of lower plasma cortisol in some PTSD patients [150]. In a rodent model of PTSD incorporating excessive traumatic recall and contextual amnesia driving intrusive memories, 11β-HSD1 deficiency maintained (appropriate) fear memory but protected against contextual amnesia and hypermnesia. It would be worthwhile exploring whether 11β-HSD1 inhibition attenuates the progression of trauma to PTSD [151].

Elevated cortisol is frequently reported in psychosis, notably schizophrenia [152]. Rising cortisol may presage cognitive decline early in the disease. Whether 11β-HSD1 inhibition may be useful in psychosis-associated cognitive decline is unexplored.

Side-effects of 11β-HSD1 inhibition

Peripheral 11β-HSD1 inhibition in humans prevents cortisol regeneration in liver and other peripheral tissues, thus reducing the half-life of cortisol [89]. This causes HPA axis activation, merely to maintain circulating cortisol levels. Does such 'compensatory' elevation of ACTH in humans [47, 126] exert adverse effects, notably adrenal tumourigenesis? Most adrenal tumours are not ACTH-dependent and adrenal hyperplasia is typically reversible, but could tertiary tumours occur? These are little reported in adults with long-term ACTH excess in pituitary-dependent Cushing's disease or ectopic ACTH secretion. Congenital adrenal hyperplasia (21-hydroxylase deficiency) with life-long ACTH and adrenal androgen excess is associated with adrenal tumours, notably benign myelolipomas [153]. Whether these have genetic, developmental or acquired aetiologies is uncertain. Overall, this potential complication of long-term, modest ACTH excess with 11β-HSD1 inhibition in adults seems improbable, but adrenal monitoring would be prudent in any phase III trials.

Another potential concern with any agent-reducing glucocorticoid action is whether it might engender an Addisonian state on severe illness/trauma. However, 11β-HSD1 inhibition does not – theoretically or in human trials – alter HPA-axis cortisol responses, so this should not be a concern.

ACTH-driven elevation of DHEA associates with androgenic effects (hirsutism) in some women with life-long *cortisone reductase deficiency* due to

HSD11B1 mutations [154]. However, DHEA levels typically fall several fold with age. Replacement to young–adult levels has been advocated for age-related disorders. Preclinically, DHEA benefits cognition in ageing and Alzheimer's models [155], but evidence in humans remains slight [156–158]. Overall, modestly raised levels of DHEA with 11β-HSD1 inhibition seem unlikely to have cognitive disadvantages.

What about changes in more potent sex steroids? In studies of 11β-HSD1 inhibitors to date, changes in testosterone and other androgenic products of DHEA have been slight and inconsistent but theoretically could contribute to hirsutism. This remains unreported. The utility of anti-androgens in prostatic disorders suggests monitoring in men in 11β-HSD1 inhibitor trials.

11β-HSD1 is barely expressed in the foetus until late gestation, when it contributes additional glucocorticoids to assist foetal lung maturation [159]. Use of inhibitors in pregnancy seems unwise, but this is hardly the target population.

Despite the well-known anti-inflammatory actions of glucocorticoid pharmacotherapy, more physiological levels of cortisol 'shape' immune and inflammatory responses, exerting subtle effects distinct from high-dose synthetic steroids. 11β-HSD1 is expressed in macrophages and other immune cells. Illustrating the complexity, 11β-HSD1 knockout mice are more prone to acute inflammation in experimental peritonitis, pleurisy and arthritis but resist 'atypical' inflammation in atherosclerosis and adipose tissue (reviewed [160]) and show less brain inflammation to peripheral immune activation [132]. The emergence/alterations in inflammatory disorders merit monitoring in clinical trials but have not been reported to date.

An evolutionary coda

Why have 11β-HSDs evolved? In phylogeny, 11β-HSD2 is found in cartilaginous fish (paralleling the emergence of MR) and 11β-HSD1 in amphibia [161], though their functions in lower taxa are unexplored. In higher vertebrates, 11β-HSD2 plausibly increases glucocorticoid signalling complexity; yielding two types of MR that bind either physiological glucocorticoids (hippocampus) or mineralocorticoids (kidney) and excluding glucocorticoids from foetal GR in mammals.

For 11β-HSD1, Hench's original use of high-dose cortisone (100 mg, ~10× physiological), and then the advent of potent selective GR agonists, spawned the notion that glucocorticoids have broad immunosuppressive actions. But at physiological doses, cortisol has much more nuanced effects on immune cells, stimulating some functions, while inhibiting others via both GR and MR. At least in rodents, 11β-HSD1 plays key roles in this complexity [160]. Similarly subtle, dose-related complexity pertains to glucocorticoid effects on the CNS, including the inverted U-shaped relationship between glucocorticoid dose and cognition engendered by MR and then GR activation [162]. Given the modest 50% boost to glucocorticoid levels inside cells in brain regions with high 11β-HSD1 expression, it seems plausible that this right-shifts the intracellular dose along the inverted-U towards GR-mediated effects in cells with the enzyme, increasing glucocorticoid exposure to shape the brain's response to circadian and stressful stimuli. Thus, glucocorticoid levels in particular CNS cells are potently determined by whole body factors such as circulating glucocorticoids and corticosteroid-binding proteins, but also local mechanisms including 11β-HSD1 amplification acting on the local density of MR, GR and nuclear co-regulators to configure cellular responses.

Therapeutic perspectives

Although 11β-HSD1 inhibitors are perceived as disappointing in human metabolic disease, this may reflect a contemporary fixation on attaining target parameters in individual components of a complex set of inter-connected disorders. The real test is whether morbidity and mortality (cardiovascular disease) are improved in populations with multiple features of the syndrome. This may never be explored.

The next 5 years will determine whether 11β-HSD1 inhibition has utility in age-related cognitive decline. The preclinical data are robust. Preliminary clinical data, though still mainly unpublished, are not discouraging for either efficacy or the magnitude of cognitive improvements. The target is more likely to be milder cognitive impairment than florid dementia, where reversibility is challenging. Given that glucocorticoids have myriad impacts on the brain, there may be other indications to explore, notably PTSD prevention and depression-associated cognitive decline.

Author contributions

Conceptualization; writing – original draft; writing – review and editing: Jonathan Seckl.

Conflict of interest statement

Jonathan Seckl is co-inventor on a composition of matter patent for UE2343, work funded by the Wellcome Trust. This has been licenced by the University of Edinburgh to Actinogen. Previously, he consulted for other companies developing 11β-HSD1 inhibitors, but not in the last 10 years.

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