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Citation: Watermeyer, Tamlyn, Gregory, Sarah, Robb, Catherine and Udeh-Momoh, Chi (2021) Therapeutic implications of hypothalamic-pituitaryadrenal-axis modulation in Alzheimer's disease: A narrative review of pharmacological and lifestyle interventions. *Frontiers in Neuroendocrinology*, 60. p. 100877. ISSN 0091-3022

Published by: Elsevier

URL: <https://doi.org/10.1016/j.yfrne.2020.100877>
<<https://doi.org/10.1016/j.yfrne.2020.100877>>

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**Therapeutic implications of hypothalamic-pituitary-adrenal-axis modulation in
Alzheimer's disease: a narrative review of pharmacological and lifestyle interventions**

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ABSTRACT

With disease-modifying treatments for Alzheimer's disease (AD) still elusive, the search for alternative intervention strategies has intensified. Growing evidence suggests that dysfunction in hypothalamic-pituitary-adrenal-axis (HPAA) activity may contribute to the development of AD pathology. The HPAA, may therefore offer a novel target for therapeutic action. This review summarises and critically evaluates animal and human studies investigating the effects of pharmacological and non-pharmacological intervention on HPAA modulation alongside cognitive performance. The interventions discussed include glucocorticoid receptor antagonists and 11β -hydroxysteroid dehydrogenase inhibitors as well as lifestyle treatments such as physical activity, diet, sleep and contemplative practices. Pharmacological HPAA modulators improve pathology and cognitive deficit in animal AD models, but human pharmacological trials are yet to provide definitive support for such benefits. Lifestyle interventions may offer promising strategies for HPAA modification and cognitive health, but several methodological caveats across these studies were identified. Directions for future research in AD studies are proposed.

Keywords:

cortisol; hypothalamic-pituitary-adrenal-axis; Alzheimer's disease; cognition; intervention; glucocorticoid receptor antagonists; carbenoxolone; lifestyle

1. Introduction

Late onset dementias, including the most prevalent form, Alzheimer's disease (AD), have received increasing global attention, with the World Health Organisation positioning dementia as a public health priority (World Health Organisation & Alzheimer's Disease International, 2012). To date, there exists no effective disease modifiers, and only moderately successful symptomatic treatments to ameliorate the cognitive and behavioural symptoms associated with AD. Biomedical research efforts have deepened our understanding of the pathophysiology and distinct characteristics of the condition, such as amyloid β ($A\beta$) senile plaques and neurofibrillary tangles (NFT) consisting of hyper phosphorylated tau (p-tau) proteins. New research criteria for AD (Dubois et al., 2016; Jack et al., 2016; Sperling et al., 2011) specify the early involvement of these biomarkers in the evolution of the disease towards a dementia syndrome. Individuals who show evidence of AD pathology but who do not demonstrate corresponding cognitive deficits meet criteria for preclinical AD, a clinically silent stage preceding frank AD dementia (Sperling et al., 2009). Preventative efforts are being redirected around these earlier preclinical AD stages, which may constitute the juncture upon which such efforts take their principal effects and demonstrate highest therapeutic efficacy.

There remain significant gaps in understanding the interaction of AD biomarkers and other possible mechanisms of disease, particularly in the preclinical stages. A growing body of research has suggested that, in addition to the classic hallmarks of the amyloid cascade hypothesis and related tau abnormalities associated with neuronal loss in AD, abnormal hypothalamic-pituitary-adrenal-axis (HPAA) activity may contribute to the development of AD pathology (Green et al., 2006; Lante et al., 2015; Toledo et al., 2012; Wang et al., 2018), resulting in accelerated clinical progression (Udeh-Momoh et al., 2019). The HPAA may therefore provide a potential target for therapeutic action in early and possibly even advanced AD. Here, we discuss studies investigating HPAA-targeted interventions on HPAA markers,

specifically, the cortisol response, alongside effects on cognitive performance. We consider both pharmacological and non-pharmacological interventions across murine and human studies. Within our investigation of human studies, we delineate studies of individuals with and without cognitive impairment and/or evidence for AD pathology. We further consider the possible mechanisms by which these interventions may support efficient HPA function in mid-to-later life, thereby potentially delaying or mitigating the clinical effects of AD-associated pathologies. Finally, potential directions for future research are highlighted.

2. HPA regulation in health and disease

2.1. HPA regulation

The HPA, which is regulated by stress and circadian cues, is one of the more widely studied neuroendocrine systems. Key to the maintenance of homeostatic balance in the body's internal environment (illustrated in Figure 1), it plays important roles in the modulation of a diverse range of physiological functions like the stress response, cognition, metabolism, and immune regulation amongst others (E R de Kloet et al., 2005; Lightman et al., 2008).

Upon activation, the hormones corticotrophin releasing factor (CRF) and arginine vasopressin (AVP) are produced by neurons in the paraventricular nucleus of the hypothalamus. These factors, released at the median eminence, travel through the hypophyseal portal circulation and act synergistically to stimulate the enzymatic conversion of pre-opiomelanocortin (POMC), the precursor molecule, into the peptide hormone adrenocorticotrophin (ACTH) by acting on receptors located on the corticotroph cells of the anterior pituitary. ACTH is then secreted from the pituitary into the systemic circulation. Upon binding to specific receptors at the cortex of the adrenal glands, it activates the steroidogenic enzymes necessary to induce the pulsatile production and release of glucocorticoid (GC) hormones, released primarily as cortisol in man,

and corticosterone in rodents (see Lightman et al., 2002; Young et al., 2004 for review). GCs signal through their endogenous intracellular receptors, the mineralocorticoid receptor (MR) and the glucocorticoid receptor (GR), to regulate the varied pleiotropic actions attributed to the hormone (Reul and de Kloet, 1985). In healthy individuals, hormone-dependent activation of these receptors inhibits the release of CRF and ACTH, thereby reducing further GC secretion from the adrenal glands, triggering a negative feedback loop that would mitigate against HPA hyperactivation (Reul and de Kloet, 1985) (shown in Figure 1). Residual HPA activation and GC secretion follows a diurnal pattern that is precipitated by a spike in GC levels during the first hour post awakening. This is referred to as the cortisol awakening response (CAR), and is followed by consistently low hormone levels secreted throughout the remainder of the day (Adam and Kumari, 2009) with hourly pulses evident (Kalafatakis et al., 2018) that are both functionally and clinically significant in terms of emotive and cognitive responses (reviewed in Oster et al., 2016). Healthier profiles of endogenous GC are associated with better cognitive function (Stawski et al., 2019). Additionally, optimal GC oscillations is thought to contribute to neuroplasticity during ageing, as disruption to the normal pulsatile pattern adversely impacted neurogenesis indices including neuronal cell morphology, density and functional connectivity (Schouten et al., 2020), with implications on functional outcomes such as sleep (Vargas et al., 2018).

2.1. HPA in disease

In the event of a disturbance to the internal environment, for example in the presence of a pathogenic stressor, including disease; activation of the HPA leads to aberrant hormone-receptor mediated activity (Spiga et al., 2011; Windle et al., 1998). Such abnormalities in GC

secretion is maladaptive and there are many ramifications of the prolonged presentation of GCs to target organs (Biddie et al., 2012; Di Dalmazi et al., 2012; Green et al., 2006).

During instances of HPAA hyperactivity whereby cortisol levels remain elevated for a prolonged period of time, as would occur in chronically stressed individuals, the HPAA can become dysregulated, leading to increased basal cortisol levels and flattened daily cortisol pattern (Duan et al., 2013; Spencer and Deak, 2017). Existing evidence implicates this aberrant secretion of GCs as a possible causative factor in the pathogenesis of conditions such as AD (E R de Kloet et al., 2005; Hartmann et al., 1997; Weiner et al., 1997). Chronic activation of its endogenous receptors by sustained exposure to GCs is largely associated with cognitive dysfunction (Brinks et al., 2007; Elgh et al., 2006). In addition, further evidence for abnormality in HPAA axis function is seen in knock-in mouse models of AD also showing increased levels of corticotrophin releasing factor (CRF) alongside elevated basal corticosteroid levels and CRF receptor 1 expression (Dong and Csernansky, 2009; Guo et al., 2012).

In MCI-AD, overproduction of GCs observed in patients is implicated in the development of cognitive deficits (Elgh et al., 2006) and may accelerate clinical progression to frank dementia, above and beyond amyloid and tau burden (Popp et al., 2015a). In these individuals, HPAA dysfunction appears to lead to anomalous GC signalling and alter synaptic function by inhibiting the induction of long-term potentiation (LTP) that is required for the enhancement of synaptic transmission (Kim and Diamond, 2002). This is important in AD pathology as such abnormal GC levels may disrupt crucial processes such as the proteolytic cleavage of amyloid precursor protein (APP) by beta-secretase (BACE), leading to the generation of the toxic amyloid beta fragments that are a distinctive feature of the disease (Catania et al., 2009; Solas et al., 2010), and induce hippocampal atrophy (Elgh et al., 2006). Of further relevance are emerging evidence of cortisol hypersecretion and cerebral hypometabolism across AD

diagnostic groups (Wirth et al., 2019 also reviewed by Notarianni, 2017). Such bio-energetic links are important given that glucose hypometabolism is a well-established feature of Alzheimer's disease, occurring decades prior to manifestation of clinical symptoms (reviewed in Neth and Craft, 2017)), and important for progression to clinical disease stage (Hammond et al., 2020). In asymptomatic adults at high risk of AD, abnormal levels of central and peripheral glucocorticoid have also been shown to predict cognitive impairment. This is evident in regions with high levels of GC receptors, and AD-sensitive areas, such as hippocampus and frontal cortices. Such abnormal glucocorticoid levels have been associated with faster progression to clinical AD stages (Echouffo-Tcheugui et al., 2018; Pietrzak et al., 2017; Tsui et al., 2020; Udeh-Momoh et al., 2019). These findings suggest a strong link between hypersecretion of GCs evident in this set of individuals, and their compromised cognitive function, and clinical progression. It is important to note that the direction of this association is still undefined (O'Brien et al., 1996). Research using longitudinal studies from pre-disease timepoints to address whether HPA axis impairments are a cause or consequence of AD-related pathology would inform our understanding of the role of GCs in AD aetiology. Studies on the genetic associations between HPAA function and AD could provide such insight.

For instance, the involvement of the GC system in AD development implicates polymorphisms in genes that regulate this system. One study of single-nucleotide polymorphisms (SNPs) in GC related genes found that a rare haplotype that alters 11 β -hydroxysteroid dehydrogenase type 1 (11 β -HSD1) transcription, and therefore hydrocortisone activation, is associated with a 6-fold increased risk for AD (de Quervain et al., 2004). Whereas, the GCR gene variant ER22/23EK has been associated with a 40% reduction in dementia risk after six-years, as well as reduced progression of white matter lesions in healthy non-demented individuals. Neuroprotective effects might therefore be realised through genetically-determined GC resistance (van Rossum et al., 2008). Such findings underscore the influential effects of

variation in GC-relevant genes upon susceptibility to AD onset and further emphasise GC function as a potential target for disease prevention and management.

Apart from genetically determined factors, environmental exposures impacting HPA activity during early or vulnerable postnatal life stages may possess similar influential effects on AD development. Early life stress, in the form of maltreatment, neglect or trauma, for example, has been associated with the onset and progression of AD-related neuropathology and cognitive decline (see Lesuis et al., 2018a for review). In rodent studies, prenatal (i.e. gestational) stress endured by the mother or post-natal stress experienced as maternal deprivation is associated with impaired HPAA-related glucocorticoid negative-feedback control, altered glutamate neurotransmission and reduced hippocampal neurogenesis (Maccari et al., 2014), as well as elevated corticosterone levels, hippocampal amyloidosis and cognitive deficits in later life (Lesuis et al., 2018b); these findings implicating early life stress in AD pathogenesis, possibly through HPA-related mechanisms. Crucially, blocking GRs with mifepristone (see Section 3.1.1.) in middle-aged rodents experiencing early life stress reduced levels of corticosterone, hippocampal burden and BACE-1 and mitigated the observed cognitive deficits (Lesuis et al., 2018b), underscoring the therapeutic potential of GR antagonists for AD prevention.

3. Pharmacological interventions on the HPAA and AD

Pharmacological interventions targeting the HPAA are a growing field of research in many diagnostic areas. The main interventions studied to date are glucocorticoid receptor (GR) antagonists and 11 β -HSD1 inhibitors. GR antagonists bind to glucocorticoid receptors and block activity thereby preventing GC hormone-receptor binding. In this way, these compounds may reduce the deleterious effect of excessive GC hormone (McMaster and Ray, 2008). Treatment with GR antagonists normalises many stress reactions in murine models (Ding et

al., 2019) demonstrating therapeutic potential of these compounds. Of particular interest is the restoration of synaptic plasticity and normalises calcium channels in CA1 neurons (Karst and Joëls, 2007; Krugers et al., 2006) which may be of importance with consideration to the role of the hippocampus in Alzheimer's disease.

11 β -HSD1 inhibitors partially block the conversion of cortisone to cortisol in humans (and 11-dehydrocortisone to corticosterone in rodents), thereby lowering cortisol (or corticosterone) (Tomlinson and Stewart, 2005). In this section, we review studies that have used various pharmacological agents to target HPA in animals and humans. Please see Table 1 for summary of human pharmacological studies and Table 3 for a summary of murine pharmacological studies.

3.1 GR antagonists

3.1.1. Animal studies

Mifepristone (also known as RU486 or RU38486, a GR antagonist) is the most widely studied compound in both murine and other animal studies. Mifepristone has an increased affinity for GRs (Madalena and Lerch, 2017; Wang et al., 2013). Treatment with mifepristone delivered via subcutaneous pellet or intraperitoneal injection in animal models has been associated with changes to AD pathology including reductions in both soluble and insoluble A β ₄₀ (Baglietto-Vargas et al., 2013; Horchar and Wohleb, 2019; Lante et al., 2015; Lesuis et al., 2018b; Pineau et al., 2016; Stein et al., 2017). As well as acting as a GR antagonist, mifepristone is primarily used as a progesterone receptor antagonist. This lack of selectivity gives rise to side effects, such as impaired cue-conditioned fear and memory recall, which may be one of the underlying causes of the inconsistency between study results. The timing of medication delivery may also be important to consider, as mifepristone does not appear to impact basal morning plasma corticosterone levels, rather it is effective as levels of corticosterone rise either due to circadian

rhythm or intracranial injection (E Ronald de Kloet et al., 2005). None of these studies combined the outcomes of pathological change and cognitive functioning, so it is impossible to know whether mifepristone-induced changes in AD pathology are associated with changes seen in cognitive functioning.

3.1.2. Human studies

A pilot study of mifepristone (200mg daily) as a treatment for patients with AD found non-statistically significant positive changes in the ADAS-Cog score after 6 weeks compared to placebo, suggesting benefit in conducting a larger, adequately powered trial (Pomara et al., 2002). No larger trials have published results, although a trial sponsored by Corcept therapeutics enrolling 160 participants was completed in 2005 investigating mifepristone in Alzheimer's disease (clinicaltrials.gov: NCT00105105, 2005). Conversely, mifepristone treatment has been seen to increase morning cortisol levels above the rise typically observed in normal HPA diurnal rhythms in younger study participants, which may limit its effectiveness as a treatment in this population (Pomara et al., 2006). This may be due to impairment in negative feedback by blocking systemic GR activity, establishing effect in older populations may more readily highlight any potential effect on late-life cognition since age itself affects overall cortisol bioavailability (Roelfsema et al., 2017). Whilst results from trials of mifepristone in murine models suggest potential for therapeutic success in human trials, this has not yet been realised. The murine models typically are exposed to high levels of stress and glucocorticoids which may be important in the therapeutic potential of mifepristone.

Other disease areas with known associated cognitive impairments have also reported on trials of mifepristone. Improvements in executive function, verbal memory and spatial working memory after treatment with mifepristone compared to placebo have been seen in Cushing's

syndrome (Fleseriu et al., 2012), chronic multi-symptom illness (Golier et al., 2016), anxiety (Lenze et al., 2014) and major depression (Watson et al., 2012). These promising trials suggest this compound warrants further exploration in patients with mild cognitive impairment (MCI) or AD.

3.2. GR modulators

3.2.1. Animal studies

Rats treated with glucocorticoid receptor (GR) modulators (CORT108297 and CORT113176) delivered by intraperitoneal injection had a partial reversal of memory deficits induced by injection of A β ₂₅₋₃₅ oligomers, whilst mice treated with the same GR modulators demonstrated a total reversal of memory deficits as measured using the T maze test (Pineau et al., 2016). This study compared these treatments with mifepristone, as described above, and were considered more effective than the non-selective treatment approach. There are no trials investigating the effects of these modulators on AD pathology in murine models.

3.3. 11 β -HSD inhibitors

3.3.1. Non-specific 11 β -HSD inhibitors: Animal studies

Carbenoxolone is a non-specific 11 β -HSD inhibitor, engaging to partially inhibit both 11 β -HSD1 and 11 β -HSD2. Via this partial inhibition of 11 β -HSD1, carbenoxolone reduces the amount of cortisol available as less is converted from cortisone. As such, some research groups have used carbenoxolone to study the impact of 11 β -HSD1 inhibition in the brain, with the accepted limitation that there will be some concurrent 11 β -HSD2 inhibition. Rats exposed to A β ₄₂ oligomers and then treated with carbenoxolone had reductions in hippocampal, cortical

and striatal reactive oxygen species levels (known to increase following injection of A β ₄₂ oligomers) and improvements in memory as measured using the active avoidance test (Sharma et al., 2019). This improvement may have arisen by carbenoxolone attenuating Connexin43 (a transmembrane protein particularly associated with hemichannels) and astrocytic activation following the oligomer injection.

3.3.2. Non-Specific 11 β -HSD inhibitors: Human studies

The effect of a non-specific inhibitor, carbenoxolone, on cognition among healthy and diabetic men has also been studied. Healthy and diabetic men were separately dosed with 300mg carbenoxolone or placebo in a crossover randomised double blind trial. Healthy male volunteers had a significant improvement from baseline in verbal fluency scores after four weeks of carbenoxolone treatment, whilst diabetic participants had a significant improvement from baseline in verbal memory scores after six weeks of treatment (Sandeep et al., 2004). This is a promising result given the dual action of carbenoxolone in targeting both 11 β -HSD1 and 11 β -HSD2 activity, suggesting the inhibition of 11 β -HSD1 in reducing cortisol levels was sufficient in producing a positive cognitive outcome, despite the simultaneous inhibition of 11 β -HSD2 working to increase cortisol levels.

3.3.3 Specific 11 β -HSD inhibitors: Animal studies

Given the limitations of carbenoxolone, as a non-specific 11 β -HSD inhibitor, development of specific 11 β -HSD1 inhibitors has begun. These inhibitors have the benefit of only targeting 11 β -HSD1 to partially inhibit the conversion of cortisone to cortisol, thereby reducing the amount of cortisol available (Wyrwoll et al., 2011). Trials of 11 β -HSD1 inhibitors in mice have showed improvements in memory function and possible changes to AD pathology.

Improvements on memory tasks were seen after treatment with compound 23 delivered in drinking water (Leiva et al., 2017), UE2316 delivered intracerebroventricularly, subcutaneously and orally (Sooy et al., 2015) and intraperitoneal UE1961 (Sooy et al., 2010). Treatment with UE2316 resulted in fewer plaques in the cortex at 4 weeks, however this effect was not seen after 44 weeks of treatment (Sooy et al., 2015).

3.3.4. Specific 11 β -HSD inhibitors: Human studies

Two studies have investigated 11 β -HSD1 inhibitors as a treatment for AD in humans. In the first study ABT-384 was investigated as a treatment option for patients with mild-to-moderate AD compared to either placebo or 10 mg of donepezil, with no effects on the primary (ADAS-Cog) or secondary (MMSE, activities of daily living) outcome measures (Marek et al., 2014). The study concluded that such compounds applied earlier in the disease process (i.e. presymptomatic and mild stages of impairment) may yield more efficacious outcomes. A second 11 β -HSD1 inhibitor phase II study, sponsored by Actinogen Medical Ltd, is ongoing in the UK, Australia and the US. The candidate compound, Xanamem, is described in a detailed paper with pharmacokinetic and phase I testing, including confirmation that the compound can cross the blood-brain barrier (Webster et al., 2017). To date, there are no peer reviewed journal articles available detailing phase II study results; however, a recently released public briefing confirms that, while cortisol inhibition was indicated by elevated ACTH levels, the primary outcome of the study (ADAS-Cog) did not satisfy evidence for treatment effect following a 10mg dose administration in patients with mild AD. Further developments continue with this compound for this population (Actinogen Medical Ltd., 2019). A Phase I trial of a 20 mg dose in healthy older adults is also underway; early results have reported statistically significant

improvements on exploratory cognitive outcomes alongside reductions in serum cortisol levels (Actinogen Medical Ltd., 2020).

3.3.5 Future avenues

Future therapeutic targets in Alzheimer's disease may also include CRH and AVP receptors. AVP is known to play a crucial role in stress and mood disorders such as major depressive disorder, with V1b antagonists trialled in anxiety and depression (Canet et al., 2019). Similarly, CRH receptors are known to reduce stress induced changes at a behavioural level and preclinical trials of small molecules have been trialled (Canet et al, 2019).

4. Non-pharmacological interventions on the HPA and AD

Lifestyle modification, in the form of diet, sleep, physical activity and contemplative practices, have recently garnered research attention as candidate interventional or rehabilitative tools for cognitive impairment. Here we review both animal and human studies that have explored the use of these strategies to modulate HPA activity and its potential impact on associated symptoms. Please see Table 2 for a summary of human lifestyle intervention studies.

4.1. Physical Activity

4.1.1. Human studies

Physical activity (PA) has been posited as a potential modifiable lifestyle factor for risk reduction of cognitive decline and AD dementia (Ashby-Mitchell et al., 2017; Barnes and Yaffe, 2011; Norton et al., 2014). However, findings from studies of PA interventional

effectiveness on cognitive outcome in healthy older adults are mixed, with systematic and meta-analytic reviews finding no or modest benefits (Kelly et al., 2014; Smith et al., 2010; Young et al., 2015) and there is limited evidence of PA intervention effectiveness in MCI (Gates et al., 2013; Öhman et al., 2014; Smith et al., 2010). Such disparity in findings might reflect heterogenous methodological approaches and quality between studies. Nonetheless, despite limited support for PA as an interventional strategy for cognitive decline, the mechanisms by which PA may influence brain pathology and/or cognition remain a focussed enquiry within lifestyle-based AD prevention research. These benefits might be mediated by the effects of exercise on hippocampal neurogenesis (Fabel et al., 2009; Liu and Nusslock, 2018; van Praag et al., 2005), which itself is reduced by stress and AD (Moreno-Jiménez et al., 2019; Oomen et al., 2007; Snyder et al., 2011). Similarly, studies have begun to explore if PA may moderate the negative effects of stress and/or aging on cortisol regulation, and how this moderation might manifest cognitively (Tortosa-Martinez and Clow, 2012). The stress hypothesis posits that the cognitive benefits of PA could be mediated by alterations in cortisol secretion (Tortosa-Martinez and Clow, 2012), owing to its role in cellular metabolism and energy mobilisation in fight- or flight-response situations (Pedersen et al., 2001). The ability to cope and adaptively recover from stress reduces with age, which has partly been explained by abnormalities in HPA function, and consequential aberrant cortisol release. Reduced stress resilience results in alterations of the immune system and higher risk of disease in older age (Kiecolt-Glaser et al., 2003), also known as immunosenescence (Jeckel et al., 2010). Notwithstanding, exercise is considered a stressor, activating stress hormones such as cortisol, ACTH, and the catecholamines (norepinephrine, epinephrine and dopamine) (Coyle, 2000). The CAR theory, proposes that a larger CAR percent change (i.e. a sharp increase of morning cortisol followed by gradual decline) is associated with better cognitive performance among healthy older adults (Evans et al., 2012, 2011). Likewise, a reduced magnitude of the CAR (or

smaller percent change) is associated with conversion from healthy aging to MCI, although not to dementia (Peavy et al., 2012). Furthermore, it has been reported that older adults with high life-stress levels who engaged in regular exercise had a lower ratio of cortisol to dehydroepiandrosterone (DHEA) relative to low active, high stress individuals (Heaney et al., 2014). DHEA plays a role in HPA regulation and is linked to improved physiological health. These findings suggest that high PA levels may support cortisol regulation among older adults who are experiencing stress, possibly via targeting the CAR.

Experimental studies investigating such inferences have, however, reported inconsistent results, most likely owing to varying methodological strategies. A systematic review of randomised controlled trials (RCT) (n=8), specifically focussing on an older population, investigated the role of chronic activity on morning cortisol (Corazza et al., 2014). Conversely, they reported minimal effect of fitness training on systemic levels of circulatory cortisol. The authors pointed out that study designs were highly heterogeneous and contained several recurring limitations which may have resulted in questionable outcomes. Notably, a single measure of morning cortisol was analysed in all studies, which may not adequately represent HPA functioning and true circadian cortisol fluctuation.

More recent studies have sought to investigate the role of PA and physical performance on cortisol measured across the day. A typical cortisol circadian rhythm among healthy adults starts with a sharp increase after awakening, i.e. CAR, with a steady decline across the day, also known as the diurnal cycle (Edwards et al., 2001). Current evidence eludes that a more dynamic cortisol secretion pattern, as opposed to a flatter profile, represents an optimal adaptive response and reduced risk of cognitive decline. Cross-sectional studies have reported that physical performance is consistently associated with a more dynamic cortisol secretion pattern (Gardner et al., 2013, 2011; Lucertini et al., 2015; Pulooulos et al., 2016; Sousa et al., 2017); however, once again there is less evidence to indicate the same associations with PA

levels (Kumari et al., 2010; Strahler et al., 2010). This may be a consequence of poor PA measurement, often via self-reporting and of short periods of time, again emphasising the need to review outcomes of experimental studies. Likewise, physical performance may be considered an indicator of fitness (American College of Sports, 2006) and hence, a more accurate indicator of overall PA engagement.

Despite an abundance of studies investigating the role of PA and physical performance on cortisol levels (see also Tortosa-Martinez et al., 2018), very few experimental studies have investigated how these observations play out as a function of cognitive health, and none, to our knowledge, have investigated associations with reduced dementia and/or AD risk among older adults. One study of cognitively healthy sedentary older adults (n=27) explored the role of an aerobic exercise intervention on cognitive health and cortisol levels across a 6-month period (Drogos et al., 2019). They reported a robust CAR, magnitude of which increased within the intervention group, again suggesting PA as a mechanism for improving HPA function. However, there were negligible differences in cognitive function before and after PA intervention as a function of CAR, although a decrease in perceived stress was noted. This study failed to include a control group and with a small sample size; results may only be speculative. Two separate RCT's investigated the effect of a six-month high intensity (Baker et al., 2010) and three-month moderate intensity aerobic exercise intervention (Tortosa-Martinez et al., 2015) on either morning cortisol or diurnal cortisol, respectively, among older adults with amnesic MCI. Those in the high intensity exercise intervention (n=33) presented with improved executive function, being augmented among women compared to men. Interestingly, morning cortisol levels were found to increase among men but decrease among women post-intervention, relative to pre-intervention (Baker et al., 2010). Considering the circadian pattern of cortisol, morning cortisol may not be adequately accurate, alongside the statistical limitation of not controlling for awakening time. Notwithstanding, this trial suggests

a possible sex bias in response to aerobic exercise, possibly based on HPA response. Tortosa-Martinez *et al* (2015) reported a significantly greater fall in cortisol concentration from peak to midday (higher CAR) alongside a more dynamic circadian cortisol pattern in the intervention group (n=19), relative to the control group (n=20). These findings were corroborated by better executive functioning. Finally, a combined resistance / aerobic 12-month intervention study of cognitively healthy older adults with coronary artery disease found, firstly, that cognition improved pre- versus post-intervention (Saleem *et al.*, 2013). Upon splitting individuals into high versus low baseline hair cortisol, they reported that memory improvements were significantly lower among those within the high cortisol group versus the low. These findings suggest that the benefits of PA on cognitive health may be more noticeable among those with lower cortisol, at least among an already high risk for cognitive decline group (i.e. those with cardiovascular disease). The only other identified study investigating the interplay between PA/cortisol/cognition was a cross-sectional study of healthy (n=30) and amnesic MCI (n=30) older adults (Dijkmans *et al.*, 2017). They reported that walking speed and performance from a six-minute walking test were both associated with greater variance in cortisol levels as well as better cognition, indicating a possible link between these variables, although, this was not statistically explored as no mediation nor moderation analyses were conducted.

4.1.2. Animal studies

In animal research there is a small but emerging focus of PA research and its effects on HPA functioning in rodent models. In aged mice, wheel running significantly increased cellular proliferation compared to sedentary controls. A slight attenuation of the effect was observed when comparing social runners to social sedentary controls. Socially-housed, aged sedentary mice had significantly higher corticosterone levels compared to all groups, however no

significant differences were observed between runners and controls in individually-housed animals when measured at the start of the active cycle; no differences were observed between any groups four hours into the active cycle (Kannangara et al., 2011). In similar work, mice exposed to a stricter treadmill exercise protocol for 12 weeks demonstrated improved cognitive function (as tested by a water maze task) and reduced expression of A β ₄₂, tau, and corticosterone levels (Um et al., 2011). Together, these studies suggest that exercise may impact corticosterone levels, amyloid expression and cell proliferation in both individually housed and socially-housed animals, providing a base of evidence that warrants further research in rodent and human research to understand how exercise may mediate the relationship between HPA dysfunction and AD.

4.2. Diet

4.2.1. Human studies

The role of diet and nutrition in reducing risk of dementia and in relation to cognitive function is a recent area of interest within the literature.

A poor dietary pattern characterised by high intake of animal protein, saturated fat and refined sugars has been associated with higher overall cortisol levels, increased secretion of catecholamine and serotonin, alongside oxidative stress (Maurer et al., 2003; Singh et al., 2012). Such diets (usually western) are typically acidogenic, high in animal protein and low in fruits and vegetables, causing a sub-clinical state of metabolic acidosis (Cordain et al., 2005). Among other negative health related effects, acidosis can also influence adrenal hormone production of cortisol whereby studies have reported a consequential increase of salivary and serum cortisol (Gibson et al., 1999) alongside an increased risk of insulin resistance and type 2 diabetes (McCarty, 2005). Epidemiological evidence has shown that adherence to diet

comprised of high vegetable intake, whole grains, fish and moderate intake of saturated fats, refined sugar and salt reduced urinary cortisol levels and elevated DHEAS among Puerto Rican women (n=1381), but not among men (Mattei et al., 2013). A further study reported that adherence to a Mediterranean diet positively moderated the HPA and cortisol regulation among a Mediterranean female only cohort (Garcia-Prieto et al., 2007). Nutrient intervention studies have also found modulation of cortisol levels. Supplementation of phospholipid phosphatidylserine, together with polyunsaturated fats among depressed older adults reduced basal cortisol concentration and regulated circadian cortisol as measured in the saliva (Komori, 2015). These results manifested clinically via reduced depressive symptomology. A further observational study was able to demonstrate a high intake of flax seed cultivars to reduce responses to stress and plasma cortisol concentrations among 35 post-menopausal women (Spence et al., 2003).

4.2.2. Animal studies

In animal studies, vitamin E prevents HPA damage induced by oxidative stress. . In young rats, hyperoxia lead to elevated levels of CRH in the hypothalamus and ACH and corticosterone in plasma. However, young rats fed vitamin E supplemented diets showed no abnormal hormone secretion, even after being subjected to hyperoxia. Furthermore, GRs in pyramidal cells of the hippocampus were markedly decreased by oxidative stress but vitamin E supplementation prevented GR reductions in this region. In addition, aged rats and vitamin-E deficient rats were studied alongside rats fed with a vitamin E supplemented diet. Aged and vitamin-E deficient rats showed changes in pathology associated with cognitive deficits, whilst the rats receiving vitamin E supplementation were protected from such changes (Kobayashi et al., 2009). In another study, Sprague Dawley rats were allocated either a ketogenic diet (KD),

a diet supplemented with ketones (KS) or a standard rodent diet. Although a ketogenic diet did not influence corticosterone levels, a KD diet was associated with sustained peripheral ketosis during a restraint stress test, despite increases in glucose. Both KD- and KS-fed rats demonstrated decreased escape latencies on a water maze paradigm after three days of treatment, with KD-fed rats additionally showing enhanced probe test performance and resilience to stress-induced cognitive deficits on the final testing day (Brownlow et al., 2017).

Together, both human and animal studies suggest that there are avenues worth exploring with regards to diet, HPA function and cognitive performance. In animal studies, whilst vitamin E supplementation was shown to effect changes in both corticosterone and hippocampus GR expression, a ketogenic diet did not impact on the HPA but did lead to cognitive improvements. It may be that some diets moderate disease via the HPA, and some work through alternate mechanistic pathways. Further research is required to understand these possible pathways, with murine models providing an opportunity to specifically manipulate and control diet intake in a more effective way than is possible in human trials. In human studies, direct links between diet and risk of cognitive decline and dementia, and links between diet and cortisol have been reported, but no study has statistically investigated the interplay between diet, cortisol and cognitive health and/or dementia risk in older age. This is an important avenue, warranting further investigation.

4.3. Sleep

Poor sleep hygiene and the risk for dementia or cognitive impairment has been indicated in several cross-sectional and longitudinal studies (Ju et al., 2013; Spira et al., 2014; Yaffe et al., 2015, 2011). Cortisol secretions, alongside melatonin secretions and core body temperature, are markers for the body's circadian rhythm function, which modulates the sleep-wake cycle

(Musiek et al., 2015). In older adults, greater amyloid deposition has been associated with decreases in circadian amplitudes and increases in sleep fragmentation, irrespective of age, while AD-related neurodegeneration, as measured via p-tau/A β ratio, corresponds to further fragmentation of rest-activity circadian rhythms (Musiek et al., 2018). In fact, one night of sleep deprivation (or total wakefulness) increased CSF A β ₄₂ relative to unrestricted sleep in healthy middle-aged men (Ooms et al., 2014), suggesting that chronic sleep deprivation may lead to gradual amyloid deposition associated with AD. Apart from amyloid clearance, sleep deprivation has been associated with elevated HPA axis response in healthy adults. Compared to rested participants, sleep deprived participants who completed a social stress test showed higher cortisol levels at baseline, prior to the stress test, as well as an amplified cortisol response following the test (Minkel et al., 2014). While additional and longitudinal research is warranted, these results indicate that healthy sleep may have an inhibitory influence on the HPA axis and glucocorticoid secretions, which if maintained over the lifespan, could prevent a range of health implications associated with elevated cortisol exposure in older age, including cognitive impairment.

Evidence from rodent studies mirror clinical findings regarding the effects of sleep on the HPA axis and AD pathology. Mice exposed to restraint stress followed by a period of sleep deprivation showed an increase in interstitial fluid amyloid- β (ISF A β). The post-restraint increase in ISF A β is thought to be mediated by CRF, however, administration of a CRF receptor antagonist prior to the sleep deprivation treatment did not affect levels of A β in mice allocated to the intervention (Kang et al., 2009). This study suggests that there are effects of both restraint stress, possibly operating via the HPA axis, and sleep deprivation on ISF A β levels, but did not support CRF antagonist as a strategy, at least in murine models of intervention. In human intervention studies, light therapy and melatonin supplementation have been trialed as circadian rhythm therapies in AD and elderly care-home residents, but these studies have

demonstrated variable results (Burns et al., 2009; Figueiro et al., 2017; Riemersma-Van Der Lek et al., n.d.; Wade et al., 2014). To our knowledge, no study is yet to explore whether modulation of HPA axis functioning contributes to sleep homeostasis and/or circadian clock functions in AD or healthy adult populations. Greater understanding of the mechanistic contributions of HPA axis integrity to such activities, or vice versa, across ageing and disease, may lead to novel or the adaption of existing lifestyle and pharmacological strategies.

4.4. Yoga & Meditation

Several cross-sectional studies investigating long-term yoga and meditator practitioners support these practices as possible methods to mitigate the effects of age-related cognitive changes. Long-term Meditators and yoga practitioners show better performance on measures of attentional and impulse control, memory, reasoning and problem-solving (Kozasa et al., 2012; Prakash et al., 2010; van Leeuwen et al., 2009). Interventional studies of naïve meditators or yogis who undergo training have shown a variable pattern of effects on cognitive outcomes (see Gard et al., 2014; Gothe and McAuley, 2015 for review). These inconsistencies might, in part, be explained by the variability in the meditation and yoga protocols applied (mindfulness-based or transcendental meditations; Bikram or Yin Yoga); the length or dose of the experimental intervention (15 min vs. 12 months); as well as the diversity of cognitive assessments used and populations studied (healthy individuals, depressed individuals, cognitively impaired). Scant interventional work with these therapies in aging or dementia populations have been conducted, but similar patterns of results have been demonstrated (Mallya and Fiocco, 2016; Smart et al., 2016) and larger, more robust studies are currently underway (Poisnel et al., 2018; Wong et al., 2016). Recently, participants with dementia using donepezil who were randomised to a mindfulness meditation condition showed stable cognitive

function over a two-year period. Those participants also receiving donepezil but randomised to active control and true control conditions deteriorated on cognitive examination over the same time period (Quintana-Hernández et al., 2016). Such findings highlight these practices as possible adjuncts to existing pharmacological care for people already experiencing the symptoms of AD dementia.

Meditation and yoga may also mediate the effects of various risk exposures associated with AD, such as cardiovascular factors (de Fátima Rosas Marchiori et al., 2015), depression and anxiety (Hofmann et al., 2010). How these practices accomplish their influence on risk factors remains speculative but support for the involvement of HPA regulation is growing. Jevning *et al* (1989) were the first group to document meditation-induced decreases in plasma cortisol in young adults (22-29 years old). They found that, compared to healthy controls, experienced practitioners with at least three years of transcendental meditation (TM) showed a sharper and faster decline in cortisol concentrations during TM as well as a slower rate of increase in cortisol following completion of the meditation. Conversely, relative to control participants, long-term yoga practitioners (at least 3 years of practice) showed elevated serum cortisol levels at a single collection timepoint taken in the morning (Vera et al., 2009), possibly reflecting greater magnitudes of the CAR in the yoga practitioners relative to controls.

Controlled trials of Yoga interventions for older individuals are sparse but show promising results. Middle-aged and older adult participants (50 – 72 years) randomized to an eight-week Yoga routine showed an attenuated cortisol response to a stressful event (a cognitive examination) relative to those randomized to an 8-week stretching routine at follow-up. No differences between self-reported stress and anxiety were found between groups following the intervention. However, within the Yoga group, the attenuated response, alongside state anxiety and perceived stress scores predicted improved performance on measures of executive function and working memory. Conversely, the active control group showed elevated cortisol responses

to the stressor and the elevated response predicted poor performance on the same cognitive measures (Gothe et al., 2016). More recently, another RCT evaluated the effects of an eight-session course of Mindfulness-Based Stress Reduction (MBSR) and light yoga against a health education course for older adults diagnosed with either an anxiety or depressive disorder *and* who reported subjective cognitive complaints. The results revealed greater reductions in cortisol concentrations in individuals allocated to the MBSR and yoga arm, but only for those individuals with high baseline cortisol levels. Additionally, those randomized to MBSR-yoga showed better clinical outcomes, in terms of self-reported anxiety, depression and worry for cognitive complaints at three- and six-month post-intervention follow-ups, compared to those randomized to the control treatment (Wetherell et al., 2017). Repeat cortisol assessments were not conducted at these later follow-ups, so sustained effects on cortisol response following continued practice could not be assessed. While these studies highlight the possible efficacy for meditation and yoga practice on HPA regulation, to our knowledge, no study to date has investigated such a relationship in the context of preclinical AD.

5. Discussion

There is growing evidence supporting the involvement of HPA disruption in the development of cognitive impairment and heightened risk for AD. HPA-based interventions may therefore show efficacy in preventing or mitigating cognitive decline. Here, we have considered both pharmacological and non-pharmacological studies investigating HPA-targeted interventions to maintain or improve cognitive performance in older age and in clinical trials of AD. Our review demonstrates that further research is required to identify exact mechanistic relationships between the HPA and cognition before proposing specific treatment(s). Nonetheless, some progress has been made in this direction and interventional strategies have been assessed.

Relative to human interventional studies, pharmacological intervention within murine models is where the majority of this progress has been made, specifically GR antagonists and 11 β -HSD1 inhibitors. Findings from these studies have been encouraging both in terms of reductions to pathological hallmarks associated with AD and for improvements to cognitive performance. Exercise and nutritional interventions in rodents have likewise provided promising findings from experimental environments in which lifestyle factors can be meticulously controlled. However, common to all animal studies of AD, there are inherent limitations in the translational value of such models, due to morphological dissimilarities (Kalback et al., 2002) that might interact differently with other pathological features, such as HPA axis disruption, and/or interventional agents or strategies. Human studies are needed to fully delineate the clinical effects of targeting HPA axis. At the same time, AD clinical studies trialling pharmacological treatments using robust RCT designs have not managed to provide definitive support for their use in mild-to-moderate dementia. It is possible that applying HPA axis modulators in earlier stages of disease may show improved efficacy for preventing or even delaying AD progression. At least one phase II study of a candidate compound (Webster et al 2017) has been trialled in prodromal AD (or MCI), although preliminary findings suggest no effects on the primary cognitive outcome. Other modulators, such as carbenoxolone and mifepristone, indicate efficacy in improving cognitive performance in individuals with metabolic and psychiatric conditions, propounding their application in AD trials, particularly in prodromal phases. Such findings might suggest that specific sub-populations may benefit from strategies modulating HPA axis activity, thus promoting a more precise and personalised approach for therapy.

Relevant to the personalised medicine approach, sex differences have been observed in HPA axis functioning and the stress response (Bangasser and Wiersielis, 2018; Curtis et al., 2006; Toufexis et al., 2014); in the emergence and progression of AD pathology (see Ferretti et al.,

2018 for review) as well as responses to the effects of physical exercise and dietary interventions (see Baker et al., 2010; Mattei et al., 2013 or Sections 4.1. and 4.2.). The human interventional studies reviewed here report gender ratios of their samples (see Tables 1 & 2), but fail, in most cases, to systematically explore sex differences in interventional outcomes as part of their planned research objectives. In animal research, the underrepresentation of females in study samples is ubiquitous (see Becker et al., 2005; Beery and Zucker, 2011; Hughes, 2007), due in part to the widespread belief that the 4-day estrous cycle of female rodents renders them fundamentally more variable, and therefore less reliable subjects, than their male counterparts (Prendergast et al., 2014). Similarly, ethnic differences in HPPA function and cognitive outcomes has been indicated (Demirovic et al., 2003; DeSantis et al., 2015; Gurland et al., 1999; Howell et al., 2017; Jackson et al., 2010; Palmer-Bacon et al., 2020; Wong, 2019) yet the interventional community has been slow to consider the implications of such findings; underscored by this review where studies were primarily conducted in westernised, educated, and wealthy populations (see Tables 1& 2). Future interventional work, both pharmacological and non-pharmacological, would benefit through direct assessment of sex-/ gender-, race-/ethnic-group differences in HPPA and/or cognitive outcomes in more socio-economically diverse human population samples. The call for animal research to address its “male bias” is equally propounded (see Beery, 2018). Along these lines, early life experiences, such as childhood stressors or social deprivation, are also implicated in AD development, potentially via HPA-related mechanisms (See Introduction Section 2) and should be considered alongside sex- and ethnic-group differences in HPA response to therapeutic strategies.

Given that AD pathogenesis may remain clinically silent years before the onset of dementia symptoms, candidate interventional strategies are now being redirected towards even earlier stages of disease i.e. for individuals who are at-risk for AD but asymptomatic for several decades. There is much debate surrounding the ethical, practical and financial consequences of

prolonged exposure of pharmacological agents to individuals who may be at risk, but not necessarily definitively on track, to develop AD (Molinuevo et al., 2016). Non-pharmacological interventions, if deemed efficacious, might offer alternative evidence-based solutions for individuals at these earlier stages of disease, influencing cognition and Alzheimer's disease risk through various mechanistic pathways, one of which might be the HPPA. The studies reviewed here spanning dietary, PA, meditation and sleep interventions provide some support for lifestyle-based HPAA modification, but cautiously, due to the lack of studies directly investigating AD and HPPA-based lifestyle interventions, this review is largely based on studies involving cognitively normal individuals; the results of which might not be fully extrapolated to pathological conditions. Furthermore, these studies suffer from methodological caveats common to non-pharmacological research generally – mostly they are cross-sectional non-randomised designs and lack sufficient statistical power to determine effectiveness. Additionally, measures of HPAA response vary among studies (i.e. saliva versus plasma) and the ascertainment protocols for these are similarly heterogeneous (e.g. single-sample versus multi-sample or diurnal assessments to index functioning). While there is no consensus on the best method for collection, it is acknowledged that measurement indicators are vulnerable to confounding from such methodological discrepancies and circadian (time of day, delay from waking) factors (Elder et al., 2014). Notably, within human intervention studies, it is very difficult to tease apart casual mechanisms of any apparent cognitive benefits following an intervention. Future interventional work would benefit from more rigorous standardised frameworks. Apart from a handful of PA studies, there exist no systematic investigations of lifestyle treatments on HPAA functioning *and* cognitive health. Furthermore, none have considered possible effects in the context of HPAA regulation, specifically for reduced AD risk. Similar to human pharmacological trials, future interventional projects in AD

might take direction from studies in other medical conditions where the relationship between lifestyle, HPAA functioning and cognitive decline have been explored.

Greater understanding of susceptibility and resilience factors to AD pathology or cognitive decline and any possible relationship with HPAA function is required before proposals for HPAA-targeted intervention can progress. For example, controversy surrounds whether depression and AD dementia share common pathological pathways, if depression engenders the brain vulnerable to the onset of AD, accelerates existing clinical dementia symptoms, or represents a prodromal stage of dementia (Dafsari and Jessen, 2020; Herbert and Lucassen, 2016; Hesper et al., 2013; Linnemann and Lang, 2020). Apart from common neuroinflammatory, cerebrovascular and neurotrophic pathways in depression and dementia, a common endocrinological – or HPAA – pathway for these disorders is proposed (Dafsari and Jessen, 2020; Herbert and Lucassen, 2016). HPAA outputs, such as cortisol, may act as precursory and acceleratory agents of symptoms in both disorders (Dafsari and Jessen, 2020; Popp et al., 2015b) and thus individual HPAA regulation may promote vulnerability for, or conversely support resilience to, later-life cognitive deterioration. Similarly, other factors, such as personality, sleep disorders and metabolic factors may mediate the effects of HPAA function on cognition and brain structures as well as present possible risk markers for AD (see Ouane and Popp, 2019 for review). The delineation of these factors, along with individual differences as discussed above (early life stress, ethnicity/race and sex/gender) in the context of HPAA function, cognition and/or AD bear important implications for therapeutic study designs, in terms of participant stratification, treatment allocation and inferences regarding treatment response (or lack thereof). This might be especially pertinent in preclinical and MCI stages of AD, offering optimal intervention windows whereby the influential effects of such factors possibly emerge.

6. Conclusion

In conclusion, the therapeutic potential of targeted HPAА functioning in AD, whether pharmacological or lifestyle-based, is yet to be fully realised due to a dearth of AD-specific clinical trials, despite growing interest in this area within broader clinical research and well documented associations between HPAА disruption and AD. This topic within AD research is still in its nascency, and as such, the small number of studies have yet to converge towards methodological robustness. Future interventional research, with individuals at risk for AD, investigating multi-compound and component approaches of HPAА modification, preferably in longitudinal RCT designs, may promote novel avenues for earlier AD and dementia prevention.

Declaration of Competing Interest

TJW, CR, SG and CU reports no competing interest.

Author contributions

All authors contributed to drafting the manuscript and critically evaluated the content.

Acknowledgements

TJW and SG would like to thank organisational members of the European Prevention of Alzheimer's Dementia (EPAD) initiative who have provided mentorship and training throughout the writing of this manuscript. SG is also grateful for funding received through EPAD for her doctoral training. This work was supported by British Society for Neuroendocrinology (BSN), Society for Endocrinology (SFE) and Alzheimer's research UK (ARUK) grants awarded to CU.

Funding statement

Funding sources had no involvement in the preparation of the manuscript.

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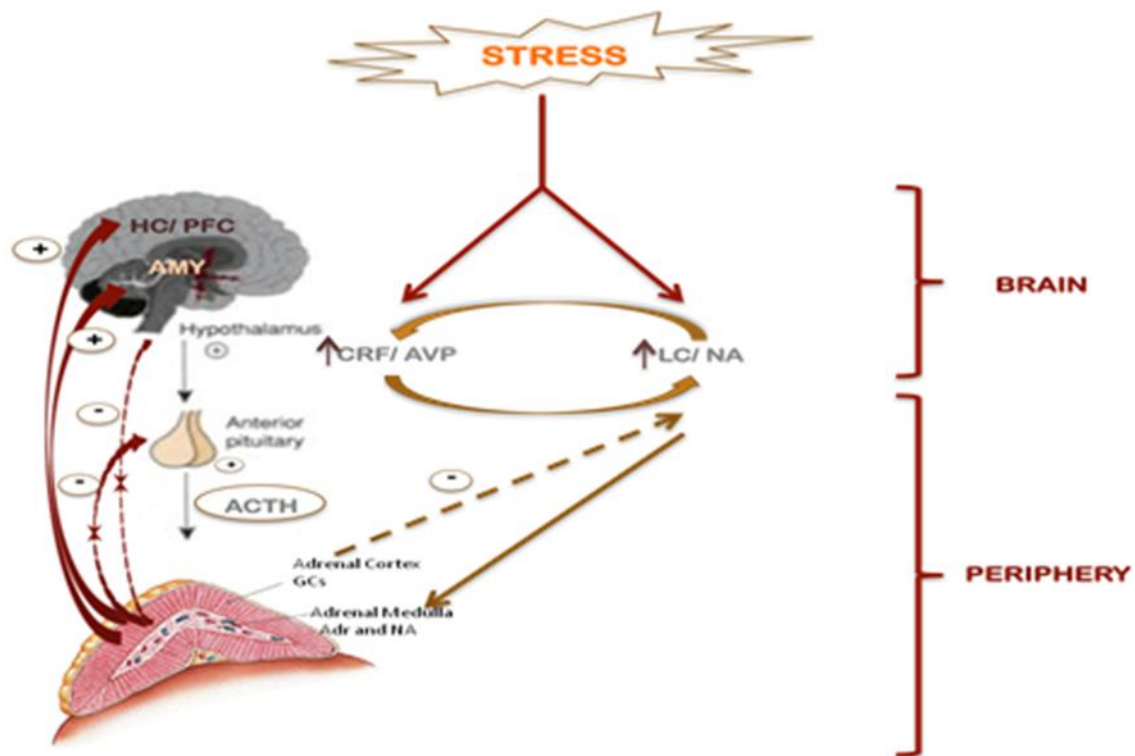
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Figure 1: Regulation of adrenal hormones during stress: interactions between HPA and SAM system



In the brain, sensory stimuli released during stress are perceived by chemoreceptors in the hypothalamus.

(A) For the HPA pathway, this leads to CRF/ AVP mediated activation of corticotrophs in the anterior pituitary. ACTH released from this organ activates the synthesis and release of GC hormones from the adrenal glands. The axis is also negatively or positively regulated by neuronal afferents from brain centres, primarily the limbic and forebrain systems (i.e. hippocampus, amygdala and prefrontal cortex). Secreted GCs feedback negatively on the first two components of the neuroendocrine axis, i.e. the hypothalamus and pituitary.

(B) For the SAM pathway, rapid release of adrenaline from the adrenal glands, along with the concomitant release of central noradrenaline, modulates neuronal responses including HPA activity itself.

Plain lines show positive innervation, whilst dotted lines show negative innervation.

HPA, hypothalamic-pituitary-adrenal; CRF, corticotrophin releasing factor; AVP, arginine vasopressin; ACTH, adrenocorticotrophic hormone; GC, glucocorticoid; SAM, sympatho-adreno-medullary.

Table 1. Characteristics and results of human studies investigating pharmacological interventions on the HPAA in AD

Study	Population	Intervention	Outcome measure (cortisol)	Cognitive Outcomes	Results
GR Antagonists					
Pomara <i>et al.</i> (2002, USA)	<u>Mean age (SD)</u> 72 (10.8)	EG: Mifepristone once daily (oral) for 6 weeks	None	Global cognition (ADAS-Cog (primary); MMSE) Neuropsychiatric symptoms (Hamilton Depression Rating Scale)	Cognition: Treatment with mifepristone resulted in a non-significant improvement in ADAS-Cog score from baseline compared to a decline with placebo treatment. (-2.67 (6.7) vs 1.67 (8.9), p=0.20 - 0.30) ^a . Neuropsychiatric symptoms: No significant difference between mifepristone and placebo.
n = 9	33.3% Female Probable AD (NINCDS- ADRDA criteria)	CG: Placebo once daily (oral) for 6 weeks			
Pomara <i>et al.</i> (2006, USA)	<u>Mean age (SD)</u> 72 (10.8)	EG: Mifepristone 200mg once daily (oral) for 6 weeks	Plasma Cortisol (Morning plasma cortisol measured at baseline, at 12h following the first drug dose, and weekly thereafter)	None	Cortisol Treatment with mifepristone increased cortisol levels $F=65.32$, $p<0.001$. The magnitude of this increase grew over the course of the study $F=63.17$; $p<0.001$
n = 9 EG: n = 19 CG: n = 10	33.3% Female Probable AD (NINCDS- ADRDA criteria)	CG: Placebo once daily (oral) for 6 weeks			
11β-HSD inhibitors					
Marek <i>et al.</i> (2014, UK, Ukraine, South Africa and Russia)	<u>Mean age (SD)</u> 72 (8.5)	EG: ABT-384 10mg (n=70) or ABT-384 50mg (n=65) once daily (oral) for 12 weeks (11 β HSD1 inhibitor)	None	Global cognition (ADAS-Cog (primary); MMSE; CIBIS) Neuropsychiatric symptoms (NPI)	Cognition No relationship between ABT-384 treatment and any primary or secondary outcomes. Donepezil treatment significantly improved ADAS-Cog (primary) compared to
n = 267		CG:			

EG: n = 135 CG: n = 132	Probable AD (NINCDS-ADRDA criteria)	Placebo (n=66) or donepezil (n=66; 5mg for 4 weeks followed by 10mg for 8 weeks), once daily (oral)			placebo (LS mean change from baseline -3.06, p=0.02).
Sandeep <i>et al.</i> (2004, UK) n = 22, randomised crossover design	<u>Mean age (SD)</u> 65.5 (5.5) Range: 55-75 0% Female Healthy Volunteers (n=10) <u>Mean age (SD)</u> 60 (4.9) Range: 52-70 25% Female Type II Diabetics (n=12)	EG: Carbenoxolone 100 mg three times daily (oral) for 4 weeks (healthy) or 6 weeks (diabetics), followed by CG treatment in crossover design CG: Placebo once daily (oral) for 4 weeks (healthy) or 6 weeks (diabetics), followed by EG treatment in crossover design	Plasma Cortisol (time of measure not reported)	Nonverbal reasoning (Raven's Standard Progressive Matrices) Verbal Fluency (Controlled Word Association Test) Memory (RAVLT, Logical Memory subset WMS-R, Visual Reproduction subset WMS-R) Attention and processing speed (Digit-Symbol Substitution Test, WAIS-R) Verbal IQ (NART)	Cortisol No changes in either population with carbenoxolone compared to placebo. Cognition Healthy participants saw an improvement in verbal fluency scores on carbenoxolone compared to placebo (p=0.006). Diabetic participants saw an improvement in verbal memory scores on carbenoxolone compared to placebo (p<0.01). No changes on any other scales.

n = number of participants; CG = control group; EG = experimental group; SD = standard deviation; RAVLT = Rey Auditory Verbal Learning Test; MMSE = Mini Mental State Examination; ADAS-Cog = The Alzheimer's disease Assessment Scale – Cognitive section; UWIST-MACL: University of Wales Institute of Science and Technology- Mood Adjective Checklist. ^aNote ADAS-Cog is negatively scored whereby higher scores indicate more impairment

Table 2. Characteristics and results of human experimental studies investigating lifestyle intervention on cortisol

Study	Population	Intervention	Outcome measure (cortisol)	Cognitive Outcomes	Results
Physical Activity ^a					
Drogos <i>et al.</i> (2019, Canada) n = 32	<u>Mean age (SD)</u> 60 (5.1) Range: 55 – 80 60% Female Cognitively healthy	EG: Moderate/vigorous aerobic exercise, 3x/week for 6 months CG: No control group	Saliva collection at: waking, 15, 30, and 45 min post-waking to assess the CAR. 3, 6, 9, and 12 h post-waking to assess daily area under the curve for cortisol.	Executive function (verbal fluency, card sorting, digit symbol, colour word) Delayed Memory (RAVLT, Figure recall) Immediate Memory (RAVLT) Attention (Auditory consonant trigrams) Global cognition	Cortisol A significant increase in CAR response (CAR/AUC) from pre- to post-intervention ($p = 0.001$), but this change was not observed in AUC ($p = 0.71$). Cognition No relationship between change in global cognition across the intervention and CAR ($\beta = -0.07$, $p = 0.72$), or AUC ($\beta = -0.14$, $p = 0.47$). Likewise, no domain specific effects were noted.
Tortosa-Martinez <i>et al.</i> (2015, Spain) N = 39 EG: n = 19 CG: n = 20	<u>Mean age (SD)</u> 76 (7.2) Range: not reported 59% Female MCI	EG: Light/moderate aerobic exercise, 3x/week for 3 months CG: Routine care	Saliva collection at: waking, 30 min post-waking, and then at 12:00 p.m., 5:00 p.m., and 9:00 p.m. to assess the diurnal rhythm of cortisol.	Global cognition (MMSE, ADAS-Cog) Immediate and Delayed Memory (Word List Memory) Executive Function (Verbal Fluency, TMT A&B)	Cortisol PA intervention resulted in a significantly greater fall in cortisol concentration from peak to midday relative to the control group ($F = 6.11$, $p = 0.03$). Cognition PA intervention enhanced indices of executive function via faster TMT-B completion ($F = 5.2$, $p = 0.05$), and a reduction in error rate for TMT-A ($F = 5.6$, $p = 0.02$). Intervention did not alter memory nor global cognition.

Saleem et al. (2013, Canada) n=56	<u>Mean age (SD)</u> : 66 (11.0) Range: Not reported 14% Female Cognitively healthy adults with coronary artery disease	EG: Unsupervised aerobic and resistance training 5x/week. Supervised aerobic walk/jog 1x/week for 36 weeks followed by 1x/month for 3 months. CG: None	Hair collected at baseline	CVLT-II	Cortisol Participants grouped by high (n=30) and normal (n=26) cortisol levels. Cognition Over 1 year both cortisol groups showed significant improvement in memory: normal cortisol (Z=1.56, $p < 0.05$) and high cortisol (Z=1.07, $p < 0.05$). Improvements in memory were significantly lower in high cortisol group (F=5.5, $p = 0.02$).
Baker et al. (2010, USA) n = 29 EG: n = 19 CG: n = 10	<u>Mean age (SD)</u> 70 (8.3) Range: 55 – 85 52% Female MCI	EG: Moderate/vigorous aerobic exercise, 4x/week for 6 months CG: Stretching 4x/week for 6 months	Plasma Cortisol (time of measure not reported)	Immediate Memory (RAVLT and Story Recall) Delayed Memory (RAVLT, Story Recall, delayed-match-to-sample) Executive Function (TMT B, Stroop colour & word, Task Switching, Verbal Fluency, Symbol Digit)	Cortisol PA intervention resulted in reduced fasting levels of cortisol relative to the control group among women only ($p = 0.05$), but not men. Cognition PA intervention improved indices of executive function among women (symbol digit: $F = 0.7$, $p = 0.04$; category fluency: $F = 0.9$, $p = 0.01$; stroop: $F = 0.8$, $p = 0.02$) and improved performance in the TMT-B test among men ($F = 0.7$, $p = 0.05$)
Diet					
Komori (2015, Japan) N = 54	<u>Mean age (SD)</u> 68.5 (3.2) Range: not reported	EG: Supplement containing PS 100 mg, omega 3 fatty acids: DHA 119 mg and EPA 70 mg, 3x/day for 12 weeks	Saliva collection at: waking, 1 hr, 2 hrs, 3 hrs and 4 hrs post-waking to assess the	None	Cortisol 8 EG individuals responded to the supplement whereas 10 did not. There was a significant normalisation of the cortisol circadian rhythm for responders post-intervention.

EG: n = 18 (depressed)	44% Female	CG:	circadian rhythm of cortisol.
CG 1: n = 18 (healthy)	Cognitively Healthy	Routine care	
CG 2: n = 18 (depressed)	(Major Depression diagnosis)		

Sleep

No human interventional studies to date

Yoga & Meditation

Jevning <i>et al</i> (1978, USA)	<u>Mean age</u> <u>(SD)</u> Not reported Range: 22 - 29	Meditation: 3-4 months of 20 – 40 minutes TM practice	Plasma Cortisol collection between 12 –4 pm before and after TM	None	Cortisol Cortisol declined, but not significantly, in experimental group during TM, when studied at post-intervention. Cortisol decreased significantly in long-term practitioners during TM and remained low afterward.
N = 30	50% female				
EG: n = 15 naive meditators (pre-post design)	Cognitively healthy				
CG: n = 15 (long-term meditators, with 3 -5 years of practice)					
Gothe et al. (2016, USA)	<u>Mean age</u> <u>(SD)</u> : 62 (5.6) Range: 50-78	EG: 8-week progressive Hathe yoga program 3x/week.	Saliva collection before afternoon cognitive testing appointment (2 samples) and after	Executive function (Task switching) Working memory (Running memory span, n-back task)	Cortisol EG had lower post-stressor cortisol levels ($F=4.55$, $p=0.04$).
n=118					

EG: n=58 CG: n=50	% Female not reported Cognitively healthy	CG: 8-week progressive stretch and strengthening exercises 3x/week.	appointment (2 samples)		Elevated cortisol was predictive of poorer accuracy in executive function tests. Cognition EG performed better on working memory and executive function tasks.
Wetherall <i>et al</i> (2017, USA) N = 103 EG: n = 47 CG: n = 56	<u>Mean Age (SD)</u> 71.9 (5.4) Range: not reported but all >65 years 75% Female SCI Clinically diagnosed with anxiety or depressive disorder	MSBR: 8 weekly sessions of meditation and light yoga (90 minutes, group based) Health education: 8 weekly sessions of tutorials with healthcare themes such as healthy eating and medication management (90 minutes, group-based).	Salvia collection at waking, 30 minutes after waking, and bedtime for 3 consecutive days. Peak daily cortisol computed from the higher of either the waking or wake + 30 minutes values on each day, and the median value of the 3 days was used.	Memory composite (immediate and delayed recall of word list and narrative story) Executive Function (verbal fluency; Stroop interference)	Cortisol Median salivary cortisol decreased in the MSBR group post-treatment, but only for individuals with high baseline cortisol levels Cognition MSBR group showed greater improvement on a memory composite score at follow-up ($p = 0.046$). No differences in executive function measures were observed for either group Other MBSR group also improved on measures for worry, depression and anxiety at follow-up

n = number of participants; CG = control group; EG = experimental group; SD = standard deviation; CAR = Cortisol Awakening Response; AUC = Area Under the Curve; RAVLT = Rey Auditory Verbal Learning Test; TM = Transcendental Meditation; SCI = Subjective Cognitive Impairment; MSBR = Mindfulness Based Stress Reduction; MMSE = Mini Mental State Examination; ADAS-Cog = The Alzheimer's disease Assessment Scale – Cognitive section; CVLT-II = California Verbal Learning Test second edition; FAIR-2-A = Frankfurt Attention Inventory 2A; TMT = Trail Making Test; PS = phosphatidylserine; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid. ^aA large number of exercise studies exploring effects on cortisol have been reviewed previously, hence, this section includes all existing studies with both cortisol *and* cognition as an outcome. * $p < 0.05$, ** $p < 0.00$

Table 3. Characteristics and results of murine studies investigating pharmacological interventions on the HPAA in AD

Study	Species information	Intervention	Outcome measure (corticosterone)	Behaviour and Cognitive Outcomes	Results
GR Antagonists					
Baglietto-Vargas <i>et al.</i> (2013) n = 20 (10 per group)	3xTg-AD mice	EG: subcutaneous pellet releasing 1.2mg mifepristone (RU 3846) per day for 21 days CG: subcutaneous vehicle pellet	None	Novel context/place/object tasks; open field; hidden Morris water maze; passive inhibitory avoidance task	Significant improvement in novel object task (p<0.01). Significant decrease in time taken to reach criterion on hidden Morris water maze (p<0.05). No differences on open field or passive inhibitory avoidance tasks.
Lante <i>et al.</i> (2015) n=104 (WTvehicle=56, WT-RU=16, Tg2576-vehicle=22, Tg2576-RU=10)	Tg2576 and WT mice	EG: RU846 (40mg/kg) delivered via drinking water and subcutaneously in interscapular region 2 or 4 days before sacrifice CG: Vehicle solution delivered via drinking water and subcutaneously in interscapular region 2 or 4 days before sacrifice	None (plasma corticosterone measured as comparator between Tg2576 and WT but not in response to treatment)	Object recognition paradigm	RU846 treated mice performed as well as WT mice on the 'where' component of the object recognition paradigm (p=0.003), with no difference from untreated mice on 'what' and 'when' components.
Lesuis <i>et al.</i> (2018)	APPswe/PS1dE9 and WT mice	EG: Intraperitoneal injection of mifepristone on 3 consecutive days	Plasma corticosterone	Barnes maze, amyloid pathology	Significant reduction in basal plasma CORT levels (p<0.001) 24 hours after treatment with no significant difference 21 days after treatment, significant reduction in hippocampal AB40 (p=0.01) and

n=58 (12 months: WT=16, APPswe/PS1dE9= 11, ELS-WT = 19, ELS- APPswe/PS1dE9=12)		CG: Intraperitoneal injection of vehicle on 3 consecutive days			AB42 (p=0.02), significant improvements in performance on Barnes maze for ELS- APPswe/PS1dE9 and control APPswe/PS1dE9 mice (p<0.001) but no effect on WT mice.
Stein <i>et al.</i> (2017)	C57BL/6 mice	EG: Spironolactone and RU38486 injected intraperitoneally at 20mg/kg	None	Electrophysiology	GR inhibition restored muscarinic long term potentiation (mLTP) to non-stressed conditions, whilst MR inhibition almost entirely blocked the expression of mLTP.
n= not provided		CG: Vehicle injected intraperitoneally			
Horchar & Wohleb (2019)	Transgenic Thy1- GFP-M and WT C57BL/6 mice	EG: Intraperitoneal injection of RU846 25mg/ml in 0.9% saline prior to exposure to stress	Plasma corticosterone	Forced swim test; novelty- suppressed feeding test; temporal object recognition task	Treatment with RU846 partially attenuated the plasma corticosterone increase following exposure to stress (p<0.007). RU846 treatment prevented stress induced immobility (p<0.05), attenuated increased latency to feed (p<0.0001), and prevented impairment in discrimination index on the temporal object recognition task (p<0.01).
n=32 (8 per group)		CG: Intraperitoneal injection of vehicle prior to exposure to stress			

**GR Antagonists & GR
modulators**

Pineau <i>et al.</i> (2016)	Sprague-Dawley rats	EG: CORT108297 10mg/kg, 20mg/kg, 40mg/kg bw intracerebroventricular injection; CORT113176 5mg/kg, 10mg/kg, 20mg/kg bw intracerebroventricular injection; mifepristone 30mg/kg bw injection CG: vehicle treatment; naïve rats	Plasma corticosterone	T-maze	Mifepristone treatment reverses HPA hyperactivity (p<0.001), but had no effect on the T-maze. CORT108297 returned corticosterone levels to naïve rats (p<0.001), with 20mg/kg dose significantly improving cognitive outcomes (p<0.001). CORT113176 reverses HPA hyperactivity (p<0.001) and doses of 10mg/kg and above improve cognitive outcomes (p<0.001).
11β-HSD inhibitors					
Sharma <i>et al.</i> (2019)	Sprague-Dawley rats	EG: Intraperitoneal injection of carbenoxolone disodium (20mg/kg) for 6 weeks in either Aβ 1–42 group rats or controls CG: Sham control with vehicle via intracerebroventricular injection, Aβ 1–42 group rats injected intracerebroventricular injection with Aβ 42 oligomers	None	Elevated plus maze; active avoidance test;	Number of entries to open arms and time spent in open arms significantly reduced in Aβ 1–42 treated group compared to sham controls (p<0.05) percentage of escaped trials significantly decreased Aβ 1–42 treated group compared to Aβ 1–42 controls.
n=not provided					
n=8					

Leiva <i>et al.</i> (2017)	SAMP8 mice	EG: Compound 23 105mg/L in drinking water	None	Novel object recognition test	Compound 23 improved both short term ($p<0.05$) and long term ($p<0.001$) memory compared to old vehicle treated mice as measured on the novel object recognition test.
	n=not provided	CG: PEG400 in drinking water			
Sooy <i>et al.</i> (2015)	C57BL/6 mice; Tg2576 mice	EG: UE2316 delivered by subcutaneously implanted Alzet osmotic minipumps for 14 days (C57BL/6) or 29 days (WT & Tg2576), or 30mg/kg/d via diet supplementation for 57 weeks (6/7 month old Tg2576)	None	Passive avoidance; Y maze test; open field test; spontaneous alternation; Morris water maze	C57BL/6: Significant increase in time spent in novel arm of Y maze in UE2316 15mg/kg/d compared to vehicle treated mice ($p<0.05$); increase in latency to enter dark compartment on passive avoidance test at both doses of UE2316 compared to vehicle ($p<0.05$). Tg2576: Significant increased latency in re-entry to dark compartment ($p<0.01$). Trend in spontaneous alternation test with treated mice increased percentage alternative ($p=0.06$). 6/7 month old Tg2576: maintenance of latency to enter dark compartment at 16/17 months compared to vehicle ($p=0.004$). No difference on open field test. Significant increase in spontaneous alternation ($p<0.05$), but no difference in total number of arm entries. No difference in swim speed, but UE2316 did reduce time take to find hidden
	C57BL/6 n=24 (vehicle=6, UE2316 5mg/kg/d=8, UE2316 15mg/kg/d=8 WT & Tg2576 N=40 (WT vehicle=10, Tg2576 vehicle=10, WT UE2316 =10, Tg2576=10) 6/7 month old Tg2576 mice n=not provided	CG: Vehicle delivered by subcutaneously implanted Alzet osmotic minipumps for 14 days (C57BL/6) 29 days (WT & Tg2576) or vehicle via diet supplementation for 57 weeks (6/7 month old Tg2576)			

platform in Morris water maze
($p < 0.05$).

Sooy <i>et al.</i> (2010)	C57BL/6J mice	EG: UE1961 10mg/kg intraperitoneal injection twice daily for 10 days	Plasma corticosterone	Y maze	Treated mice spent more time in novel arm compared to vehicle ($p < 0.001$), plasma corticosterone levels were higher in treated mice compared to vehicle treated mice ($p < 0.005$).
n=20 (9-10 per group)		CG: Vehicle intraperitoneal injection twice daily for 10 days			

GR= glucocorticoid receptor; MR= mineralocorticoid receptor; n = number of animals used; CG = control group; EG = experimental group; WT= wildtype;
DSMO= dimethyl sulfoxide; ELS= early life stress; PEG400= polyethylene glycol 400; mLTP= muscarinic long term potentiation