The Centre for Dementia Prevention

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Xanamem™: an 11ß-HSD1 Inhibitor in current development for the management of Alzheimer's disease (AD)

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Disclosures

- ***I have been supported for travel to this meeting by Actinogen who I also have a consultancy arrangement with through the University of Edinburgh.***

- ***I have also provided paid consultancy work over the last 5 years for:***
  - *AbbVie, Eisai, Sanofi-Aventis, Merck, Janssen, Nutricia, Novartis, Prana Biotechnology, Actinogen, Roche, Biogen, Lundbeck, Aptiv Solutions and GSK*

- ***I also co-lead the EPAD Consortium which is a public:private partnership with several pharmaceutical companies and SMEs***

Presentation Overview

1. Role of HPA Axis and Cortisol in Alzheimer's disease

2. Mechanism of action, pre-clinical and clinical work with central 11β-HSD-1 Inhibition

3. The Xanadu Study of Xanamem™ in Mild Alzheimer's Dementia

Elevated circulating cortisol levels may contribute to AD pathogenesis[1,2].

- Direct:

  [1] increase levels of amyloid precursor protein (APP) and BACE leading to increased Aβ42 formation

  [2] reduced Aβ42 degradation via attenuation of insulin degrading enzyme[3]

- Indirect:

  [1] Insulin resistance,

  [2] angiopathic and antiangiogenic actions

  [3] increased excitatory (N-methyl-D-aspartate) neurotransmission

  [4] Increased postsynaptic calcium signaling promoting neurotoxicity metabolic endangerment of neurons, and deleterious alterations in neuroimmune function[4]

[1]Peskind ER, et al *Neurology*. 2001;56:1094–1098. [2]Cernansky JG et al *AmJPsychiatry*. 2006;163:2164–2169. [3]Green KN et al. *J Neurosci*. 2006;26:9047–9056. [4]Wang Y et al. *Endocrinology*. 2011;152:2704–2705.

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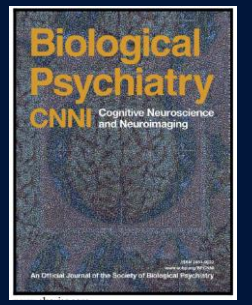
aibl
The Australian Imaging, Biomarkers and Lifestyle Flagship Study of Ageing

Plasma cortisol, brain amyloid-β, and cognitive decline in preclinical Alzheimer's disease: a 6-year prospective cohort study[1]

[1]Pietrzak RH et al., Biological Psychiatry, Cognitive Neuroscience and Neuroimaging (ePrint) 2016

METHOD

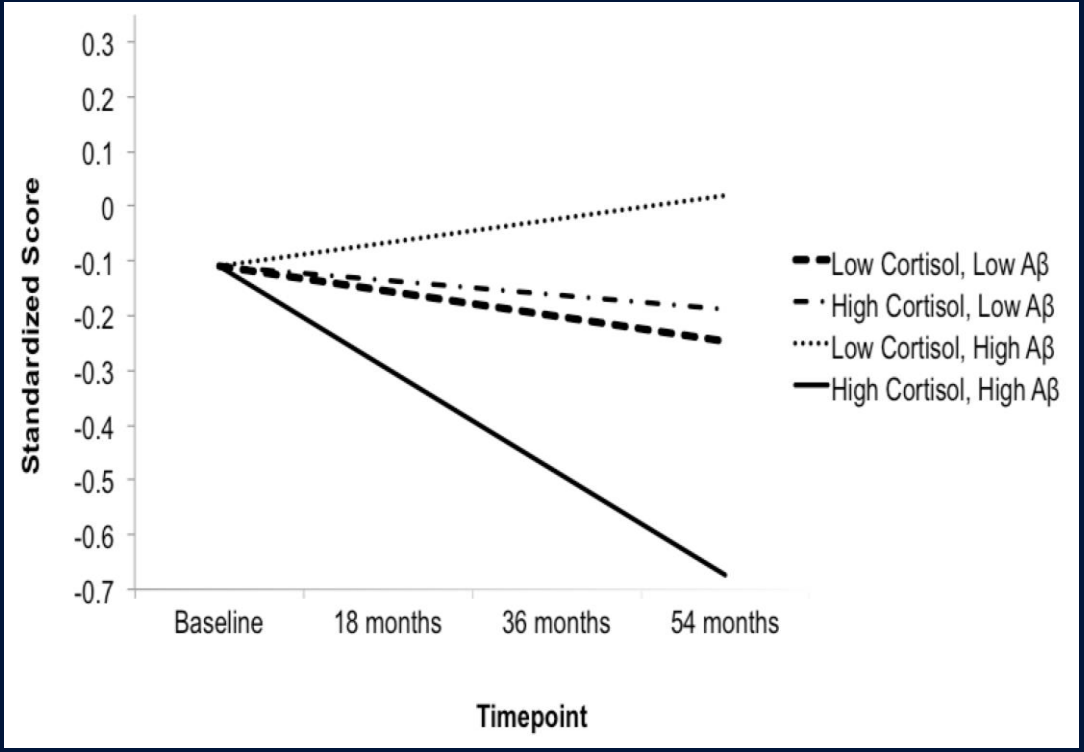
- Cognitively normal older adults (n=416) enrolled in the AIBL study underwent Aβ neuroimaging at a single timepoint. Fasted cortisol were dichotomized using a median split procedure.
- Five cognitive composites were derived: Episodic Memory, Executive Function, Attention, Language and Global Cognition
- Latent growth curve models were conducted to evaluate the relation between baseline plasma cortisol and Aβ levels, other risk factors, and cognitive composite scores over the 72-month study period.



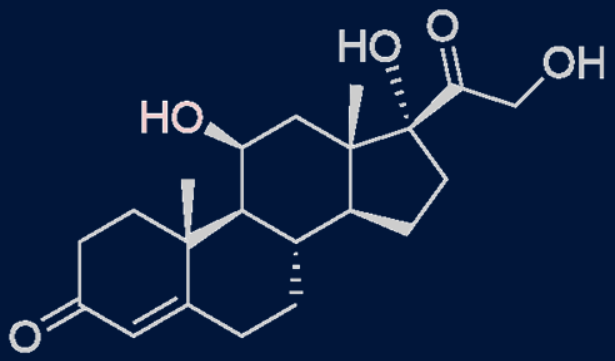
RESULTS

•High baseline plasma cortisol levels associated with 2.2 times the risk of Aβ+ and associated with greater decline in global cognition (Cohen's d=0.42), episodic memory (Cohen's d=0.69), and attention (Cohen's d=0.31)*.

•*Effects were independent of age, education, premorbid intelligence, *APOE* and *BDNF* genotype, subjective memory complaints, vascular risk factors, and depression and anxiety symptoms.

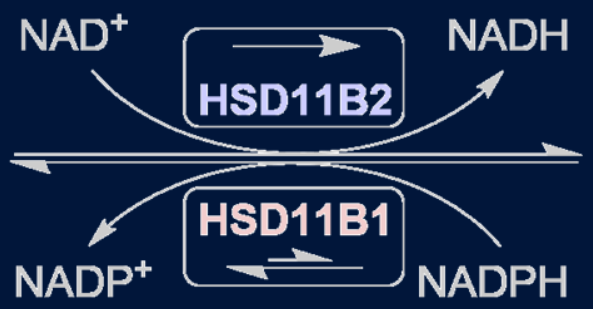


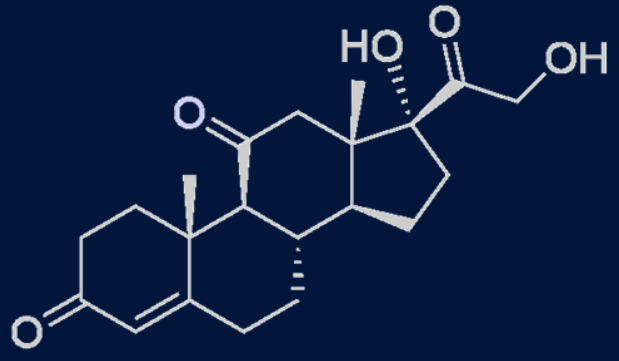
Function of 11β-HSD1



cortisol

ACTIVE





cortisone

INACTIVE

Cognitive and Disease-Modifying Effects of 11β-Hydroxysteroid Dehydrogenase Type 1 Inhibition in Male Tg2576 Mice, a Model of Alzheimer's Disease

Karen Sooy, June Noble, Andrew McBride, Margaret Binnie, Joyce L. W. Yau, Jonathan R. Seckl, Brian R. Walker, and Scott P. Webster

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METHODS

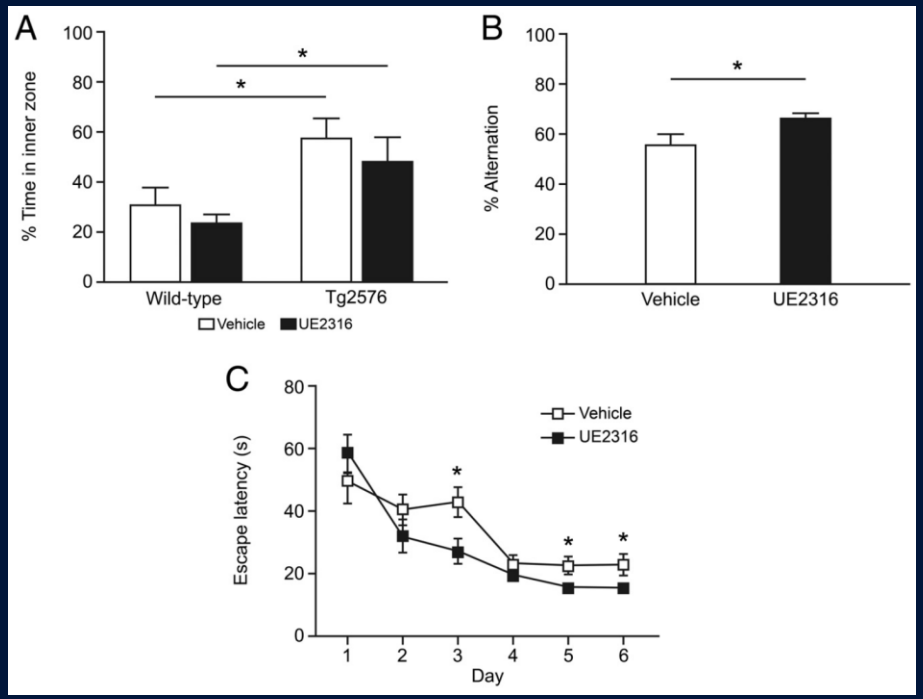
Short Term Study:
14 month old mice: UE2316 10mg/kg/d through SC route (n=20 1:1 active:placebo)
Long Term Study:
6-7 month old mice fed UE2316 (n=32) or control diet (n=16) for up to 57 weeks

Behaviour:
Memory in Passive Avoidance, Y-Maze Testing, Open Field Testing, Spontaneous Alteration and Morris Water Maze
Immunohistochemistry
Cortical Amyloid Plaque Number and Plaque Area

(Sooy et al., Endocrinology 156: 4592–4603, 2015)

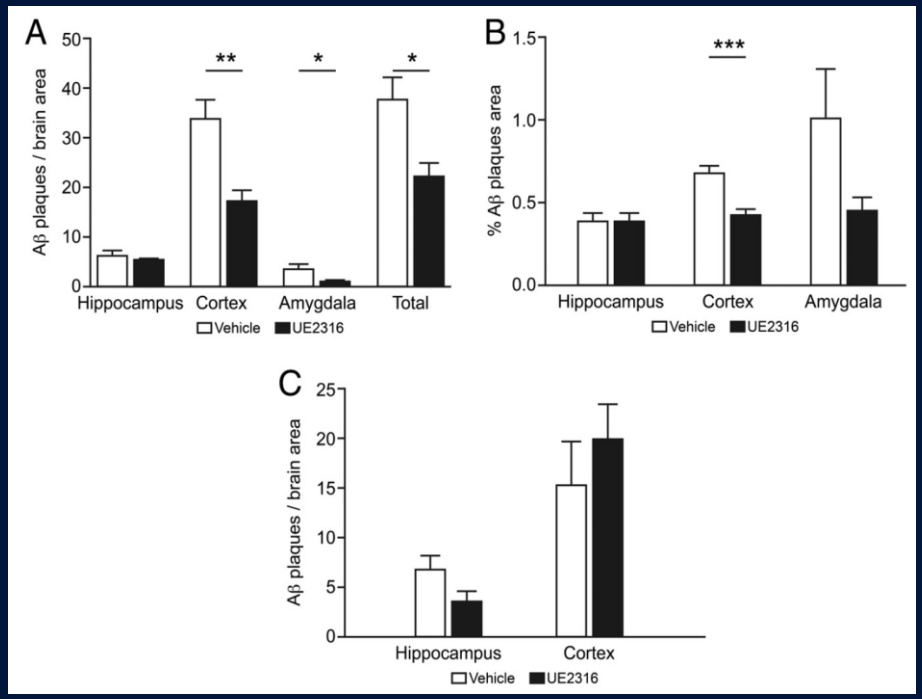
11β-HSD1 Inhibition in TG2476 Mice

Selected Behavioral Improvements



Impact of 11β-HSD-1 inhibition on [A] Open field [B] Spontaneous Alteration and [C] Morris Water Maze

Reduced Amyloid Plaque Burden



Impact of 11β-HSD-1 inhibition on [A] Short Term Plaque Number, [B] Short term Plaque Area and [C] Long Term Plaque Number

(Sooy et al.Endocrinology 156: 4592–4603, 2015)

11β-Hydroxysteroid dehydrogenase inhibition improves cognitive function in healthy elderly men and type 2 diabetics

Thekkepat C. Sandeep*, Joyce L. W. Yau*, Alasdair M. J. MacLullich†, June Noble*, Ian J. Deary‡, Brian R. Walker*, and Jonathan R. Seckl*§

In two double-blind, placebo RCT crossover studies, carbenoxolone

- Improved verbal fluency ($P < 0.01$) after 4 weeks n=10 elderly men (aged 55–75 y)
- Improved verbal memory ($P < 0.01$) after 6 weeks n=12 type 2 diabetics (52–70 y).

Influence of carbenoxolone on cognitive function in healthy elderly men and patients with type 2 diabetes

		Healthy elderly subjects			Patients with type 2 diabetes		
Cognitive domain	**Neuropsychological measures**	**Placebo with amiloride mean (SD)**	**Carbenoxolone with amiloride mean (SD)**	***P***	**Placebo with amiloride mean (SD)**	**Carbenoxolone with amiloride mean (SD)**	***P***
Executive function	Verbal fluency	40.6 (12.4)	44.2 (10.6)	**0.006**	42.2 (8.4)	42.7 (6.4)	0.48
Memory							
Visual	WM visual reproduction	59.2 (18.2)	66.2 (8.4)	0.28	59.9 (13.3)	60.2 (7.9)	0.94
Verbal	WM logical memory	47.0 (19.2)	53.2 (18.1)	0.13	49.7 (13.8)	49.7 (17.7)	0.78
	Rey AVLT	51.5 (10.5)	53.9 (8.5)	0.47	55.2 (8.0)	58.8 (5.2)	**0.005**
Nonverbal reasoning	RSPM	45.1 (5.9)	46.3 (8.5)	0.45	44.0 (6.6)	45.4 (8.0)	0.17
Processing speed	DSST	50.7 (7.8)	51.9 (8.5)	0.70	50.3 (6.7)	50.6 (5.5)	0.78

WM, Wechsler Memory Scale-revised; AVLT, Rey Auditory Verbal Learning Test; RSPM, Ravens Standard Progressive Matrices; DSST, Digit Symbol Substitution test. Values in bold indicate a significant difference compared with placebo.

Sandeep et al. 11-Hydroxysteroid dehydrogenase inhibition improves cognitive function in healthy elderly men and type 2 diabetics. *Proc Natl Acad Sci USA*. 2004;101:6734–6739

Summary of Background

- Strong biological basis for aetiological role of elevated central cortisol in AD pathology.
- Epidemiological work associates elevation of cortisol with AD pathology and clinical progression
- Interventions studies in pre-clinical and clinical models with 11-βHSD1 showing promise
- Rational target for further clinical trials for symptomatic and potentially disease modifying treatments for Alzheimer's dementia.

XanADu (Xanamem in AD)

- A Phase II, Double Blind, 12-Week, Randomised, Placebo-Controlled Study to Assess the Safety, Tolerability and Efficacy of Xanamem™ in Subjects with Mild Dementia due to Alzheimer's Disease
- Primary objective: Performance of Xanamem™ from Baseline to end of treatment compared to placebo in ADAS-Cog v14 (2 points) & ADCOMs
- Secondary objectives include RAVLT, CDR-SOB, MMSE, NPI &$NTB_{(exec)}$

XanADu (Xanamem in AD)

- Key subject inclusion criteria includes:
  - Mild dementia due to Alzheimer's disease
  - MMSE 20 to 26 (inclusive)
  - CDR of 0.5 to 1.0
  - On a stable dose of acetylcholinesterase (AChEI) and/or memantine (at least 3 months prior to Screening) OR treatment-naïve. Initiating AChEIs or memantine during the study will not be permitted

XanADu (Xanamem in AD)

- Initiating in US, Australia and UK in 2017
- 174 patients with mild Alzheimer's dementia to be randomised
- Excellent PK and Brain Penetrance to achieve optimal central 11b-HSD1 inhibition with no/minimal peripheral effects

Summary

- Epidemiological, biological and (limited) trial evidence associates elevations in cortisol with Alzheimer's disease and clinical progression.

- 11β-HSD1 Inhibition is a targetable and rational approach to symptomatic and disease modification in Alzheimer's disease.

- The XanADu study is the first Phase 2 trial of Xanamem for symptomatic benefit in Mild Alzheimer's dementia – initiating in 2017.