Neuroactive steroids as predictive markers for Alzheimer´s disease

B. Bendlová[1], M. Hill[1], J. Včelák[1], D. Vejražková[1], P. Lukášová[1], G. Vacínová[1], O. Bradnová[1], K. Dvořáková[1], R. Rusina[2], I. Holmerová[3], M. Vaňková[1]
[1]Institute od Endocrinology, Prague; [2]Thomayer Hospital, Prague; [3]Faculty of Humanities, Charles University, Prague

Many studies have demonstrated a link between Alzheimer´s disease (AD) and type 2 diabetes (T2D), but the connection underlying this relationship is not completely clear. Diabetic pathologies may lead to both AD and vascular damage. Neuroactive steroids and their metabolites play an important regulatory role in the nervous system affecting the neuronal plasticity, stress response, learning and memory.

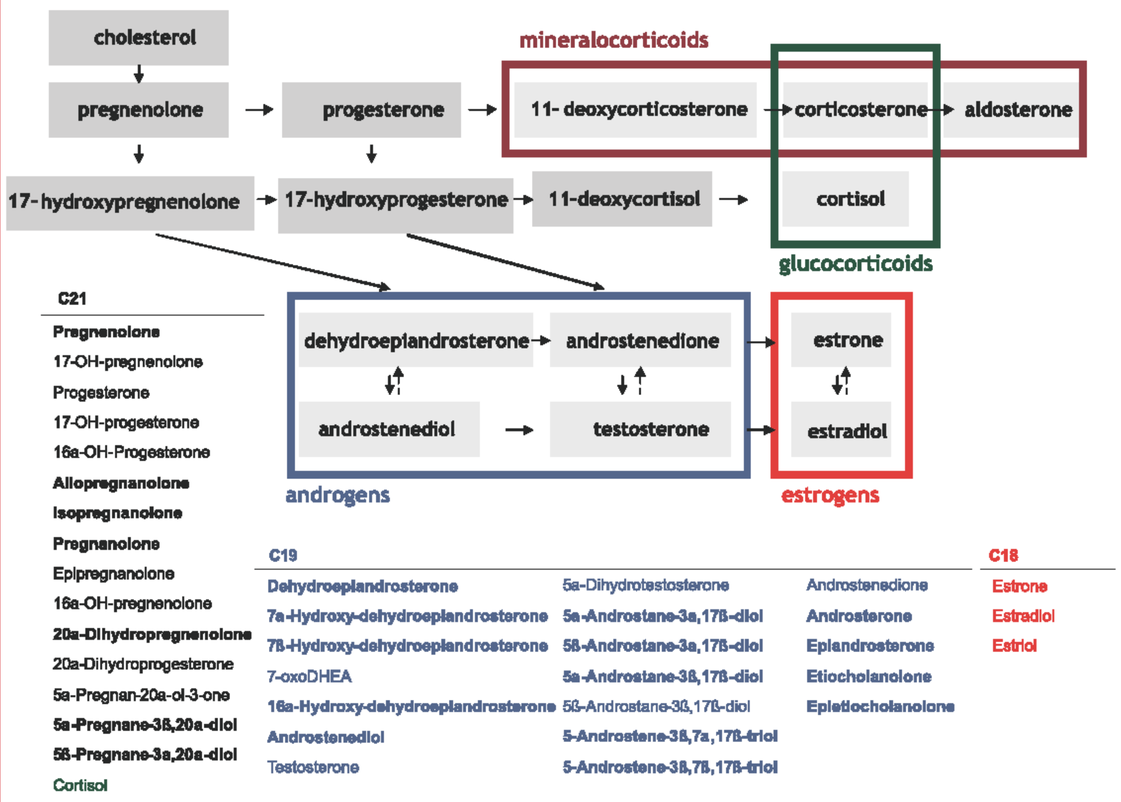
The aim of the study was to compare the steroid metabolome in AD patients and controls, to evaluate its possible relation to glucose metabolism and to propose the predictive model for AD.

Subjects:

	AD (n=48)	Controls (n=33)
Men / Women	18 / 30	11 / 22
Age (years)	72.3 ± 10.42 / 74.4 ± 9.1	69.6 ± 4.44 / 67.5 ± 6.55
BMI (kg/m^2)	26.3 ± 3.61 / 25.7 ± 4.08	27.6 ± 3.28 / 27.9 ± 5.71

Methods:

- Neuropsychological examination and brain MRI for exclusion/confirmation of neurological diagnosis
- Glucose and lipid metabolism, anthropometric examination
- Extended spectrum of steroid hormones (GC-MS): 38 steroids + their conjugates
- Statistical software NCSS 2004, Statgraphics Centurion XVI 16.0.07, SIMCA-P
- Kruskal-Wallis One-Way ANOVA on Ranks, multivariate regression with reduction of dimensionality (O2PLS), predictive model for AD
- Patients taking corticosteroids, fluoxetine (an inhibitor of serotonin uptake), HRT, estrogenes, NSAIDs were excluded



Conclusions:

AD patients have higher levels of insulin in the periphery, however, the direct relationship between glucose tolerance and steroid metabolome was not confirmed.

C21 steroid levels were consistently higher in AD, suggesting an increased activity of the zona fasciculata of adrenal gland.

Conversely, levels of stable 5α/ß reduced catabolites of C19 steroids, particularly their sulfates, are consistently reduced in AD (unlike insignificantly different unreduced androgenic precursors showing a diurnal variation). This indicates a decrease in the activity of the adrenal zona reticularis in AD.

Results:

Glucose metabolism

Normal glucose tolerance	AD (n=32)	Controls (n=14)	p*
HbA1c [mmol/mol]	37.5 ± 2.48	37.7 ± 3.38	0.09
glyceamia [mmol/l]	4.9 ± 0.21	5.2 ± 0.22	0.001
proinsulin [mmol/l]	3.9 ± 4.66	2.2 ± 2.1	0.09
insulin [mIU/l]	10.1 ± 4.61	7.2 ± 3.23	0.02
C-peptide [nmol/l]	0.8 ± 0.02	0.7 ± 0.23	0.28
HOMAF	149 ± 60.9	84 ± 36.2	0.0007
HOMAR	2.2 ± 1.07	1.6 ± 0.78	0.09

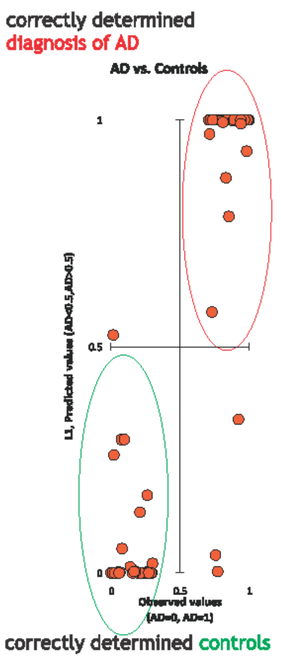
Mean ± SD, Kruskal-Wallis One-Way ANOVA on Ranks (NCSS 2004)

Impaired glucose tolerance	AD (n=16)	Controls (n=19)	p*
HbA1c [mmol/mol]	39.8 ± 2.92	37.3 ± 5.3	0.28
glyceamia [mmol/l]	5.9 ± 2.28	6 ± 0.37	0.36
proinsulin [mmol/l]	5.9 ± 2.3	5.9 ± 4.82	0.99
insulin [mIU/l]	17 ± 6.14	12.3 ± 5.24	0.09
C-peptide [nmol/l]	1.3 ± 0.49	1 ± 0.29	0.13
HOMAF	145 ± 52.6	99 ± 42.42	0.05
HOMAR	4.4 ± 1.63	3.3 ± 1.47	0.14

Steroids

Women	AD (n=30)	Controls (n=22)	p*
Pregnenolone	1.6 ± 1.38	0.9 ± 0.48	0.03
16α-hydroxy-pregnenolone	0.2 ± 0.15	0.1 ± 0.11	0.02
16a-hydroxy-progesterone	0.7 ± 0.54	0.5 ± 0.72	0.02
5ß-Pregnan-3α,20α-diol C	13.5 ± 7.15	8.6 ± 3.71	0.005
Androsterone C	220.2 ± 201.1	403.5 ± 227.87	0.001
Epiandrosterone C	77.6 ± 55.23	152.2 ± 85.52	0.001
Epietiocholanolon C	8.9 ± 7.26	16.5 ± 11.55	0.003
5α-Androstan-3ß,17ß-diol C	15.9 ± 11.61	48,4 ± 44.71	0.0001
5ß-Androstan-3ß,17ß-diol C	3.3 ± 1.88	4.6 ± 2.35	0.049
Men	**AD (n=18)**	**Controls (n=11)**	**p***
Pregnanolone	0.07 ± 0.034	0.04 ± 0.030	0.01
5ß-Pregnan-3α,20α-diol C	22.9 ± 13.21	10.8 ± 4.17	0.006
16α-hydroxy-dehydroepiandrosterone	0.06 ± 0.0444	0.03 ± 0.026	0.03
5α-Androstan-3ß,17ß-diol C	81.1 ± 56.82	137.4 ± 61.54	0.02

Mean ± SD, Kruskal-Wallis One-Way ANOVA on Ranks (NCSS 2004); C conjugated forms [nmol/l]



Prediction vs. observation

Confidence intervals for sensitivity, specificity, two-level likelihood ratios and diagnostic odds ratio

Sensitivity	0.9375	CI: 0.675 to 1.188
Specificity	0.9697	CI: 0.421 to 0.579
Positive likelihood ratio	30.937	CI: 7.806 to 122.608
Negative likelihood ratio	0.064	CI: 0.048 to 0.086
Diagnostic odds ratio	480	CI: 47.73 to 4826.57

Supported by grants IGA MH CZ NT/13543/4, NT/13544/4, MH CZ 00023761.
Contact: bbendlova@endo.cz

DOI: 10.3252/pso.eu.17ece.2015
Poster presented at: ECE2015 16-20 May 2015 DUBLIN, IRELAND 17th EUROPEAN CONGRESS OF ENDOCRINOLOGY