PET Study on the characterization of an APP/Tau rat model of Alzheimer's disease

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Introduction

To better understand the complex pathomechanisms of Alzheimer's disease, the availability of a transgenic animal model overexpressing both human tau and human amyloid-beta (Aβ) would be helpful. In the present study, we evaluated a new transgenic rat animal model generated by crossing of amyloid precursor protein (APP) rats with tau rats by performing positron emission tomography (PET) scans at the age of 7, 13 and 21 months with [^{11}C]PiB [1] and [^{18}F]THK-5317 [2]. In addition, immunohistochemical analyses of brain sections from PET-scanned animals were used to correlate the findings.

Methods

APP/Tau rats were generated by crossbreeding male McGill-R-Thy1-APP transgenic rats [3] with Swedish double mutation (K670N/M671L) and Indiana mutation (V717F) with female hTau-40/P301L transgenic rats [4]. APP/Tau double transgenic rats aged between 7 and 21 months were subjected to dynamic [^{11}C]PiB scan and dynamic [^{18}F]THK-5317 scan. For regional brain analysis, a template was generated from anatomical MR images of selected animals which was co-registered with the PET images. Regional analysis was performed by application of the simplified reference tissue model ([^{11}C]PiB data), whereas [^{18}F]THK-5317 data were analysed using a 2-tissue compartment model and Logan graphical analysis. In addition, immunofluorescent labeling (tau, amyloid) and cerebrospinal fluid analyses was performed.

[^{11}C]PiB	n	age (months)	weight (g)	inj. activity (MBq)	inj. mass (nmol/kg)	molar activity (GBq/µmol)
female APP/hTau	3	6.7 ± 0.3	257.7 ± 32.7	23.6 ± 6.1	3.2 ± 1.2	29.9 ± 5.0
male APP/hTau	3	7.1 ± 0.1	493.0 ± 51.4	26.3 ± 0.7	6.1 ± 4.1	16.2 ± 16.8
female APP/hTau	8	12.1 ± 0.6	334.5 ± 30.8	14.8 ± 2.2	0.4 ± 0.1	115.1 ± 12.9
male APP/hTau	10	12.4 ± 0.7	540.6 ± 47.6	16.7 ± 3.3	0.3 ± 0.0	109.3 ± 22.7
female APP/hTau	8	20.5 ± 0.5	347.0 ± 48.8	21.1 ± 1.1	0.6 ± 0.2	21.1 ± 1.1
male APP/hTau	10	20.6 ± 0.3	606.9 ± 43.8	31.0 ± 16.8	0.5 ± 0.3	31.0 ± 16.8

[^{18}F]THK-5317	n	age (months)	weight (g)	inj. activity (MBq)	inj. mass (nmol/kg)	molar activity (GBq/µmol)
female ntg	6	7.0 ± 0.2	273.3 ± 17.6	19.2 ± 5.2	1.5 ± 0.6	52.5 ± 16.7
female APP/hTau	7	7.0 ± 0.4	263.4 ± 21.2	17.8 ± 3.1	1.4 ± 1.7	149.9 ± 122.8
male ntg	6	7.1 ± 0.1	491.2 ± 57.5	16.2 ± 3.8	0.7 ± 0.1	53.7 ± 15.2
male APP/hTau	7	7.1 ± 0.3	485.6 ± 65.8	17.4 ± 3.8	0.3 ± 0.1	182.0 ± 118.6
female ntg	6	12.8 ± 0.5	300.3 ± 38.0	15.0 ± 1.5	0.9 ± 0.5	71.3 ± 45.1
female APP/hTau	11	12.5 ± 0.5	319.7 ± 28.7	11.6 ± 4.3	0.7 ± 0.6	83.6 ± 66.3
male ntg	2	13.4 ± 0.4	632.5 ± 0.7	8.8 ± 3.9	0.4 ± 0.5	194.8 ± 257.6
male APP/hTau	10	12.9 ± 0.4	520.3 ± 53.4	15.9 ± 4.3	0.4 ± 0.3	135.4 ± 99.1
female ntg	4	20.7 ± 0.4	354.0 ± 82.9	18.5 ± 2.6	0.9 ± 1.0	103.1 ± 46.1
female APP/hTau	6	20.7 ± 0.6	342.8 ± 52.1	16.2 ± 1.2	0.2 ± 0.1	388.9 ± 236.8
male ntg	4	21.0 ± 0.3	538.3 ± 54.4	16.3 ± 2.5	0.6 ± 0.5	88.0 ± 70.8
male APP/hTau	10	20.9 ± 0.3	594.5 ± 48.9	15.2 ± 2.6	0.2 ± 0.3	181.4 ± 112.6

Results

PET quantification yielded BP_{ND} for [^{11}C]PiB and V_T for [^{18}F]THK-5317 as outcome parameters in male and female APP/Tau and ntg rats at the age of 7, 13 and 21 months. Amyloid staining showed an age-dependent significant increase in cortical and hippocampal regions of APP/Tau rats (see Figure 1), which was confirmed in the BP_{ND} of [^{11}C]PiB and resulted in a positive correlation (see Figure 2).
Tau staining yielded a trend towards higher levels in the cortex and hippocampus of APP/Tau rats compared with ntg littermates, but without reaching statistical significance (see Figure 1).
[^{18}F]THK-5317 Logan derived V_Ts in APP/Tau rats showed a significant increase in the striatum and brainstem in 21-month compared to 7-month old animals, whereas significantly higher V_Ts in hippocampus, thalamus and hypothalamus were only found in female animals (see Figure 3).
No correlation was found between tau immunofluorescence labeling results and the respective [^{18}F]THK-5317 V_T values.

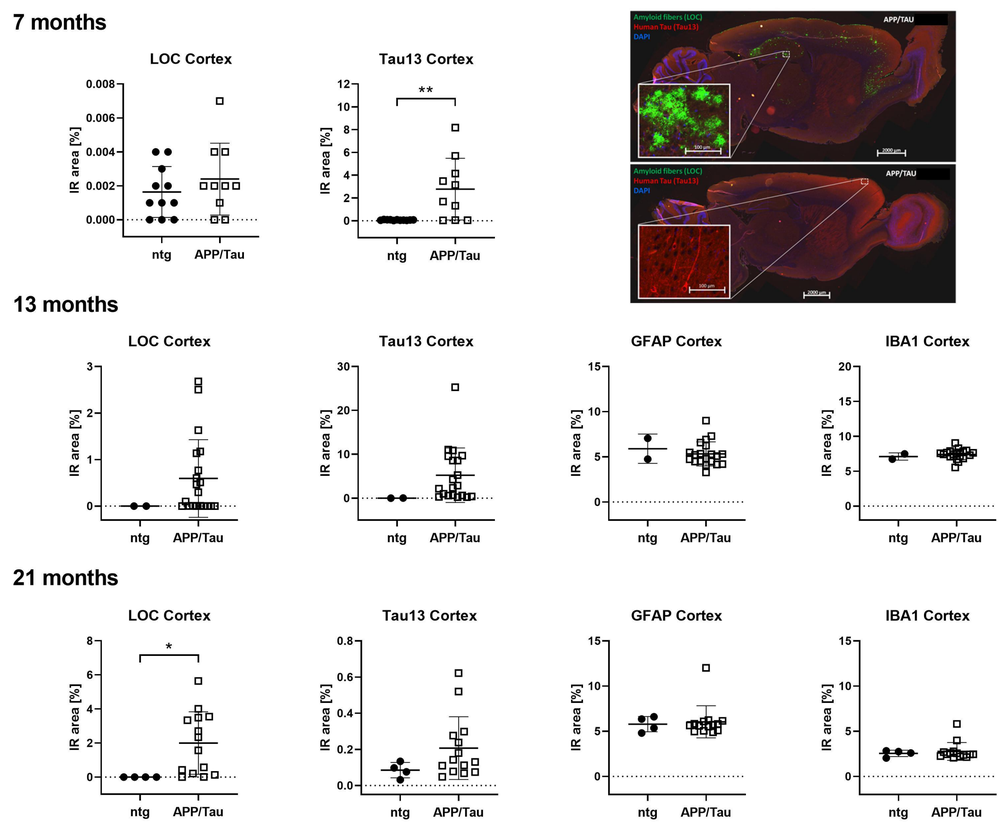

Figure 1: Quantification of human amyloid fibrils and human tau in the cortex and hippocampus of 7, 13 and 21-month old APP/Tau and ntg rats. LOC, Tau13, GFAP, and IBA1 immunoreactive (IR) area in the cortex. IR area is given in mean percent ± SD. *p< 0.05, **p< 0.01, two-tailed unpaired t-test.
Insert: Representative images of immunofluorescent labeling of whole brain slices showing LOC (green) and Tau13 (red) antibody labeling in 2 male APP/Tau rats (upper image amyloid- and tau-positive, lower image amyloid-negative, tau-positive). Slices were counterstained with DAPI (blue) to visualize nuclei. Insert in the upper image shows amyloid labeling in the hippocampus. Insert in the lower image shows human tau labeling in the cortex.

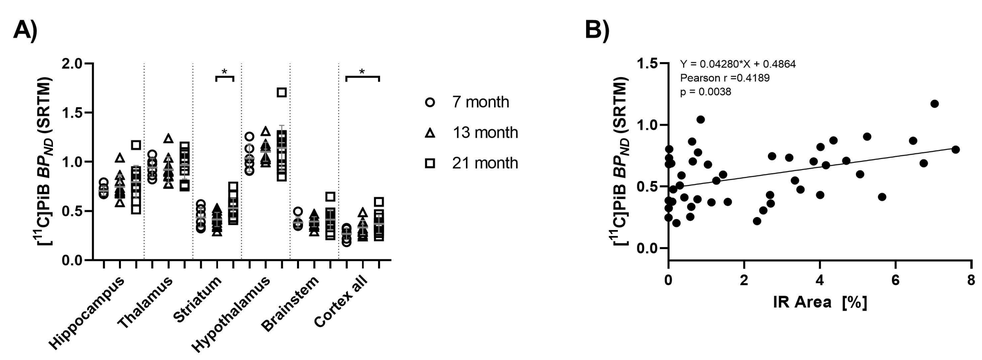

Figure 2: A) [^{11}C]PiB binding potential (BP_{ND}) obtained with the simplified reference tissue model (SRTM) in various brain regions of APP/Tau rats pertaining to different age groups (circles: 7 months, n=6; triangles: 13 months, n=11; squares: 21 months, n=12). Male and female animals were grouped together and only amyloid-positive animals based on immunofluorescent labeling analysis were included. * p<0.05, one-way ANOVA followed by Tukey's multiple comparisons test.
B) Correlation of [^{11}C]PiB BP_{ND} of male and female APP/Tau rats with the corresponding amyloid immunoreactive (IR) area of immunofluorescent labeling (all age groups, n=46; only amyloid-positive animals are included).

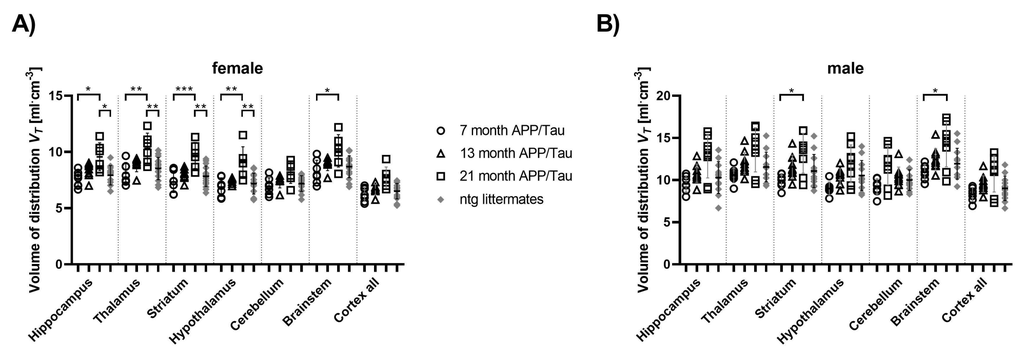

Figure 3: Volume of distribution (V_T) of [^{18}F]THK-5317 obtained with Logan graphical analysis in 7, 13 and 21 months old A) female and B) male APP/Tau and ntg rats (female APP/Tau: 7 months: n=7; 13 months: n=7; 21 months: n=6; female ntg: n=15; male APP/Tau: 7 months: n=7; 13 months: n=10; 21 months: n=8; male ntg: n=12). *p<0.05, **p< 0.01, ***p< 0.001; one-way ANOVA followed by Tukey's multiple comparisons test.

Conclusion

PET imaging showed an age-related increase in [^{11}C]PiB and [^{18}F]THK-5317 binding in several brain regions in the APP/Tau group but not in the non-transgenic animals. Although a positive correlation was observed between amyloid labeling and regional [^{11}C]PiB brain uptake, rather low human tau and amyloid fibril expression levels and an unstable brain pathology were observed, calling into question the future use of this animal model.

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References

1. Klunk WE, Engler H, Nordberg A, Wang Y, Blomqvist G, Holt DP, et al. Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. Ann Neurol. 2004;55(3):306-19.
2. Okamura N, Furumoto S, Harada R, Tago T, Yoshikawa T, Fodero-Tavoletti M, et al. Novel 18F-labeled arylquinoline derivatives for noninvasive imaging of tau pathology in Alzheimer disease. J Nucl Med. 2013;54(8):1420-7.
3. Leon WC, Canneva F, Partridge V, Allard S, Ferretti MT, DeWilde A, et al. A novel transgenic rat model with a full Alzheimer's-like amyloid pathology displays pre-plaque intracellular amyloid-beta-associated cognitive impairment. Journal of Alzheimer's Disease. 2010;20(1):113-26.
4. Korhonen P, van Groen T, Thornell A, Kyrylenko S, Soininen ML, Ojala J, et al. Characterization of a novel transgenic rat carrying human tau with mutation P301L. Neurobiology of Aging 2011;32(12):2314-5.