Human Alzheimer's Disease Tau Seeds Increase Tau Seeding and Uptake in Different *In Vitro* Models

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BACKGROUND

Tau aggregation and its cellular propagation plays a crucial role in the pathology of several neurodegenerative diseases, especially Alzheimer's disease (AD). The process of propagation is mediated by extracellular tau, which is taken up by cells and serve as seeds for tau aggregation. The development of new compounds to block tau seeding or uptake activity is currently an active field of research. Consequently, reliable *in vitro* models mirroring this tau pathology are needed.

MATERIAL & METHODS

To monitor tau seeding and uptake, we established *in vitro* assays in different cell types: (1) stably transfected tau overexpressing SH-SY5Y cells (2) mouse primary neurons isolated from wild type mice (3) mouse primary neurons isolated from Tau P301S (PS19) mice. Cells were treated with tau seeds isolated from human AD brains (AD-Tau seeds) in the presence of lipofectamine to induce tau seeding or in the absence of lipofectamine to monitor tau uptake. As positive control, the anti-tau antibody HT7 was co-incubated with AD-tau seeds, to counteract tau seeding and uptake. Tau aggregation was assessed using the HTRF-based Tau Aggregation Kit from Cisbio.

RESULTS

Tau seeding and uptake was detectable as increased HTRF signal after incubation of all cell types with human AD-tau seeds compared to vehicle control. The HT7 antibody significantly reversed the AD seed-associated tau aggregation in the seeding and uptake assay.

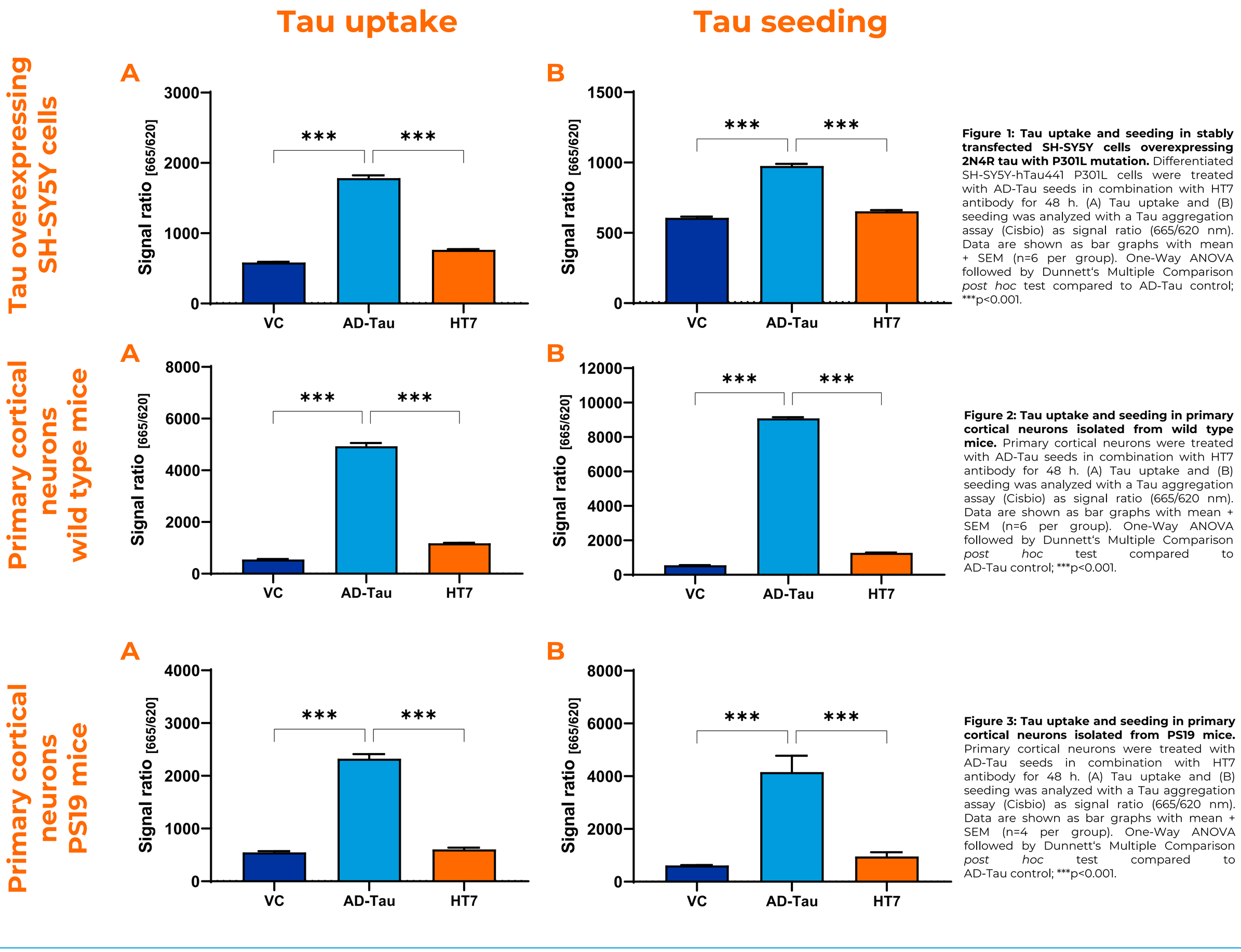

Figure 1: Tau uptake and seeding in stably transfected SH-SY5Y cells overexpressing 2N4R tau with P301L mutation. Differentiated SH-SY5Y-hTau441 P301L cells were treated with AD-Tau seeds in combination with HT7 antibody for 48 h. (A) Tau uptake and (B) seeding was analyzed with a Tau aggregation assay (Cisbio) as signal ratio (665/620 nm). Data are shown as bar graphs with mean + SEM (n=6 per group). One-Way ANOVA followed by Dunnett's Multiple Comparison *post hoc* test compared to AD-Tau control; ***p<0.001.

Figure 2: Tau uptake and seeding in primary cortical neurons isolated from wild type mice. Primary cortical neurons were treated with AD-Tau seeds in combination with HT7 antibody for 48 h. (A) Tau uptake and (B) seeding was analyzed with a Tau aggregation assay (Cisbio) as signal ratio (665/620 nm). Data are shown as bar graphs with mean + SEM (n=6 per group). One-Way ANOVA followed by Dunnett's Multiple Comparison *post hoc* test compared to AD-Tau control; ***p<0.001.

Figure 3: Tau uptake and seeding in primary cortical neurons isolated from PS19 mice. Primary cortical neurons were treated with AD-Tau seeds in combination with HT7 antibody for 48 h. (A) Tau uptake and (B) seeding was analyzed with a Tau aggregation assay (Cisbio) as signal ratio (665/620 nm). Data are shown as bar graphs with mean + SEM (n=4 per group). One-Way ANOVA followed by Dunnett's Multiple Comparison *post hoc* test compared to AD-Tau control; ***p<0.001.

SUMMARY and CONCLUSION

The here presented *in vitro* systems for tau seeding and uptake are suitable to screen for the activity of compounds that block tau propagation.

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