α-Tubulin Post-translational Modifications as Potential Translational Biomarkers in Major Depressive Disorder

Shani Waninger, Aimée Freeburn, John Kealy, Massimiliano Bianchi

Ulysses , Cherrywood Business Park, Dublin, Republic of Ireland.

ULYSSES NEUROSCIENCE

Introduction

Neuronal microtubules (MTs) are cytoskeletal protein elements, which are comprised of the tightly regulated polymerization of α- and β-tubulin dimers, both of which are subject to post-translational modifications (PTMs). Neurons possess two compartmentalized pools of MTs, less and more dynamic, and α-tubulin PTMs such as tyrosination and acetylation are associated with the dynamic status. Increased levels of MT dynamics are required for structural neuronal plasticity phenomena. α-Tubulin acetylation at Lys40, tyrosination and detyrosination at the C-terminus generate Acet-Tub, Tyr-Tub and Glu-Tub respectively, which are hallmarks of less or more dynamic MTs. Specifically, increases in the Acet/total α-tubulin ratio and decreases in the Tyr/Glu-Tub ratio indicate a shift towards less dynamic MTs.

Dysregulation of α-tubulin PTMs may be associated with neuropsychiatric disorders characterized by synaptic pathology, including major depressive disorder (MDD). Previous studies indicate decreased brain microtubule dynamics in animal models of depression which can be rescued by antidepressant treatment (Barbiero et al., 2022). Recent data show decreased plasma Acet-Tub in healthy volunteers treated acutely with the antidepressant dose of ketamine (Colic et al., 2019).

Methods

Clinical Study

Plasma samples were obtained from psychiatric clinic in Regensburg (Germany). Patients were under no anti-depressant treatment regime before at the time of plasma sampling. α-Tubulin PTM ratios (Ace-Tub/Tot-Tub; Tyr-Tub/Glu-Tub) were measured using infrared western blot (IFWB) in plasma of subjects diagnosed with moderate (N=37) or severe MDD (N=35) and compared with healthy controls (N=40).

Post-mortem Study

Post-mortem hippocampus samples from MDD patients and healthy controls were provided by the Stanley Medical Research Institute. The treatments and the specific time of brain removal are unknown. A comparison of post-mortem hippocampal brain tissue α-tubulin PTM ratios of MDD subjects (N=12) and healthy controls (N=8) was performed using IFWB.

References

Barbiero I, Bianchi M, Kilstrup-Nielsen C. Therapeutic potential of pregnenolone and pregnenolone methyl ether on depressive and CDKL5 deficiency disorders: Focus on microtubule targeting. J Neuroendocrinol. 2022 Feb;34(2):e13033.

Colic L, McDonnell C, Li M, Woelfer M, Liebe T, Kretzschmar M, Speck O, Schott BH, Bianchi M, Walter M. Neuronal glutamatergic changes and peripheral markers of cytoskeleton dynamics change synchronically 24 h after sub-anaesthetic dose of ketamine in healthy subjects. Behav Brain Res. 2019 Feb 1;359:312-319.

Results

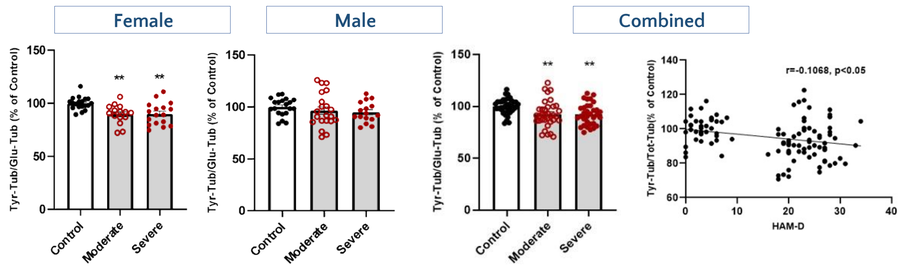

Figure 1. Tyrosinated α-tubulin is decreased in subjects diagnosed with MDD . (A) Tyr-Tub/Glu-Tub was significantly decreased in the plasma of moderate and severe female MDD subjects compared with healthy controls ($p<0.01$), but not in males. **(B)** Combined Tyr-Tub/Glu-Tub was significantly lower in the plasma of moderate and severe MDD subjects compared with healthy controls ($p<0.01$). Tyr-Tub/Glu-Tub was significantly negatively correlated with HAM-D score clinical depression score ($r=-0.1068$, $p<0.05$).

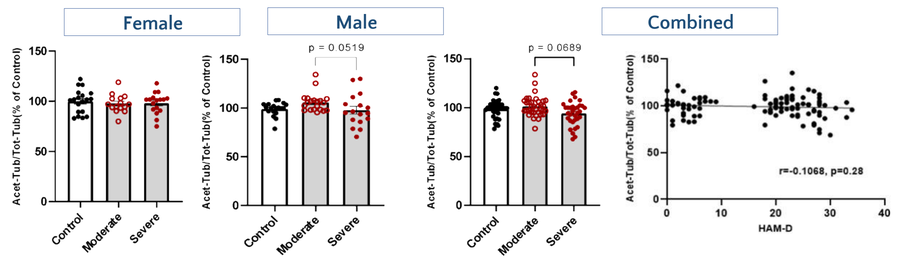

Figure 2. Acetylated α-tubulin is decreased in subjects diagnosed in MDD. Subjects diagnosed with severe MDD showed a trend towards lower plasma Acet-Tub/Total-Tub compared with moderate patients for both male ($p=0.05$) and combined cohorts ($p=0.07$).

Conclusions

The decrease in plasma and post-mortem tissue Tyr-Tub/Glu-Tub in MDD subjects indicates that they have less dynamic microtubules. Less dynamic MTs are associated with reduced synaptic plasticity and behavioral and cognitive impairments. The increase in post-mortem Acet-Tub supports decreased MT dynamics although there is a trend of a decrease in plasma Acet-Tub. Together, the data suggest a potentially dysfunctional MT state, even if not clearly defined, and the association with MTs adopting a less dynamic state in MDD α-tubulin. α-Tubulin PTMs represent a potential plasma biomarker of disease progression in neuropsychiatric disease and MTs may serve as a novel therapeutic target.

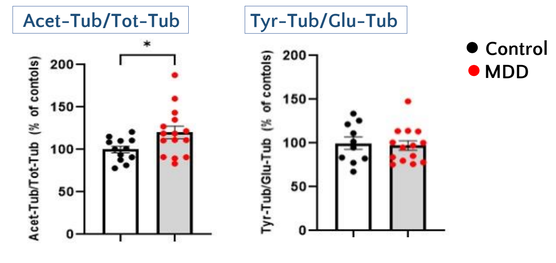

Figure 3. Acetylated α-tubulin is increased in the post-mortem orbitofrontal cortex of subjects diagnosed with MDD. The post-mortem orbitofrontal cortex of MDD subjects had a significant increase in Acet-Tub/Tot-Tub compared to healthy samples ($p<0.05$). No difference in Tyr-Tub/Glu-Tub was observed.

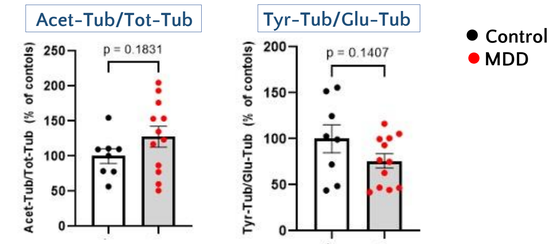

Figure 4. Acetylated α-tubulin is increased and tyrosinated α-tubulin is decreased in the post-mortem hippocampus of subjects diagnosed in MDD. Post-mortem analysis of the hippocampus of MDD subjects showed a trend towards increased Acet-Tub/Tot-Tub and decreased Tyr-Tub/Glu-Tub compared to healthy samples.

Contact

Please contact us for more information on our clinical and pre-clinical biomarker services.

Email: shani.waninger@ulysses-neuro.com

Phone: 858-342-5044

vCard

Poster