Ketamine and not fluoxetine demonstrates antidepressant efficacy in the Wistar Kyoto rat accompanied by distinct effects on microtubular proteins: identification of a novel plasma biomarker.

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The Innovation Hub for the Neurobiology of Cognition, Mood and Aging

INTRODUCTION

- Alteration in the expression of microtubular proteins associated with microtubule dynamics and neuronal plasticity has been linked with the pathogenesis and treatment of major depressive disorder (MDD).
- Acetylated α-Tubulin (Acet-Tub) associates with less dynamic microtubules and was found to be increased in the hippocampus in a rat model of depression [1] as well as by a single injection of the Selective Serotonin Reuptake Inhibitor (SSRI) fluoxetine [2]. In contrast, chronic fluoxetine decreased it.
- One third of MDD patients are unresponsive to antidepressant drugs, a recognised subtype of MDD known as treatment resistant depression (TRD).
- Ketamine is an anaesthetic and recreational drug and the only effective drug in TRD when used at sub-anesthetic dosage.
- To date no biomarker of disease or pharmacological efficacy has been identified in TRD.
- The endogenous 'depressed' Wistar Kyoto (WKY) rat is unresponsive to SSRIs and was used here as a purported model of TRD.
- **Aim: To investigate the antidepressant efficacy of ketamine compared with fluoxetine (SSRI) in the WKY rat model of TRD and to explore the feasibility of plasma Acet-Tub as biomarker in TRD.**

METHODS

Forced Swimming Test (FST): Male WKY rats (approx. 200g) were administered either fluoxetine (10 mg.kg^{-1}, i.p.), ketamine (5 mg.kg^{-1}, i.p.) or corresponding vehicle solution (0.9% saline i.p.). Depressive-like behaviour (i.e. immobility) was then tested in the FST 30 min and 7 days post drug administration and compared with 'healthy' Sprague-Dawley (SD) rats. FST was performed as previously described [3]. WKY rats demonstrate spontaneous immobility in the FST compared with SD rats [4], therefore no pre-test was required.

Infrared Western Blotting (IFWB): Twenty-four hours after each FST exposure plasma was isolated. The expression of plasma Acet-Tub was measured using a protocol of IFWB adapted from previous studies [1].

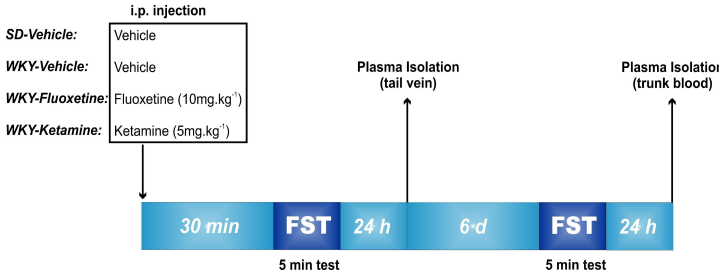

Figure 1. Experimental design

CONCLUSION

- Acute ketamine demonstrates a rapid and long-lasting antidepressant efficacy in WKY rats, fluoxetine has no effect.
- WKY rats exhibit consistent overexpression of plasma Acet-Tub in line with the previous observed decreased hippocampal microtubular dynamics [5].
- Acute fluoxetine augments plasma Acet-Tub expression in WKY rats, an effect previously observed in the hippocampus of Lister hooded rats [2].
- Ketamine has no effect on plasma Acet-Tub in this experiment, however subsequent refined studies demonstrated a replicable decrease in plasma Acet-Tub expression in WKY rats following ketamine treatment (Prenderville *et al.,* manuscript in preparation).
- **Plasma Acet-Tub may represent a potential biomarker of disease progression and treatment responsiveness in TRD.**
- **Acet-Tub is currently being analysed in plasma from a cohort of TRD patients to explore translational potential of this discovery.**

REFERENCES

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RESULTS

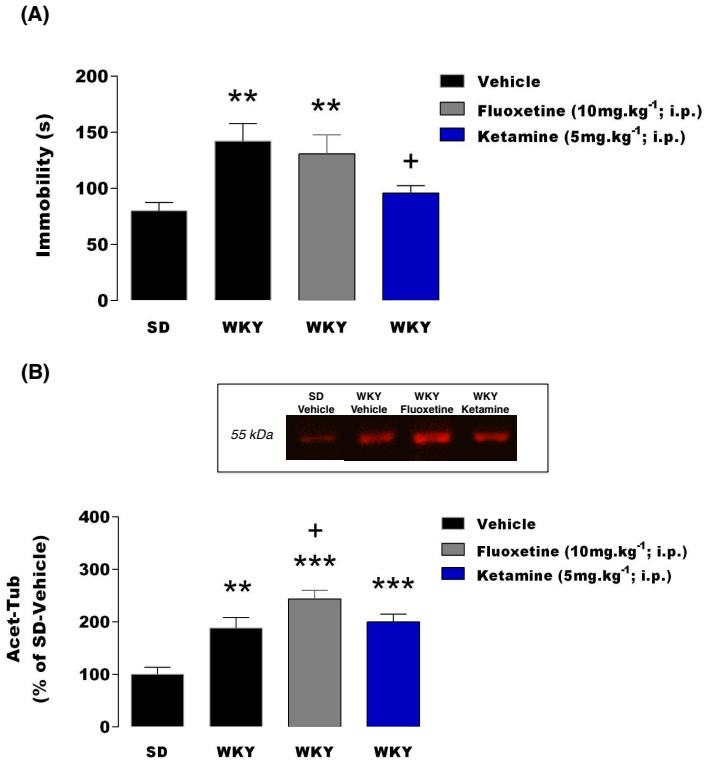

Figure 2. Immobility in FST 30 min post drug administration and plasma Acet-Tub expression 24 h post drug administration

*(A) WKY-Vehicle and WKY-Fluoxetine exhibited increased immobility in the FST compared to SD-Vehicle (**p<0.01). Immobility was significantly reduced in WKY-Ketamine compared to WKY-Vehicle (+p<0.05). (B) WKY-Vehicle, WKY-Fluoxetine and WKY-Ketamine overexpressed plasma Acet-Tub compared with SD-Vehicle (**p<0.01, ***p<0.001). Acet-Tub overexpression was augmented in WKY-Fluoxetine (+p<0.05). One-way ANOVA, Fisher's LSD. Data: Mean ± SEM.*

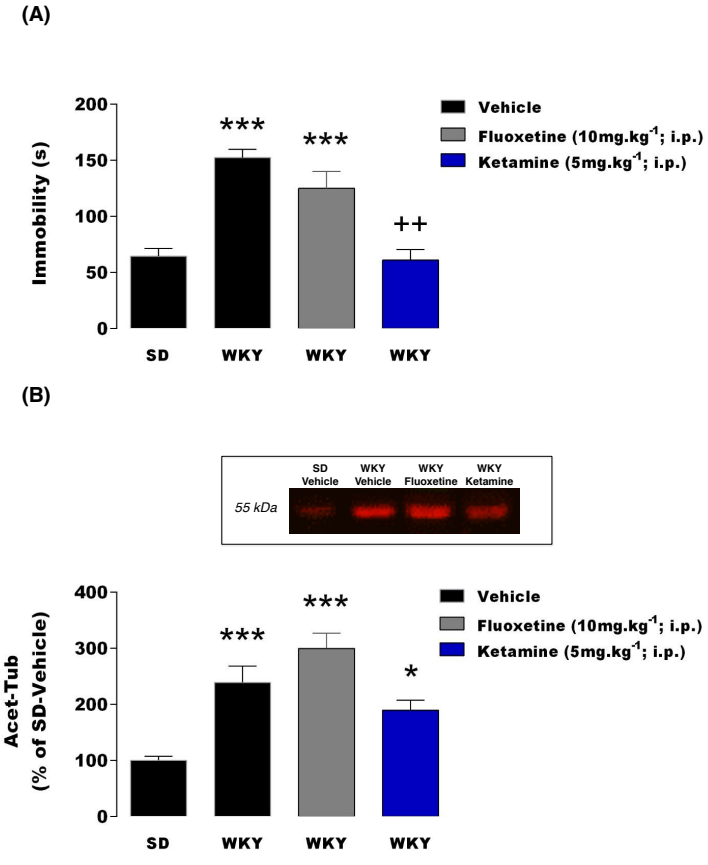

Figure 3. Immobility in FST 7 days post drug administration and plasma Acet-Tub expression 8 days post drug administration

*(A) WKY-Vehicle and WKY-Fluoxetine exhibited increased immobility in the FST compared to SD-Vehicle (***p<0.001). Immobility was significantly reduced in WKY-Ketamine compared to WKY-Vehicle (++p<0.01). (B) WKY-Vehicle, WKY-Fluoxetine and WKY-Ketamine overexpressed plasma Acet-Tub compared with SD-Vehicle (*p<0.05, ***p<0.001). One-way ANOVA, Fisher's LSD. Data: Mean ± SEM.*