Ketamine and 3β-Methoxy-pregnenolone exhibit an antidepressant effect in the endogeneously 'depressed' Wistar Kyoto rat: a microtubular mechanism?

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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) is associated with less microtubule dynamics. Acet-Tub is increased in the rat hippocampus by models of depression [1] and by a single injection of the Selective Serotonin Reuptake Inhibitors (SSRI) fluoxetine, while chronic fluoxetine decreased it [2]
- The classic steroid-derivative 3β-Methoxy-pregnenolone (MePreg) was recently assessed as a neuronal microtubule modulator showing preclinical antidepressant efficacy [1].
- One third of MDD patients are unresponsive to antidepressant drugs, a recognized 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.
- No biomarkers of disease or pharmacological efficacy have been identified so far 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 MePreg compared with ketamine in the WKY rat model of TRD and to explore the feasibility of plasma Acet-Tub of disease progression.**

METHODS

Forced Swimming Test (FST): Male WKY rats (approx. 200g) were administered either MePreg (10 mg.kg^{-1}, s.c.), ketamine (5 mg.kg^{-1}, i.p.) or corresponding vehicle solutions (0.9% saline i.p. and sesame oil, s.c.). Depressive-like behaviour (i.e. immobility) was then tested in the FST 90 (MePreg) or 30 (Ketamine) min and 7 days post drug administration and compared with 'healthy' Sprague-Dawley (SD) rats. FST was performed as previously described [3], but 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].

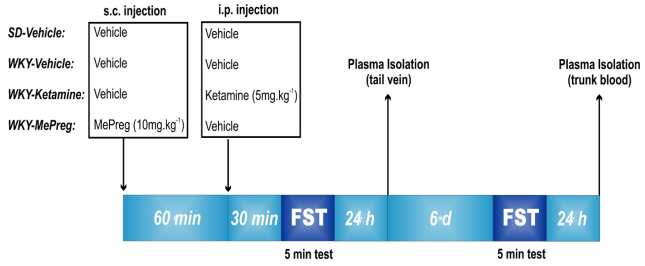

Figure 1. Experimental design

CONCLUSION

- Ketamine and MePreg demonstrate a rapid antidepressant efficacy in WKY rats in the first FST exposure.
- The antidepressant efficacy of ketamine is also observed in the second FST exposure at 7 days post-administration suggesting an apparent long lasting efficacy, while MePreg has no effect.
- WKY rats exhibit overexpression of plasma Acet-Tub in line with the previous observed decreased hippocampal microtubular dynamics [5].
- Ketamine and MePreg demonstrate temporal attenuation of plasma Acet-Tub overexpression consistent with the temporal profile of their antidepressant efficacy.
- **Microtubular proteins represent a novel therapeutic target for future drug development in TRD and a potential biomarker of disease progression.**

REFERENCES

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RESULTS

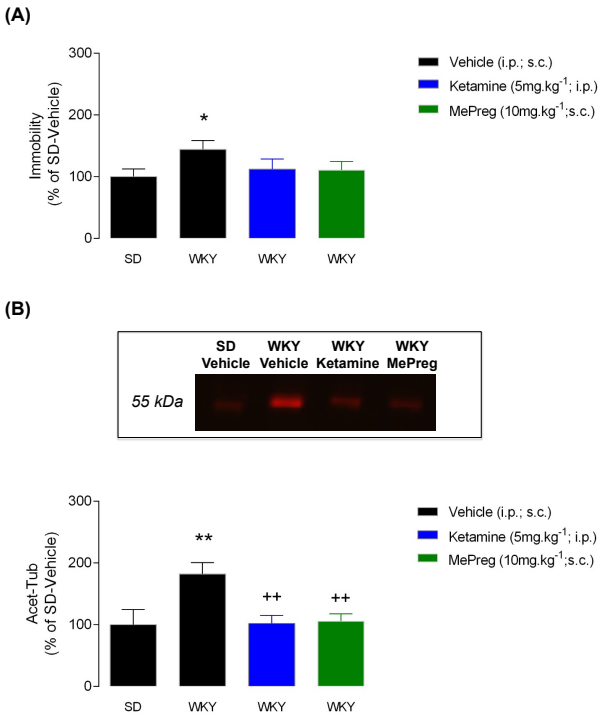

Figure 2. Immobility in FST 30 min post drug administration and plasma Acet-Tub expression 24 h post drug administration

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

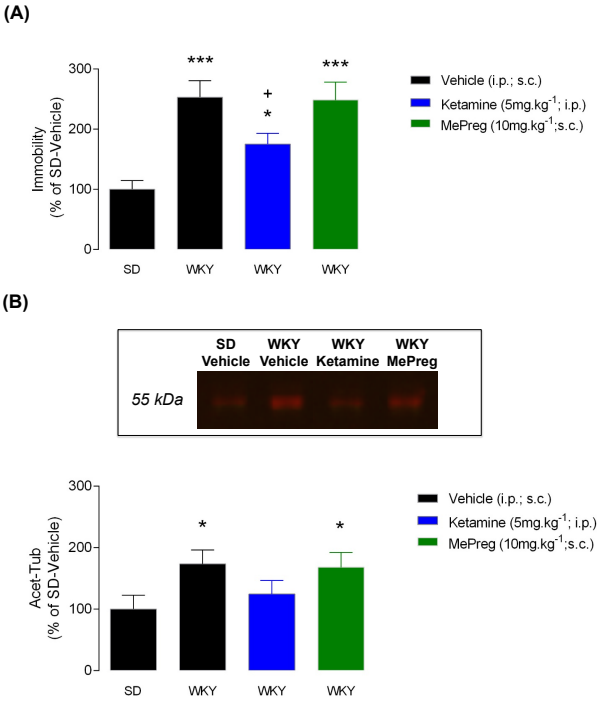

Figure 3. Immobility in FST 7 days post drug administration and plasma Acet-Tub expression 8 days post drug administration

*(A) WKY-Vehicle, WKY-Ketamine and WKY-MePreg exhibited increased immobility in the FST compared to SD-Vehicle; (***p<0.001, *p<0.05). WKY-Ketamine exhibited reduced immobility compared to WKY-Vehicle (*p<0.05). (B) WKY-Vehicle and WKY-MePreg overexpressed plasma Acet-Tub expression compared with SD-Vehicle (*p<0.05). One-way ANOVA, Fisher's LSD. Data: Percentage of SD-Vehicle Mean ± SEM.*