3β-Methoxy-pregnenolone exerts antidepressant efficacy in 'depressed' Wistar-Kyoto rats and in aged Wistar rats

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INTRODUCTION

- The antidepressant efficacy of 3β-Methoxy-pregnenolone (MePreg) was firstly shown in psychiatric patients in 1950's [1] and [2].
- Later it was shown that MePreg is a neuronal microtubule modulator exerting consistent antidepressant efficacy in animal models [3].
- More efficacious antidepressant drugs are required for the treatment of two subpopulations of depressed patients, namely treatment resistant depression (TRD) and depression in the aged population.
- Ketamine is an anaesthetic and recreational drug and the only effective drug for use in TRD when used at a sub-anaesthetic dose.
- The endogenous 'depressed' Wistar Kyoto (WKY) rat is unresponsive to SSRIs and was used here as a purported model of TRD.
- Fluoxetine is a selective serotonin uptake inhibitor (SSRI) that is used as first line treatment of depression in the aged population.

- **Aim 1: To investigate the antidepressant efficacy of MePreg compared with ketamine in the WKY rat model of TRD.**
- **Aim 2: To investigate the antidepressant efficacy of MePreg compared with fluoxetine in the aged rodent.**

METHODS

Efficacy of MePreg in TRD Assay: Male WKY rats (approx. 100g) were administered either ketamine (5 mg.kg^{-1}; i.p.), MePreg (10 mg.kg^{-1}; s.c.), or corresponding vehicle solutions (sesame oil, 0.25ml.rat^{-1}; s.c. and 0.9% saline 1ml.kg^{-1}; i.p.). Depressive-like behaviour (i.e. immobility) was tested in the forced swimming test (FST, 5 min test) 30 min post drug administration and compared with 'healthy' Sprague-Dawley (SD) rats. FST was performed as previously described [4], but WKY rats demonstrate spontaneous immobility in the FST compared with SD rats [5], therefore no pre-test was required.

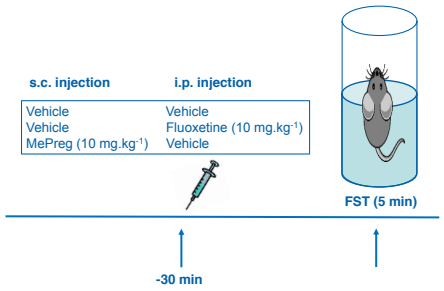

Figure 1. Experimental Design 1

Efficacy of MePreg in Depression and Aging Assay: Young (3-4 mth; approx. 200g) and aged (24-25 mth; approx. 640g) male WIS rats were exposed to the pre-swim FST (15 min test) and were administered either fluoxetine (10 mg.kg^{-1}; i.p.), MePreg (10 mg.kg^{-1}; s.c.), or corresponding vehicle solutions (sesame oil, 0.25ml.rat^{-1}; s.c. and 0.9% saline 1ml.kg^{-1}; i.p.) 24, 5 and 1 hr prior to FST (5 min test).

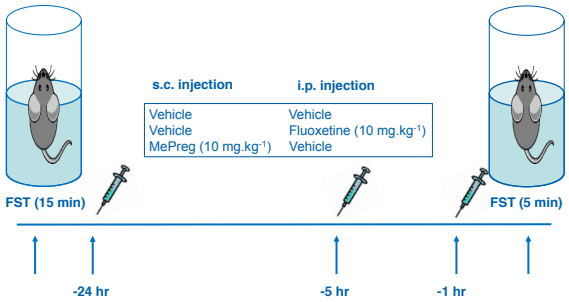

Figure 2. Experimental Design 2

CONCLUSION

- Ketamine and MePreg show similar and rapid antidepressant efficacy in WKY rats.
- Aged rats have a "natural" depressive-like phenotype in the FST. MePreg displays antidepressant efficacy in both young and aged WIS, to a level comparable to the SSRI fluoxetine.
- **MePreg represents a tool compound for the development of novel antidepressant drugs, with a novel mechanism of action, for the treatment of both TRD and depression in the aged population.**

RESULTS

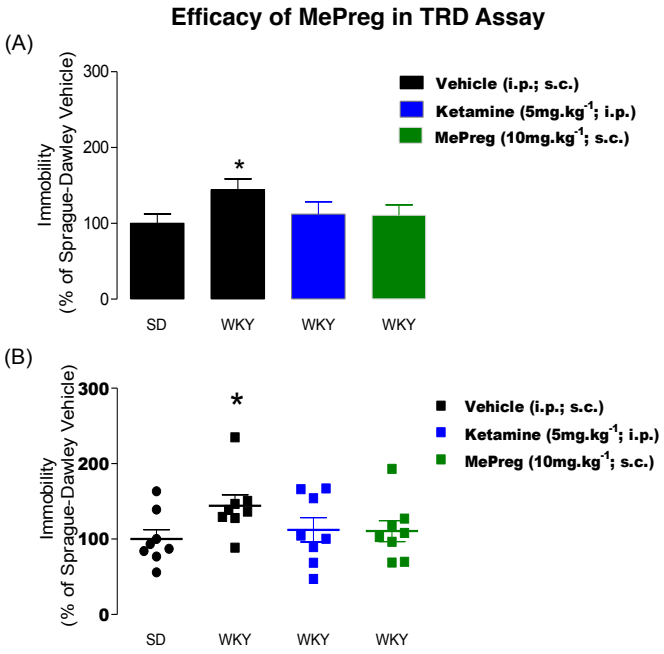

Figure 3. Immobility in FST 30 min post drug administration
*(A) WKY Vehicle exhibited increased immobility in the FST in comparison to SD Vehicle (*p<0.05). (B) Individual data for the treatment groups.*
Data: Percentage of SD Vehicle, Mean ± SEM (n=8).

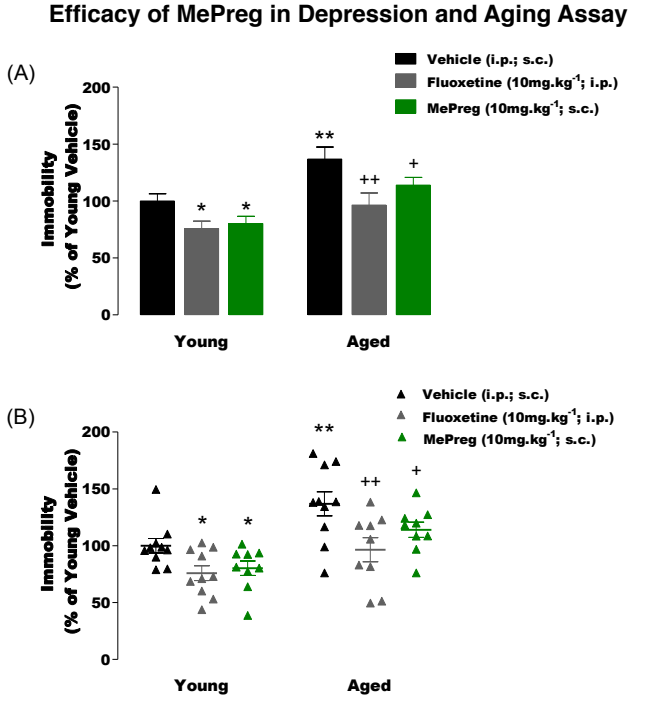

Figure 4. Immobility in FST 1 hr following final drug administration
*(A) Aged Vehicle treated rats exhibited increased immobility in the FST in comparison to Young Vehicle treated rats (**p<0.01). Fluoxetine and MePreg decreased immobility time in the FST (*p<0.05) in Young rats and attenuated the increased immobility time (+p<0.05; ++p<0.01) observed in Aged rats. (B) Individual data for the treatment groups.*
Data: Percentage of Young Vehicle, Mean ± SEM (n=9-10).

REFERENCES

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