Transpharmation

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Effect of acute and chronic antidepressant treatment on the Wistar Kyoto in forced swim test and on corticosterone expression

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Introduction

The link between HPA axis dysregulation and depressive behaviour has long been established. An increase in circulating cortisol or corticosterone (CORT) brought on by stress has been directly linked to the onset of depressive symptoms. In preclinical studies, it has been demonstrated that chronic CORT injections increase immobility in the Forced Swim Test (FST), a popular paradigm for assessing antidepressant efficacy in rodents. Furthermore, chronic exposure to CORT through direct injection or by stress leads to a heightened state of stress masking effects of acute stressors, such as the FST, on CORT[1].

Here, Sprague Dawley (SD) rats are used as a control strain and Wistar Kyoto (WKY) rats as a "depressed" strain in a FST paradigm. SD rats have been used extensively in FST studies with their behaviour being well characterised compared to WKY[2]. Fitting as a "healthy" control, SDs have a lower baseline and reactivity CORT levels compared to WKY[3].

Aim: To compare acute and chronic antidepressant treatments in the FST and on CORT expression in SD and WKY rats. To answer if behavioural endpoints in these animals are analogous to CORT expression.

Table 1. Summary of treatments and dosing regimen

	Vehicle	ESC Acute	DMI Acute	ESC Chronic	DMI Chronic	PME	Ketamine
Dose	VEH 1 + VEH 2	10mg/kg s.c. +VEH 2	10mg/kg s.c. + VEH 2	10mg/kg s.c. + VEH 2	10mg/kg s.c. + VEH 2	10mg/kg s.c. + VEH 1	5mg/kg s.c. + VEH 2
Class	N/A	SSRI	TCA	SSRI	TCA	Neurosteroid derivative	Anaesthetic
Days	1-21	21 (VEHs 1-20)	21 (VEHs 1-20)	1-21	1-21	21 (VEHs 1-20)	21 (VEHs 1-20)
Primary Action	N/A	Reuptake inhibitor (SERT)	Reuptake inhibitor (NET)	Reuptake inhibitor (SERT)	Reuptake inhibitor (NET)	Microtobule dynamics modulator	NMDAR Antagonist

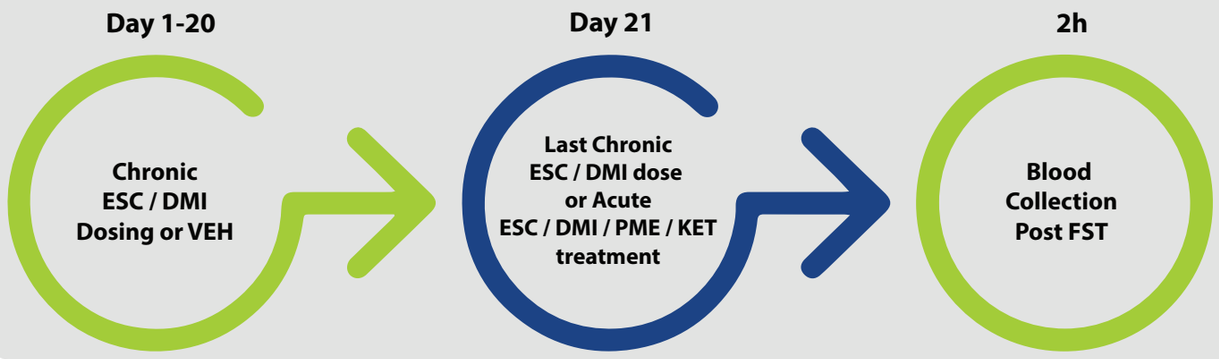
Methods

Male SD and WKY rats 3-4 months old, 350-400g, housed 2-3/cage, 12-hour day/night cycle, food/water ad lib.

Randomly assigned groups (n=10) were administered chronically (daily for 21 days) with Escitalopram (10mg/kg,s.c.), Desipramine (10mg/kg,s.c.), or corresponding vehicle solution (Injectable water,s.c.). Pregnenolone-Methyl-Ether (PME; 10mg/kg,s.c.), Ketamine (5mg/kg,s.c.), Escitalopram, or Desipramine were administered acutely on day 21 to rats receiving daily injection of vehicles for 20 days. PME's vehicle is sesame oil, therefore all rats received an additional daily administration of sesame oil, s.c. On day 21, animals were sacrificed 2h post treatment and plasma was obtained from trunk blood.

On day 21, FST was performed 2h following last administration of treatments. No pre-test session was required as WKYs exhibit spontaneous immobility in the FST. Naïve SD and WKY rats (n=4/strain) were included in the analysis to confirm elevated CORT.

Total time spent immobile (sec) in the FST was determined by stopwatch. Blood plasma CORT (ng/ml) was measured by ELISA (ENZO Life Science). Two-way ANOVA with blocking factor followed by planned comparisons were conducted in InVivo Stat and are represented as Mean±SEM.



Conclusions

While some of the antidepressant treatments are efficacious in reducing immobility in this FST paradigm, this does not occur concomitantly with a similar reduction in CORT as might be expected. Furthermore, it is evident that CORT expression in blood plasma is not as sensitive a measure for antidepressant efficacy as the FST, at least with this dosing regimen.

References

[1] Johnson SA, Fournier NM, Kalynchuk LE: Effect of different doses of corticosterone on depression-like behavior and HPA axis responses to a novel stressor. Behav Brain Res 2006;168:280–288.
[2] López-Rubalcava C, Lucki I: Strain differences in the behavioral effects of antidepressant drugs in the rat forced swimming test. Neuropsychopharmacology 2000;22:191–199.
[3] Carere C, Maestripieri D: Animal personalities: Behavior, physiology and evolution. 2013.

Results

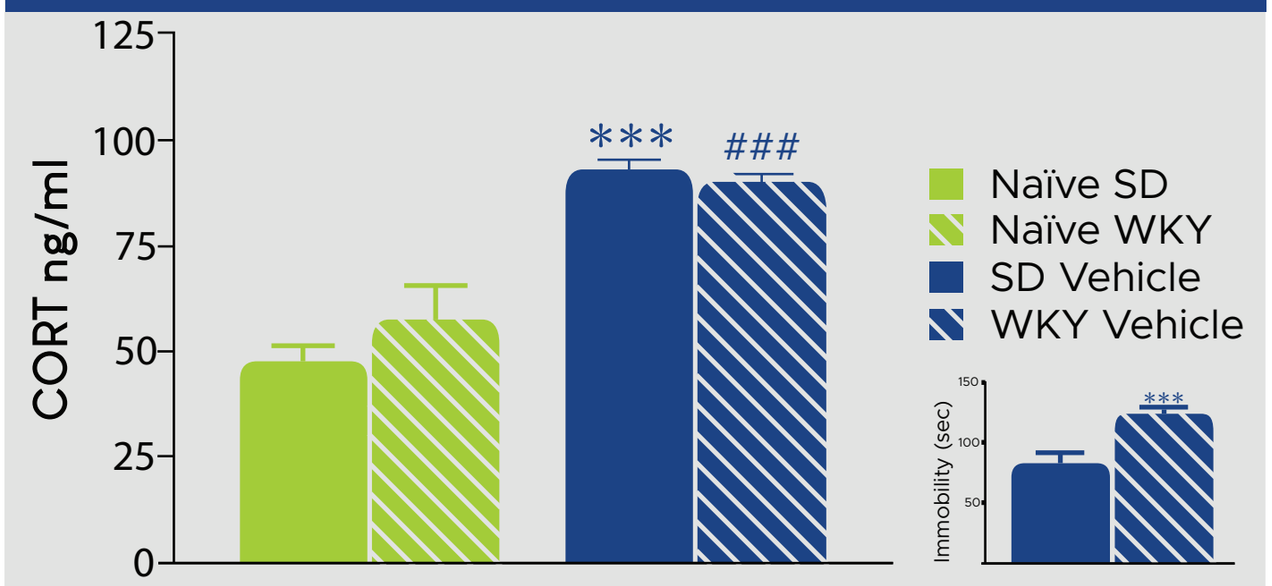


Figure 1. Test animals show higher plasma CORT than naïve animals.
Experimental vehicle SD and WKY rats showed higher plasma CORT expression compared to naïve animals (***p<0.001 vs Naïve SD, ###p<0.001 vs Naïve WKY). INSET: *WKY rats exhibit higher immobility in the FST compared to SD (***p<0.001 vs SD Vehicle).*

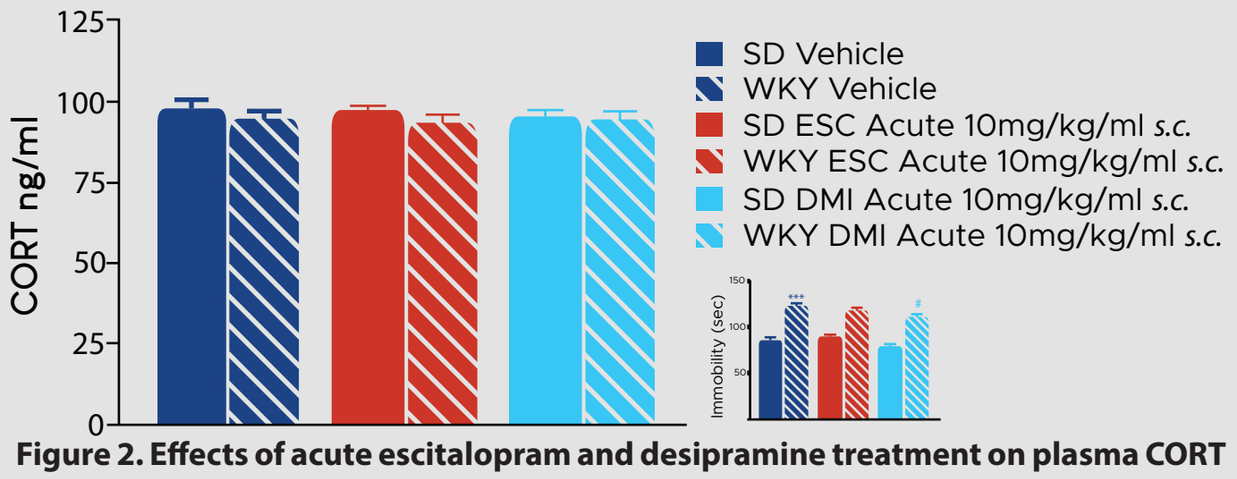


Figure 2. Effects of acute escitalopram and desipramine treatment on plasma CORT in SD and WKY rats.
No significant differences were found between animals treated acutely with escitalopram or desipramine and corresponding vehicle groups. INSET: *WKY rats treated acutely with desipramine showed a significant reduction in immobility compared to vehicle (#p<0.05 vs WKY Vehicle).*

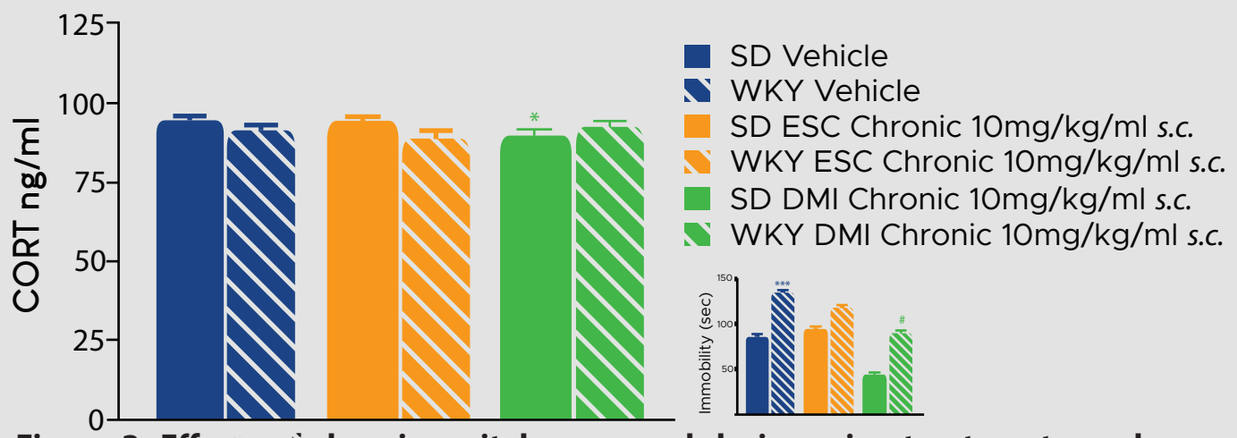


Figure 3. Effects of chronic escitalopram and desipramine treatment on plasma CORT in SD and WKY rats.
SD rats treated chronically with desipramine showed significantly reduced plasma CORT compared to vehicle (*p<0.05 vs SD Vehicle). Chronic escitalopram showed no effect on plasma CORT for either strain. INSET: *Chronic Desipramine treated animals showed significantly reduced immobility in both SD (***p<0.001 vs SD Vehicle) and WKY (###p<0.001 vs WKY Vehicle).*

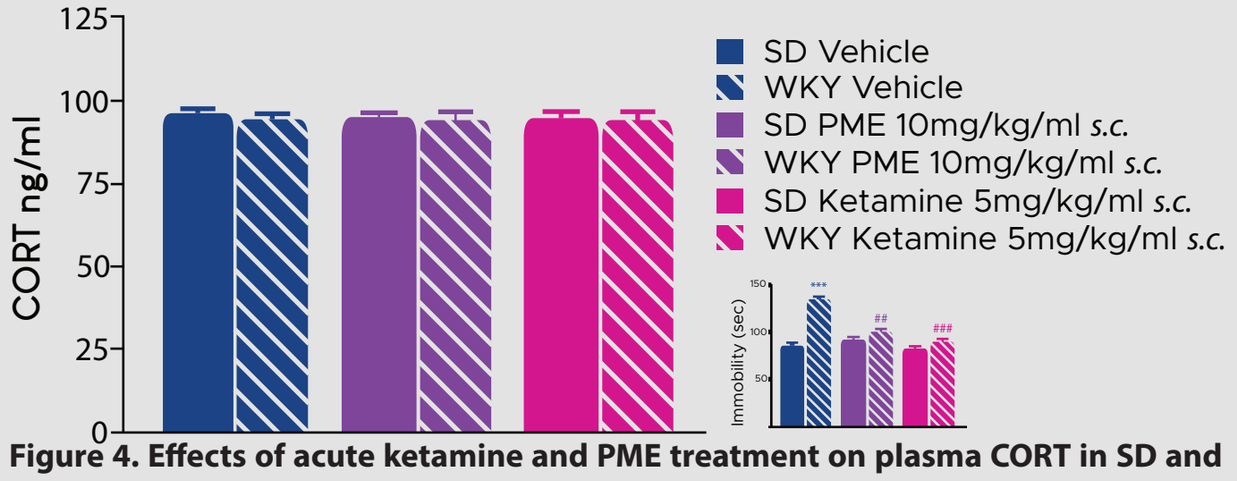


Figure 4. Effects of acute ketamine and PME treatment on plasma CORT in SD and WKY rats.
No Significant differences were found in plasma CORT expression between ketamine and PME treated animals and their corresponding vehicle group. INSET: *Acute-Ketamine (###p<0.001 vs WKY Vehicle) and Acute-PME (##p<0.01 vs WKY Vehicle) both significantly reduced immobility in WKY compared to vehicle.*

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