Efficacy of low doses of neuroleptic drugs on aggressive behaviour and corticosterone levels in CD-1 male mice

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Science that translates into results

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Introduction

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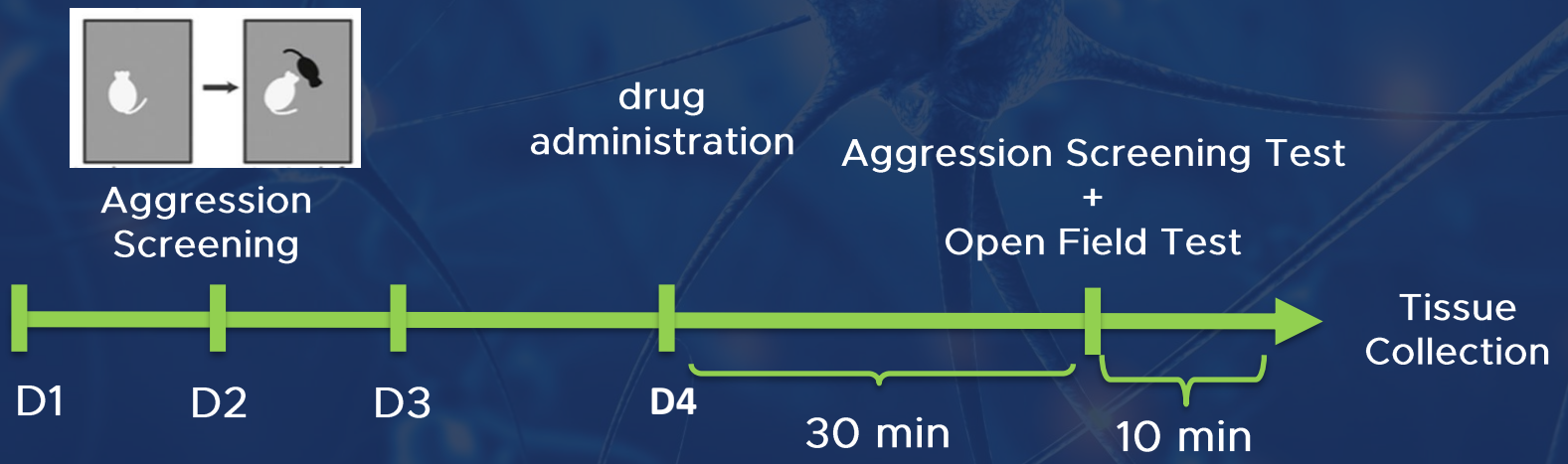
- ✓ Several psychiatric disorders are associated with increased aggression [1] resulting in impairment in social skills.
- ✓ Current treatments which target aggressive behaviour can induce sedation, affect mobility and induce idleness. Therefore, a better understanding of the behavioural and neurobiological aspects of aggression is necessary.
- ✓ Here we investigate the effects of two low doses of antipsychotic drugs: risperidone and S15535 on aggressive behaviour in the CD-1 male mice. Risperidone is an atypical antipsychotic used to treat schizophrenia [2] acting at several 5-HT (serotonin) receptor subtypes. S15535 is a highly selective 5-HT1A receptor ligand that acts as an agonist and antagonist at the pre- and post-synaptic 5-HT1A receptors, respectively.
- ✓ In addition, we are investigating if either drug affects levels of corticosterone (CORT), a hormone previously associated with aggression.

[1] Pompili E. Focus on aggressive behaviour in mental illness. Riv Psichiatr 2017; 52(5): 175-179
[2] Mathews M. et al., Long-acting risperidone in the treatment of Schizophrenia. Psychiatry 2005; 2(2): 36–39.

Methods

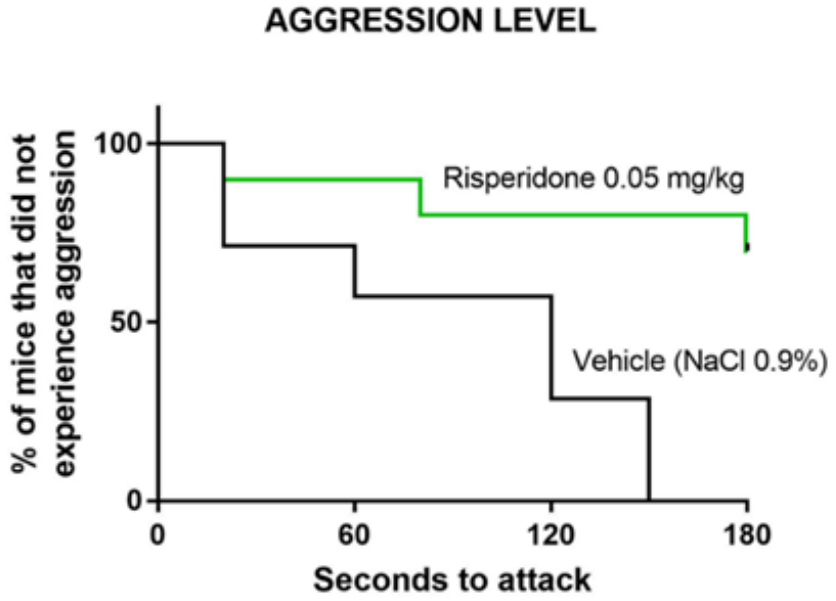
For the experimental design, **CD-1** male mice underwent 3 days of aggression screening, single trial per day. An unfamiliar intruder, **C57BL/6J** male mouse was introduced to their home cage for a maximum of 180s each day. The latency to the first attack was measured. The most aggressive subjects were selected based on the following criteria:

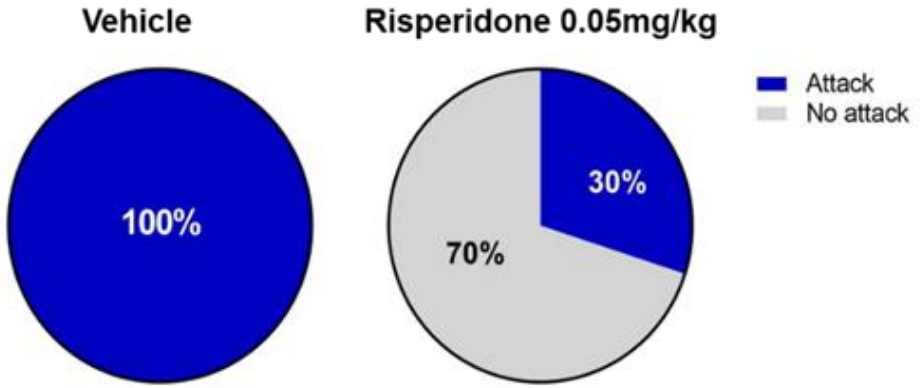
1) Mice which attacked in at least 2 consecutive sessions and the latency to attack on 2 of the sessions was < 90 seconds.
2) Mice which attacked in at least 2 consecutive sessions and latency to attack on one of the days was < 90 seconds.
3) Mice which attacked on one or more (not consecutive) sessions and the attack on Day 3 was < 90 seconds.

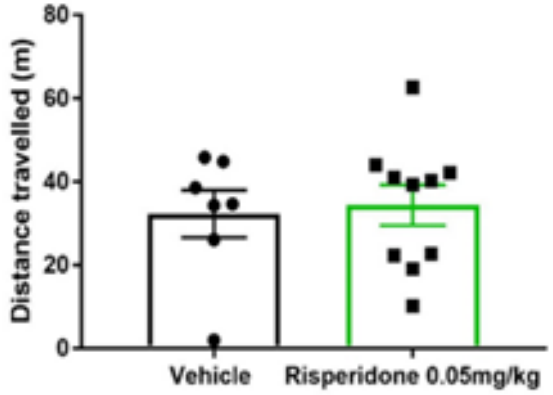


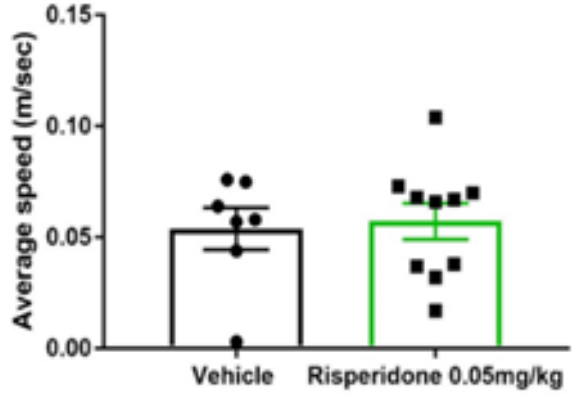
Selected CD-1 mice were then treated with vehicle, risperidone (0.05 mg/kg i.p.) or S15535 (0.5 and 2.5 mg/kg s.c.). Thirty minutes post-treatment mice underwent a single aggression screen followed by locomotor assessment in the open field. Corticosterone levels in the trunk blood were analysed in aggressive and non-aggressive mice using ELISA kit (Enzo, USA).

Effect of a low dose of risperidone on latency to attack



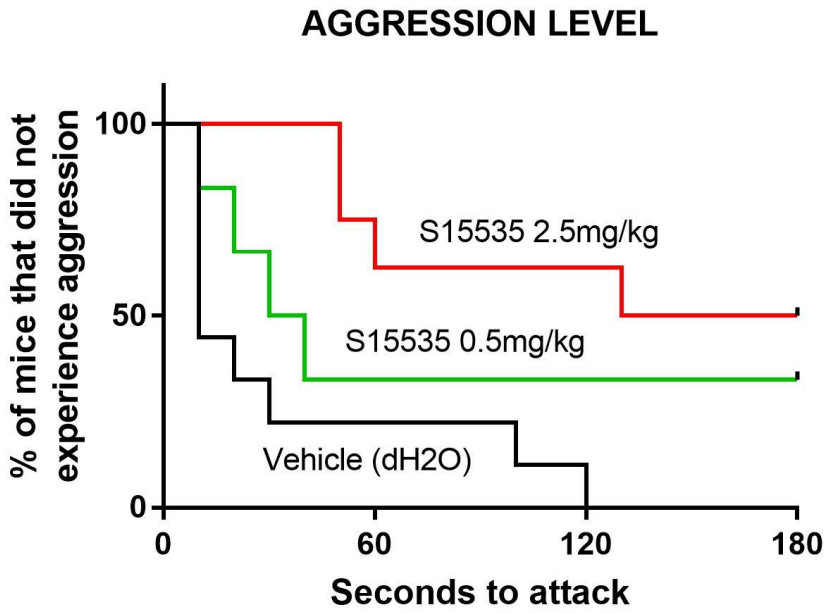


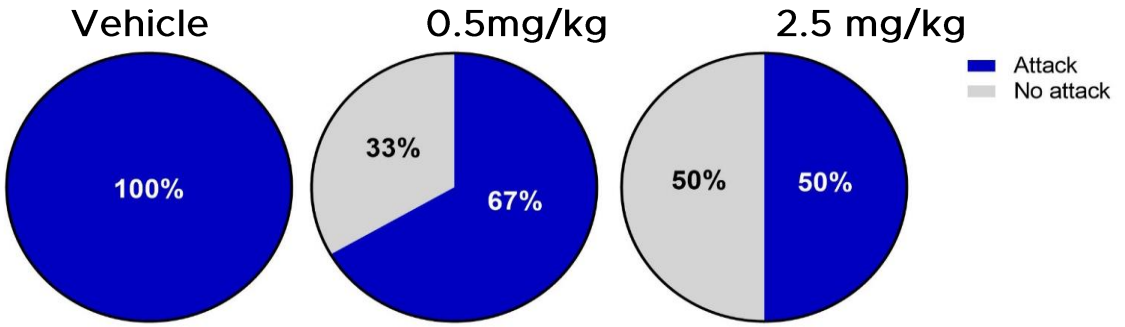


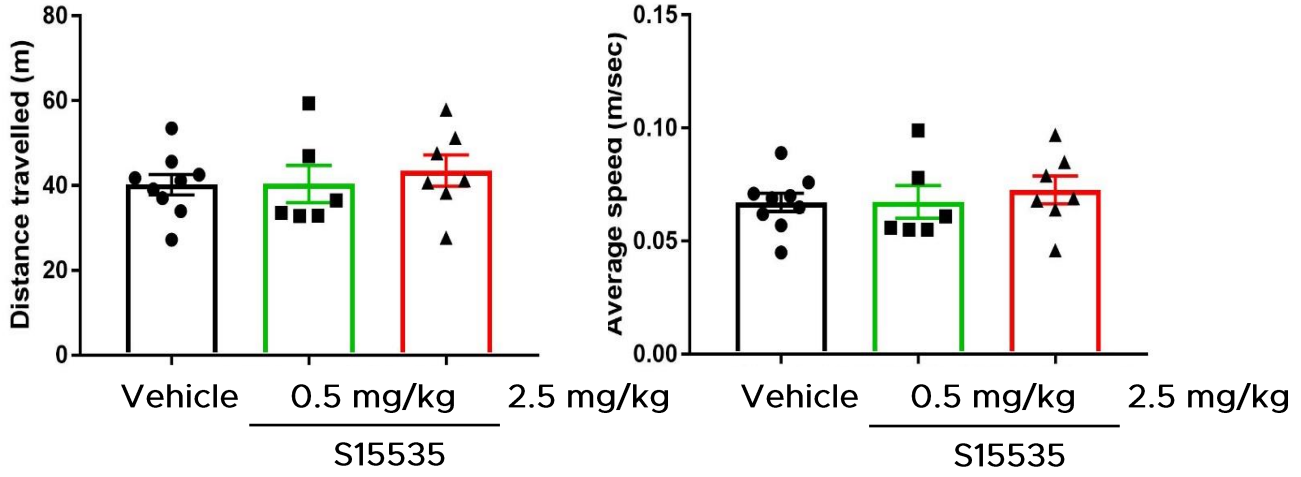


Low dose of risperidone (0.05mg/kg) significantly decreased aggression 30 min after administration. Log-rank Mantel-Cox test: Chi square = 9.9206, df = 1, ****p = 0.0024**, n = 7-10 per group. **70%** of animals after administration of the low dose of risperidone (0.05mg/kg) didn't initiate the attack. Low dose of risperidone (0.05mg/kg) has no effect on animal locomotion, Mean ± SEM.

Effect of S15535 on latency to attack



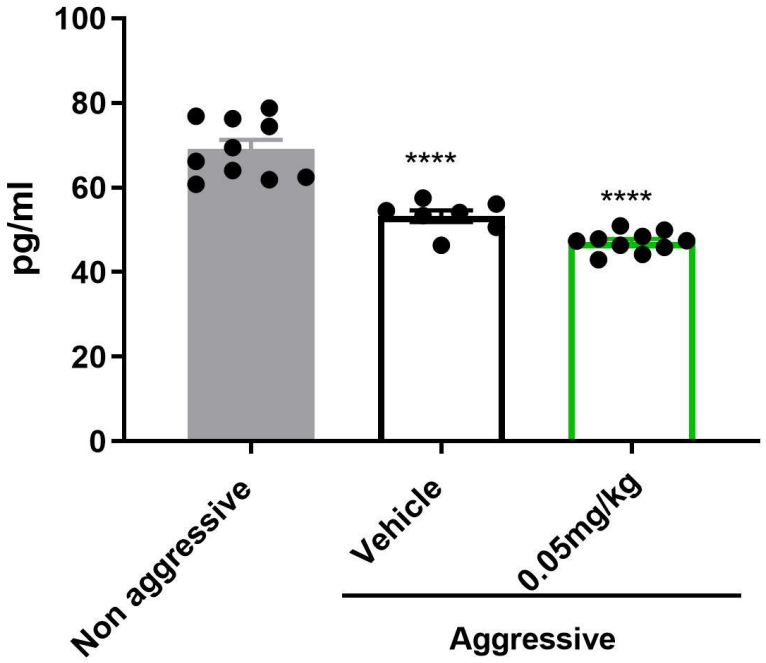




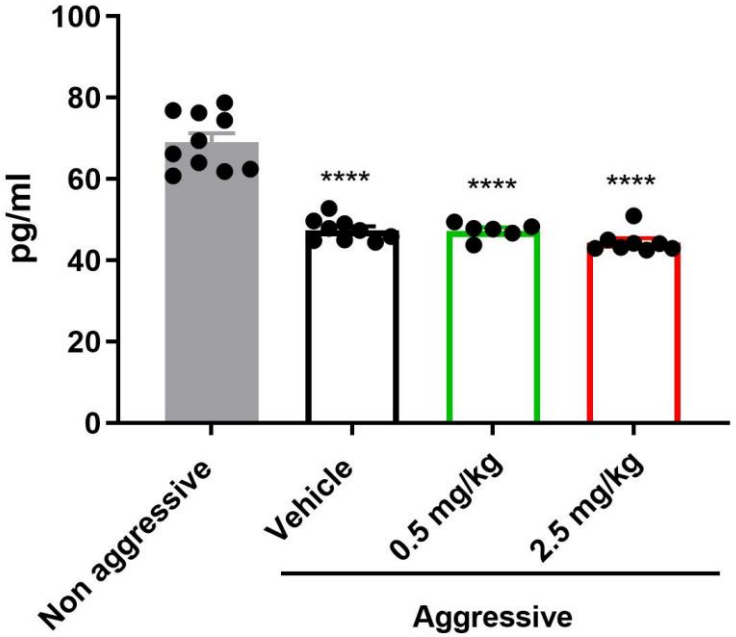
Higher dose of S15535 (2.5mg/kg) significantly decreased aggression. Log-rank Mantel-Cox test: Chi square = 9.42, df = 1, ****p = 0.0016**, n = 6-9 per group**. 33%** of animals after a lower dose and **50%** of animals after a higher dose of the S15535 didn't initiate an attack. S15535 had no effect on animal locomotion. One-way ANOVA test, mean ± SEM.

Plasma corticosterone levels in non-aggressive and aggressive CD1 mice.

Risperidone



S15535



Non-aggressive CD1 mice showed a significantly higher level of corticosterone when compared with aggressive subjects. Brown Forsythe ANOVA test; ****p<0.0001, mean ± SEM, n = 6-10 per group.

Conclusions

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- ✓ The low (0.05 mg/kg) dose of **risperidone** resulted in a significant reduction ($p<0.005$) of aggressive behaviour as measured by latency to attack and 70% of CD-1 mice did not initiate an attack post-administration.
- ✓ The higher dose of **S15535** (2.5 mg/kg) successfully reduced aggression level ($p<0.005$), 50% of CD-1 mice did not initiate an attack post-administration.
- ✓ Neither low dose of risperidone nor both doses of S15535 had any effect on the locomotor activity.
- ✓ Encounter with the “unfamiliar” mouse resulted in the stressful response in the non-aggressive CD1 males.
- ✓ Thus, the low doses of the 5-HT1A receptor modulators may represent a therapeutic target for aggressive behaviour.

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