The effect of the second generation of antipsychotic risperidone on aggressive behaviour in male CD-1 mice.

SOKOLOWSKA E[1,2], STOJEK E[2], KOZAREVA DA[2], PRENDERVILLE JA[2]
[1]Transpharmation Poland Ltd., University of Warmia & Mazury in Olsztyn, Poland, [2] Transpharmation Ireland Ltd., Trinity College Dublin, Ireland

Transpharmation
Science that translates into results

Introduction

Aggression is a serious medical problem associated with several psychiatric disorders, causing impairment of skills that are important for social, academic success, and quality of life [1]. Current treatments are severely limited and include behavioural training and a small set of psychopharmacological agents that, although widely used, are not effective. Today, aggression associated with mental disorders is largely treated with sedatives causing fatigue, immobility and induce idleness, often resulting in an inability to perform basic cognitive functions following drug administration, rather than addressing source of the symptoms.

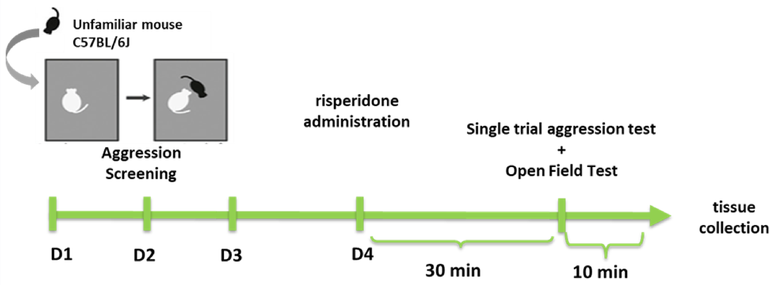
The aim of this study was to assess the anti-aggressive effect of risperidone; an atypical antipsychotic used to treat schizophrenia [2] acting at several 5-HT (serotonin) receptor subtypes.

This study was funded by Transpharmation Ltd., UK

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 in order to established aggression level. The most aggressive subjects were selected based on the following criteria:

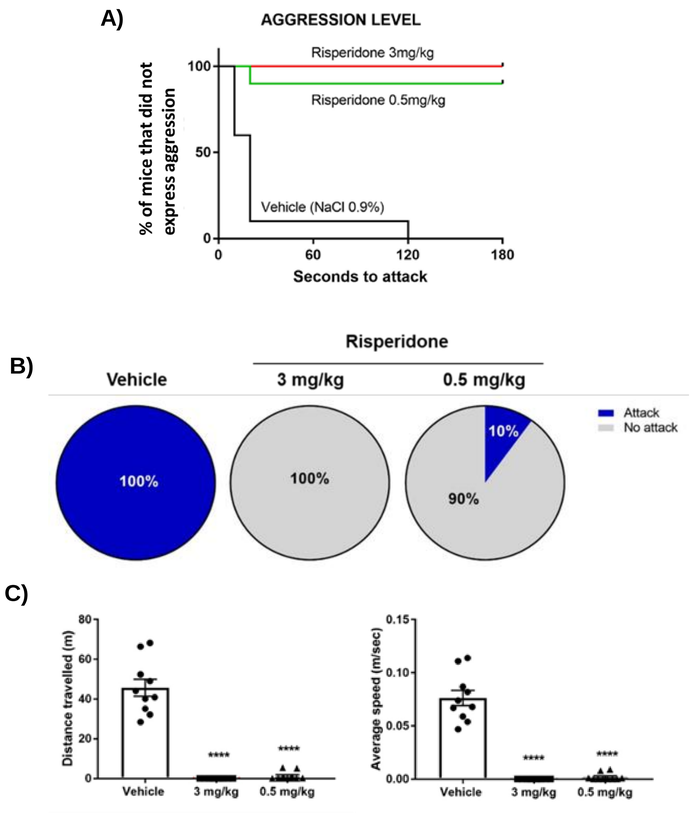
1) Mice which attacked in at least 2 consecutive sessions and the latency to attack on 2 of the sessions was < 90 seconds.
2) Mice which attacked in at least 2 consecutive sessions and latency to attack on one of the days was < 90 seconds.
3) Mice which attacked on one or more (not consecutive) sessions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



Selected **CD-1** mice were treated with vehicle (0.9% NaCl, i.p.) or risperidone (0.05, 0.5 and 3 mg/kg i.p.). Thirty minutes post-injection all mice underwent a single aggression screen to assess the efficacy of a drug followed by the locomotory assessment (ANYmaze, Stoelting Europe) in the open field.

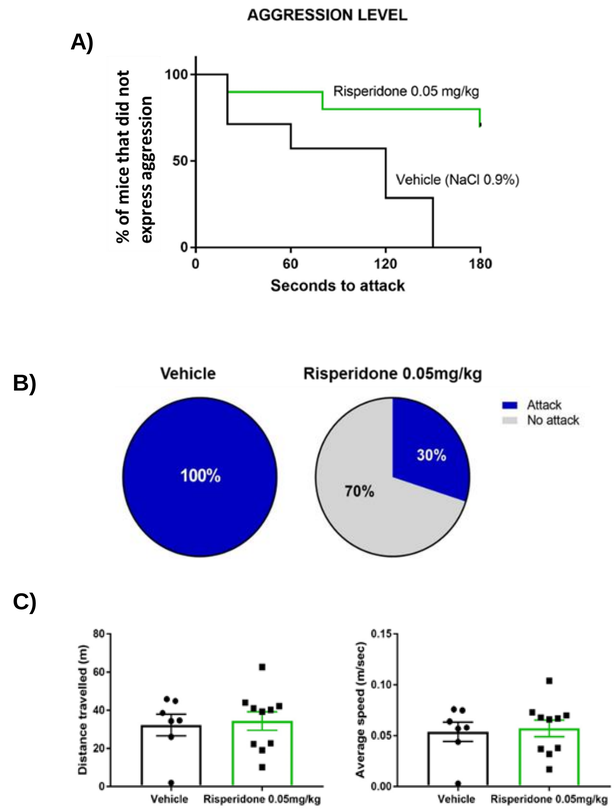
Results

Effect of high and medium doses of risperidone on latency to attack.



A) Both risperidone doses significantly decreased aggression 30 min after administration. Vehicle vs. risperidone 3 mg/kg, Log-rank Mantel-Cox test: Chi square = 20.41, df = 1, ******p <0.0001**, n =10 per group. Vehicle vs. risperidone 0.5 mg/kg, Log-rank Mantel-Cox test: Chi square = 17.07, df = 1, ******p <0.0001**, n =10 per group. **B)** High (3 mg/kg) and medium (0.5 mg/kg) dose of risperidone prevented further attacks. **C)** Both risperidone doses significantly decreased locomotor activity, ******p<0.0001**, Mean ± SEM.

Effect of a low dose of risperidone on latency to attack.



A) 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. **B) 70%** of animals after administration of the low dose of risperidone (0.05mg/kg) didn't initiate the attack. **C)** Low dose of risperidone (0.05mg/kg) has no effect on animal locomotion, Mean ± SEM.

Conclusion

- **Both, high (3 mg/kg) and medium (0.5 mg/kg) doses of risperidone significantly decreased further attacks (p<0.0001), however at the same time, both doses significantly affected locomotor activity (p<0.0001).**
- **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.**
- **Thus, the low doses of the 5-HT1A receptor modulators may represent a therapeutic target for aggressive behaviour.**

Reference

[1] Archer J. The nature of human aggression. *Int J Law Psychiatry.* 2009 Jul-Aug;32(4):202–208.
[2] Mathews M. et al., Long-acting risperidone in the treatment of Schizophrenia. *Psychiatry* 2005; 2(2): 36–39.

Contact

www.transpharmation.co.uk
ewa.sokolowska@transpharmation.co.uk
@ Transpharm_IRL
+48 515 244 120