Assessment of Haloperidol-induced Tremulous Jaw Movement in Rats Using Loose Restraint and a Video Recording System

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1 BACKGROUND

- Chronic administration of haloperidol to rats induces a tremulous jaw movement, also referred to as vacuous chewing, characterized by involuntary rapid downward deflections of the lower jaw.
- These jaw movement have been widely used as a model of the motor complications associated with Parkinson's disease; anti-parkinsonian drugs reliably reverse the jaw movements.
- More recently, haloperidol-induced jaw movements have been used as a model of antipsyhotic-induced extrapyrimadal syndrome (EPS); promising treatments for EPS, such as adenosine A2A receptor antagonists reliably reverse haloperidol-induced tremulous jaw movements.
- The model has a significant value for the advancement of novel chemical entities both to help derisk putative antipsychotics in development, or to assess the efficacy of novel candidates designed to reverse antipsychotic-induced extrapyramidal syndrome.
- While the rat model has much higher throughput than the Cebus monkey model, which is the gold standard animal model of EPS, a high-throughput execution of the model has not yet been developed.
- The most challenging barrier to increasing the throughput of the model is that it requires a live human observer to score the moments and it is difficult to video the behavior because the observer must "bob and weave" with the rats in order to maintain a line of sight to the jaw.
- The purpose of the present study was to evaluate a novel approach to the scoring of TMJs that will allow for a high throughput means of measuring TMJs in rats

2 MATERIALS AND METHODS

Here we developed a system to loosely restrain the rats during video recording forcing the animals to face the camera. Treatment with haloperidol resulted in pharmacological limitation of rat movement provide an opportunity to use a loose restraint as sufficient tool to maintain the directionality of the animals allowing for video recording, and post-hoc recording of the jaw movements. Moreover, the use of post hoc video recording allows for scoring by more than a single investigetor to allow for confirmation of the findings by an independent observer. Here we show that, using this video recording system, we achieve reliable recordings and measurement of the haloperidol-induced jaw movements. This system provides a novel way to execute the haloperidol jaw movement assay much higher throughput, and reliability way than has been previously reported.

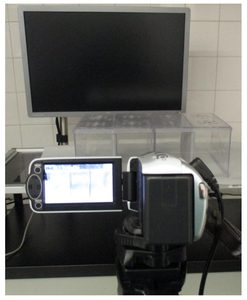


Figure 1. Loose restraint for video recording. Test device consist of up to four chambers with transparent walls allowing the video monitoring of the rats.

Figure 2. Rat in loose restraint for video recording.

3 HALOPERIDOL LMA & CATALEPSY

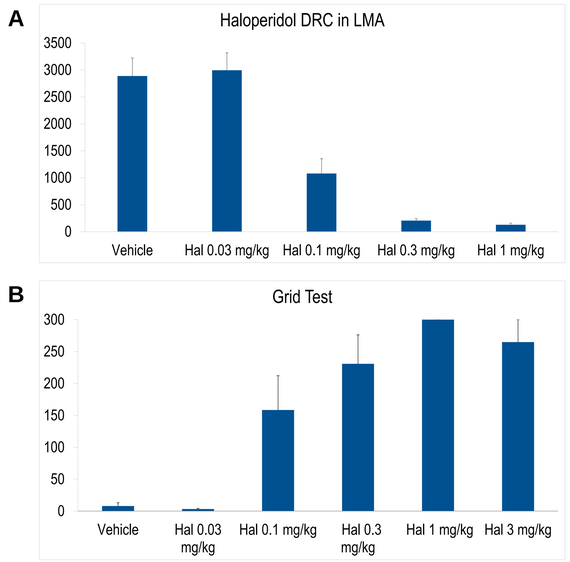
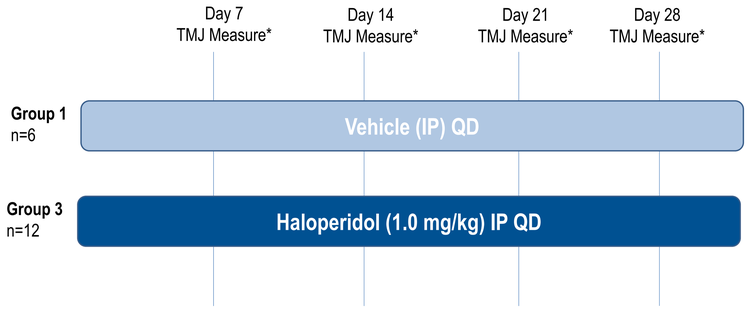


Figure 3. (A) Dose response curve of haloperidol in LMA. 0.3 & 1 mg/kg produced a maximal reduction in motor activity.
(B) Reference dose response curve with haloperidol induced catalepsy. 1 mg/kg, acute, delivery is the minimal dose of haloperidol that produces the maximal cataleptic response. This dose was chosen for the TMJ study below.

4 STUDY DESIGN



• TMJ recordings for 60 min, 30 min following haloperidol delivery
** See next slide for reversal study design

Figure 4. Naïve rats were treated daily with haloperidol daily (QD) fro 28 days. Their behavior was recorded weekly.. Data from the 1 mg/kg group is displayed to the right.

5 RESULTS: COUNT & DURATION OF TMJ

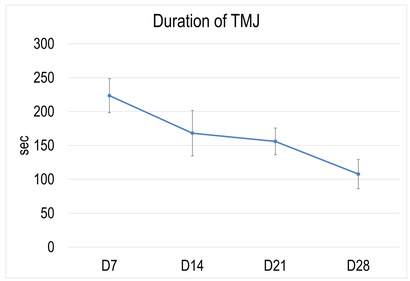


Figure 5. Duration of jaw movements in different timepoints during the validation. Data are presented as mean ± SEM and considered significant if $p < 0.05$. N = 8/group. There was no statistical differnece between the timepoints (test that was done).

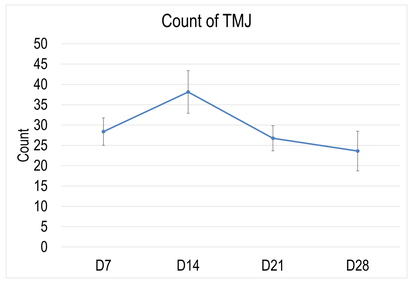


Figure 6. Count of jaw movements in different timepoints during the validation. Data are presented as mean ± SEM and considered significant if $p < 0.05$. N = 8/group. There was no statistical differnece between the timepoints (test that was done).

6 CONCLUSIONS

- One of the primary side effects associated with antipsychotics is extrapyramidal syndrome, which are involuntary movements
- An important advancement in the treatment of schizophrenia will be to identify novel efficacious mechanisms that do not have an EPS liability
- Testing for the potential of EPS with novel therapeutics currently is done with methods that are low throughput or expensive or both
- These data demonstrate that the use of camera tracking in rats provides a means of increasing throughput in the TMJ model
- This novel approach provides a way to assess the EPS liability of novel antipsychotics in a cost-effective manner
- Further work to assess other antipsychotic mechanisms and potential reversal agents are planned