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Erratum

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Modeling Migraine Chronification and Its Relief

The Effects of THC on Recurrent NTG-induced Migraine Endpoints in Rats

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ABSTRACT

This study investigated the analgesic effects of a THC pro-drug in a rodent model of recurrent migraine. Rats received 4 nitroglycerin-induced (NTG: 10mg/kg/2ml) migraine episodes every third day for 12 days; saline, cremaphor-vehicle, propranolol (10mg/kg/ml), or THC-VAL-HS (0.5, 1.0, and 2.0 mg/kg/ml) were given IP 30 minutes before NTG. Behavioral endpoints of photosensitivity, activity, orbital tightening, and tactile allodynia were assessed 110 m after NTG. Migraine severity increased over the course of the four episodes, pointing toward chronification and an important step in model validation. However, neither propranolol nor THC-VAL-HS significantly attenuated any of the migraine-related endpoints. These data are in contrast with clinical reports that marijuana mitigates migraine severity. These findings suggest that higher doses of THC-VAL-HS and/or other cannabinoid constituents in marijuana may be responsible for such anecdotal anti-migraine activity of cannabis.

INTRODUCTION & BACKGROUND

As migraine research has progressed, the translational relevance of available models has improved. The first generation of models sought to determine the effects of administered nitroglycerine (NTG) in rats on the outcome of some potentially relevant clinical endpoints (Tassorelli et al. 2003). In preliminary studies, rats were administered NTG and tested for signs of hyperalgesia, largely through the tail flick apparatus. This experiment found significant increases in hyperalgesia at 2 and 4 hours post-NTG injection. These results validated a clinically relevant induction of migraine and revealed the possible role of nitrovasodilators in pain

modulation. Though this experimental format may have had its merits, it lacked translational relevance to the clinical picture. The clinical need focuses on episodic migraine, which is characterized by recurrent migraine episodes. Additionally, the endpoints measured in this current model of migraine are not diagnostic criteria for migraine in the clinical picture.

In the second generation of migraine modelling, translational relevance improved by relying on multiple NTG administrations and migraine inductions (Pradhan et al. 2013). In this experiment, mice were injected with NTG every other day for 9 days, resulting in 5 total NTG

injections. This experiment found significant increases in hyperalgesia related to von Frey mechanical sensitivity (technically these endpoints measured allodynia), and that these effects not only persisted, but worsened with episodic migraine induction. The implementation of recurrent NTG administration helped to improve the translational relevance of this migraine model, in regards to frequency, though they still neglected more clinically relevant endpoints of episodic migraine by focusing solely on hyperalgesia.

The third generation of migraine models sought to include more relevant diagnostic endpoints in its assessment of episodic migraine (Sufka et al. 2016). This experiment subjected rats to 5 NTG injections over the course of 15 days and measured the effect on the novel endpoints of expressed facial pain (using the Rat Grimace scale) and photophobia and decreased movement (both quantified using a Light/Dark box). The results of this experiment showed a significant decrease in locomotor activity and an increase in light sensitivity over the course of the five test sessions. These changes helped to further refine the model and aid in producing a more clinically relevant representation of the chronic migraine episodes necessary for a clinical diagnosis of episodic migraine.

The final generation of modelling, and the one that is utilized in this experiment, sought to add an additional clinically relevant endpoint representative of tactile allodynia (Harris et al. 2017). This experiment followed the recurrent

administration of NTG that previous models utilized, but added a new apparatus in an attempt to quantify the development of tactile allodynia associated with chronification of migraine. This new apparatus is a circular arena consisting of two half fields of sandpaper of differing grit and seeks to quantify movement data as well as preference for one half field or the other. Through the implementation of this new apparatus, a significant increase in tactile allodynia, as measured by a decrease in movement and a preference for spending time on the smoother sandpaper, was recorded during the course of this experiment. However, this increase only occurred during the 5th episode, which indicates that tactile allodynia may be a more accurate indicator of the chronification of migraine.

Additionally, anecdotal evidence points to the possible efficacy of cannabis in alleviating symptoms of migraine. As early as the year 700 B.C.E., Indian ayurvedic medicine touted the ability of cannabis to be utilized for migraine pain (Russo, 1998). These anecdotal reports continued and persist even to this day, attesting to the possible benefits of cannabis use for migraine treatment (Russo, 1998).

However, reports of the analgesic properties of cannabis extend beyond anecdotal evidence and have been experimentally tested as well. A 1972 study sought to compare the analgesic properties of THC to those of morphine (Buxbaum, 1972). To accomplish this goal, rats were administered intraperitoneal

injections of THC or morphine and then subjected to hot plate and tail flick tests. This experiment found that an intraperitoneal injection of THC had analgesic effects equipotent to morphine in rats.

Furthermore, the analgesic effects of THC have also been demonstrated in human trials (Noyes Jr et al. 1975). Patients suffering from continuous pain attributed to cancer were administered varying doses of THC, and had their pain relief compared to the effects of codeine. This experiment found that a 20 mg dose of THC was slightly more effective at relief and reduction of pain than a 120 mg dose of codeine. This experiment speaks to the analgesic properties of THC and provides some validity for anecdotal efficacy in humans.

Thus, using both the recurrent migraine protocol with its clinically relevant

endpoints and the evidence of THC's efficacy as an analgesic, this study utilized a THC pro-drug formulation in the recurrent migraine model in rats .

MATERIAL & METHODS

Rats received 4 NTG migraine episodes every third day over a 12 day period. Nitroglycerin (10 mg/kg/2mL) was administered IP 30 minutes after IP injections of either saline, cremaphor-vehicle, 20 mg/kg/mL propranolol or THC (0.5, 1.0, or 2.0 mg/kg/mL). Orbital tightening was captured 30 minutes post nitroglycerin administration. Behavioral endpoints were assessed 110 minutes post nitroglycerin administration and included measures of photophobia and activity in the light/dark box and spontaneous tactile allodynia in an arena. Sample sizes were n = 5-10.

RESULTS

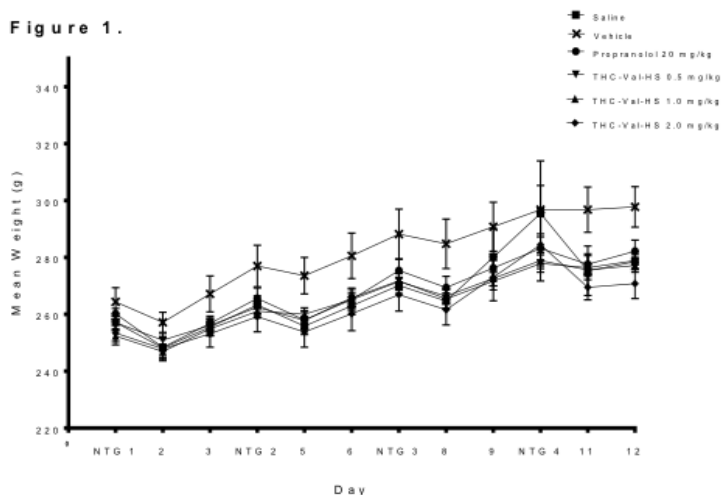


FIGURE 1. Weight Data- In general, weight increased for all test groups across all test sessions. On the day following a migraine episode, weight decreased among all groups. A

significance was found for Day but there was no significant effect for Treatment and no significant Day x Treatment interaction.

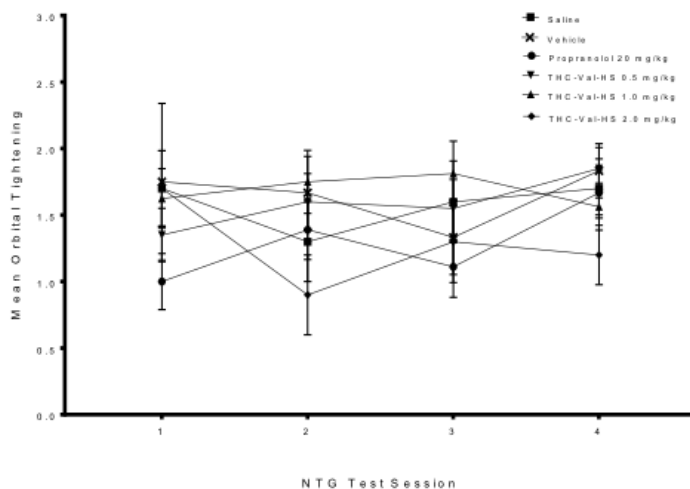


FIGURE 2. Orbital Tightening- Orbital tightening measures were collected 30 minutes post nitroglycerin administration. No systematic pattern showing changes or worsening of orbital tightening nor any separation among treatment groups in a consistent manner was detected from these data. No significant effect was found for Day or Treatment and there was no significant Day x Treatment interaction.

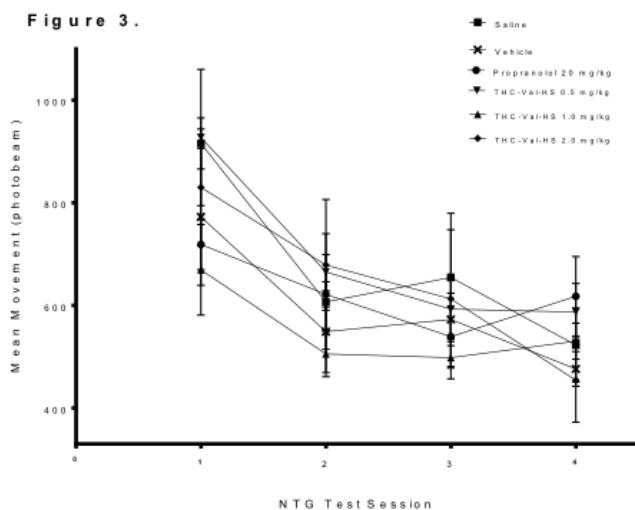


FIGURE 3. Movement data in L/D Box- Mean movement data was collected 110 minutes post-NTG administration. Movement generally decreased for all treatment groups across all test sessions. There was found to be a significant effect for Day, but no significant effect for Treatment and no significant Day x Treatment interaction.

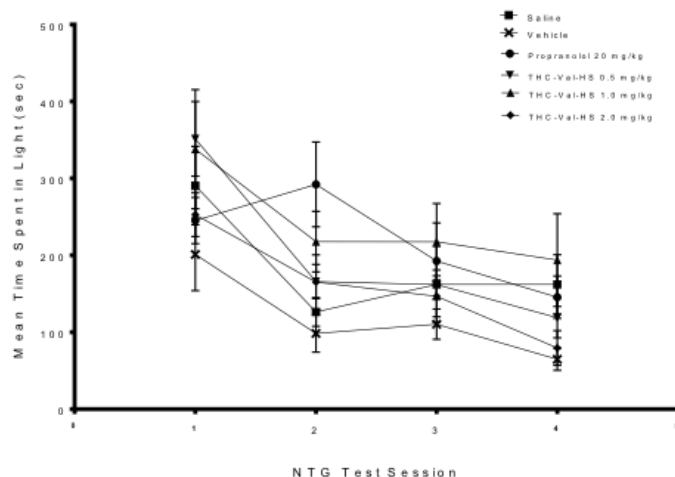


FIGURE 4. Photosensitivity in L/D Box- Time spent in light was quantified 110 minutes post-NTG administration. Time spent in light generally decreased for all treatment groups across all test sessions. There was found to be a significant effect for Day, but no significant effect for Treatment and no significant Day x Treatment interaction.

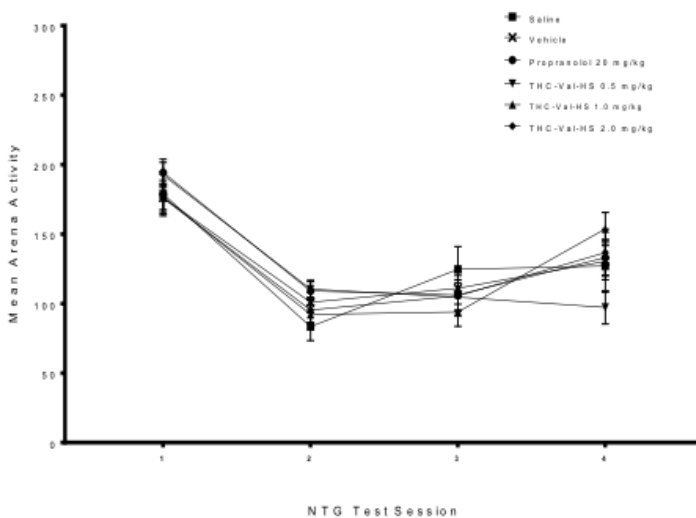


FIGURE 5. Movement Data in Open Arena- Mean movement data was collected 110 minutes post-NTG administration. Movement generally decreased for all treatment groups across all test sessions. A significant effect was found for Day, but there was no significant effect for Treatment and no significant Day x Treatment interaction.

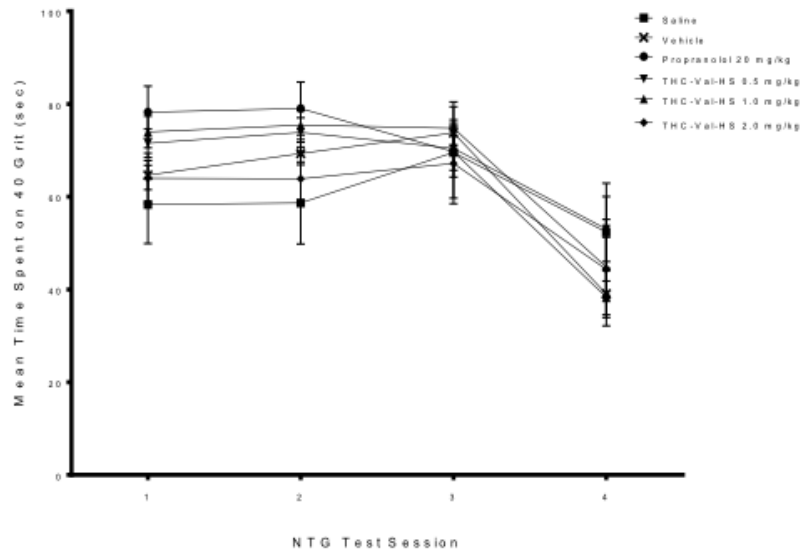


FIGURE 6. Time Spent in Half Field- Time spent on the 40-grit half of the open tactile arena was quantified 110 min post-NTG administration. There was a significant effect for Day, but no significant effect for Treatment and no significant Day x Treatment interaction.

DISCUSSION

This experiment suffers from some limitations and has some opportunities to improve. First, orbital tightening is presented as an early indicator of photosensitivity, yet this measure is not temporally connected to measures of photosensitivity in the light-dark box. This experiment would benefit from having these two endpoints more closely linked, perhaps by removing subjects from the light-dark box to assess orbital tightening scores.

Second, data about weight progression and its relation to migraine-induced nausea over the course of the recurrent migraine protocol is tenuous. Thus, we can only infer that these changes in weight data are related to migraine-induced nausea simply because it appears

to mirror the clinical presentation of migraine. Evidence that body weight changes in this “staircase” design may be a surrogate measure for nausea could be obtained from an experiment that utilized a compound that was known to induce nausea in animals.

Third, the novel measure of spontaneous tactile allodynia in the open arena could benefit from validation through additional studies. It would be beneficial to determine if this arena apparatus generalizes to other models that present spontaneous allodynia, such as a cisplatin-induced neuropathy model (Authier et al. 2000). If spontaneous allodynia in other models can be measured by movement in the arena apparatus, the next step would be to determine whether spontaneous allodynia differs from evoked allodynia in pharmacological sensitivity.

Finally, the absence of a prophylactic agent in attenuating these migraine endpoints is a limitation in regards to drug screening. Model validity could be greatly improved with an increase in pharmacological sensitivity. Efficacious and non-efficacious migraine therapies should screen positive and negative in the model,

CONCLUSION

The current model of episodic migraine appears to accurately model chronification, though some of its paradigms could use validation with other measures. Neither propranolol nor THC-Val-HS attenuated any of the migraine endpoints on any test

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