Understanding the Mechanisms of Opiate Induced Respiratory Depression in Mice Using the PiezoSleep Sensor System

SIGNALSOLUTIONS
Sensor Systems, Software, Sleep

Problem

Prescription of opioids has nearly quadrupled from 1999 to 2014. From 1999-2017, almost 400,000 people died from an overdose involving any opioid in the USA alone, including prescription and illicit opioids [1], and the yearly deaths more than tripled during this period. Opioids in high doses can cause respiratory depression leading to death. There is substantial inter-individual variability in response to opioids. The mechanisms and predictors of overdose and vulnerability to overdose are poorly understood.

Solution

Genetic analysis in the laboratory mouse can identify variable mechanisms of respiratory depression and lethality associated with opioid overdose.

Issues

- Previous studies in mice have revealed strain differences in opiate lethality and respiratory sensitivity.
- Effects of genetic variation on morphine overdose susceptibility has been poorly characterized to date

Goal

Determining precise quantitative metrics associated with morphine overdose lethality to facilitate genetic dissection of the mechanisms underlying susceptibility and resistance.

Method

Researchers at **The Jackson Laboratory**, **Dr. Jason A. Bubier** and **Dr. Elissa J. Chesler**, have characterized the variation in respiratory response to morphine in the eight Collaborative Cross (CC) /Diversity Outbred (DO) founder strains using the PiezoSleep system. For respiratory phenotyping, there are several advantages of using the **PiezoSleep** sensor system over conventional **Plethysmography** systems.

Plethysmography	PiezoSleep
Need to confine the animal, restrict normal movement, and limit the ability to eat or drink	Animal in a home-cage setting with no restrictions on movement, food, and water
Monitoring limited to 2 to 5 hours	Long term monitoring possible (days, weeks)
Monitoring rapid response to drugs requires surgical implantation of a cannula or catheter in the animal to administer the compound.	Totally non-invasive
Not suitable for high throughput studies	Easily scalable for high throughput studies of up to 80 cages

The researchers at The Jackson Laboratory, adapted the PiezoSleep sensor system to detect respiratory rhythms, and have defined a high-throughput technology to monitor the respiratory depression associated with morphine administration.

Quantitative parameters post Morphine administration

Using the piezo data, the researchers at The Jackson Laboratory were able to determine the **Survival time** and **Recovery time** for each mouse strain, post administration of morphine. These quantitative measurements were used to calculate the heritability of these morphine sensitivity traits.

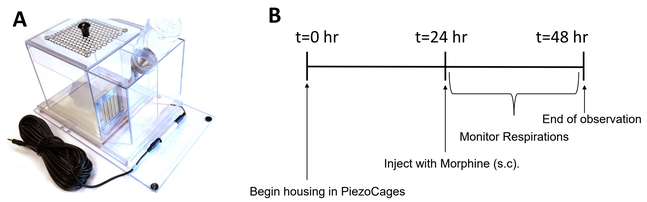


Figure 1. (A) Mouse cage used with the PiezoSleep system. (B) Timeline for experimental testing. Mice were housed at ~10 AM in the cages with food, water, bedding and 24 hours later injected with morphine or fentanyl. Their respirations were monitored for 24 hours and their survival confirmed.

Morphine Survival vs Morphine Recovery

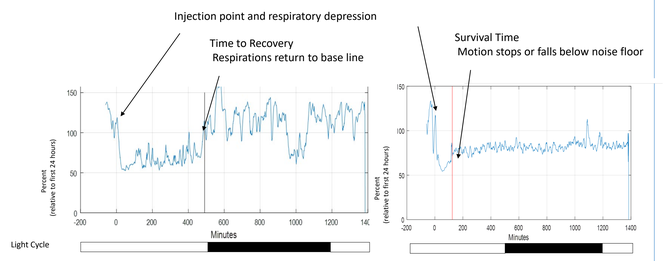
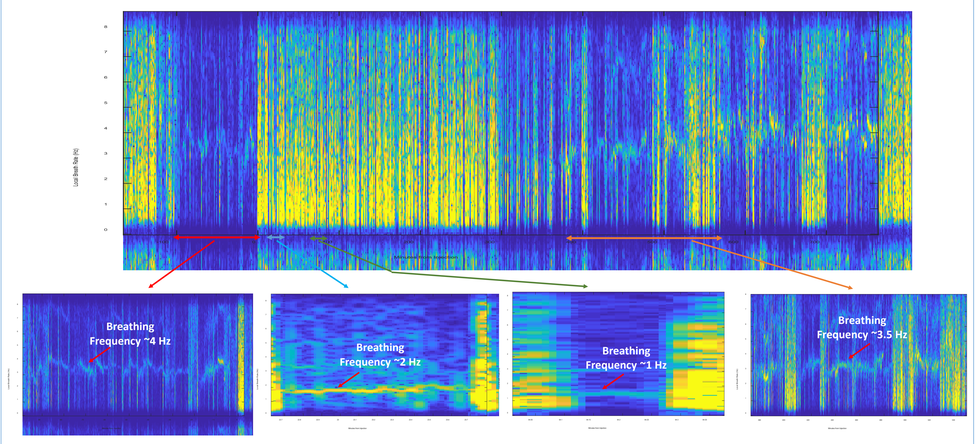


Figure 2. Time 0 is 24 hours after the start of the recording (dosage time). The blue line represents the local average breath rates taken every 12 minutes and normalized by the baseline (average BR over first 24 hours). For mice that recover, the black vertical line is the recovery time, where the average breath rate exceeds the baseline threshold. For mice that die, the red vertical line corresponds to the time when breathing and activity stop (signal falls below the noise floor). The time 0 is the time of injection, and axis is in minutes post injection.

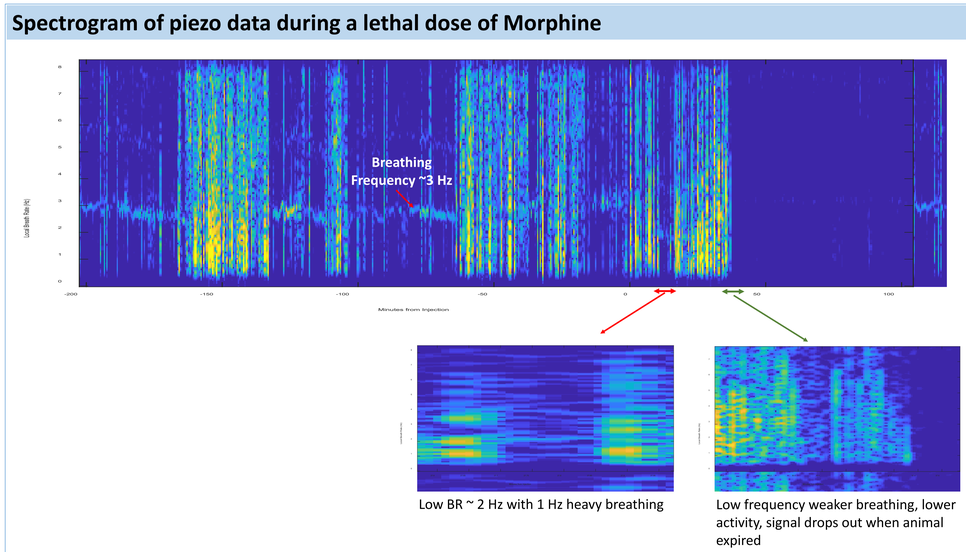
Main Results

- Using the eight progenitor inbred strains of the Collaborative Cross, the researchers at The Jackson Laboratory detected heritable variation in morphine LD_{50}.
- The LD_{50} among CC/DO founder strains ranged from 212 mg/kg - 882 mg/kg with several strain × sex interactions.
- Using the piezo data they were able to determine the Survival time and Recovery time for each strain.
- These quantitative measurements were used to calculate the heritability of these morphine sensitivity traits (time to death ICC= 0.338, time to recovery ICC= 0.345).

Spectrogram of piezo data during Morphine Recovery



Spectrogram of piezo data during a lethal dose of Morphine



Low BR ~ 2 Hz with 1 Hz heavy breathing

Low frequency weaker breathing, lower activity, signal drops out when animal expired

Conclusions

The high-throughput PiezoSleep system has enabled researchers at The Jackson Laboratory to use forward genetic approaches to map the genomic regions responsible for the phenotypic variation in respiratory physiology and response to morphine in the Diversity Outbred population.

References

[1] Scholl L, Seth P, Kariisa M, Wilson N, Baldwin G., Drug and Opioid-Involved Overdose Deaths – United States, 2013-2017. WR Morb Mortal Wkly Rep. ePub: 21 December 2018.

Acknowledgement

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