Epigenetic mechanisms underlying vulnerability to opioid addiction

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Background

Opioid addiction is a major public health problem leading to over 68,500 deaths in 2020. However, although many people try opioids, only 8-12% of these individuals develop opioid use disorder. Epigenetic changes in gene expression within the brain as a result of opioid exposure are thought to underlie vulnerability to addiction but it is still unclear which changes are important. The goal of this study was to evaluate the correlation between individual differences in demand for morphine in an i.v. self-administration model in rats and changes in gene expression measured in the same animals using RNA-seq.

Methods

WIA: Rats were trained to self-administer i.v. morphine (0.4 mg/kg/infusion or saline) on a fixed ratio 1 (FR1) schedule in which one response on an "active" lever produced one infusion. Once behavior was stable, the FR requirement (number of responses needed to produce an infusion) was progressively increased each day (up to FR 96). 24 hours after FR 96, brains of the subjects were collected and the medial Prefrontal Cortex was dissected.

RNA-Seq: Performed using Illumina NovaSeq at a depth of ~100 million reads per sample

Data Analysis: The behavioral data was analyzed using an exponential demand function that yields a parameter (alpha) that reflects the rate morphine consumption declines in response to the increase in FR requirement (cost).

Conclusions

- Reliable self-administration was observed for morphine but not saline rats
- Increases in FR requirement produced a progressive decrease in morphine consumption, and there was considerable individual variability in alpha
- The correlation between the RNA-seq data and demand data identified changes in gene expression which are associated with neural signaling, neural development/protection, and neuroinflammation

Results: Although this study is still ongoing, thus far the data is indicating that individual differences in opioid demand correlate with expression of genes previously implicated in opioid addiction.

Table 1: This table demonstrates a comparison of the high total DEG in the low vulnerability group, versus the Sal in comparison to the high vulnerability group versus Sal.

	Mor n.	Sal n.	Total DEG	Upregulated	Downregulated
High versus Sal	6	5	99	46	53
Low Versus Sal	5	5	260	119	141

Figure 1: Figure A shows the clear difference in infusions of the morphine group and the saline group. Figure B reports the impact of the increasing FR value on the number of infusions. Figure C shows that the high demand rats tend to have higher responses even with an increasing FR/ unit dose. Figure D is a summation graph of alpha scores, comparing high vs low demand groups.

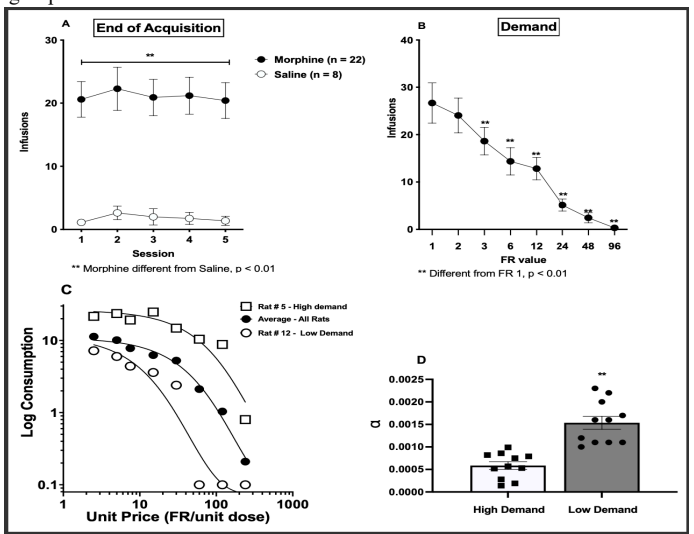
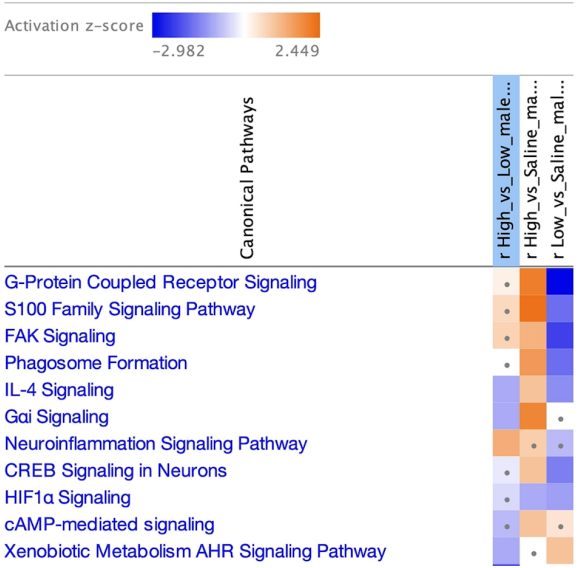


Figure 2: This figure shows strength of activation in each gene pathway. As shown with the contrast and strength of each color (blue and orange respectfully), there are differing activations for high vs low saline and high vs low morphine groups.



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