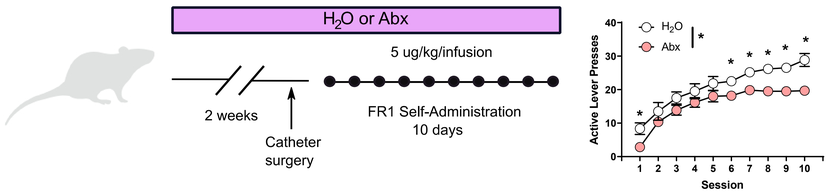
Microbiome knockdown causes a dose-dependent shift in the reinforcing efficacy of fentanyl in male rats

Rebecca S. Hofford[1], Katherine R. Meckel[2], Weiwei Wang[3], Michelle Kim[2], Arthur Godino[2], Tukiet T. Lam[3], & Drew D. Kiraly[1,2]

[1]Department of Psychiatry, [2]Nash Family Department of Neuroscience, Icahn School of Medicine at Mount Sinai, [3]Yale/Keck MS & Proteomics Resource, Yale University

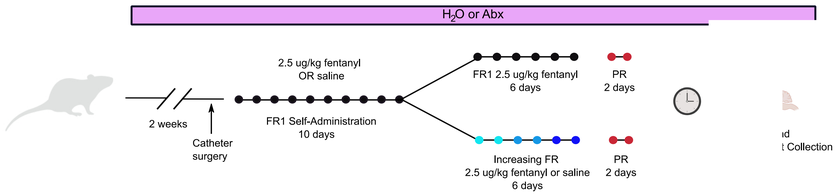
Abx reduces high dose fentanyl intake

Exp. 1



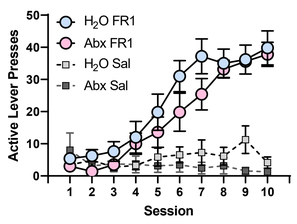
Abx increases motivation for fentanyl

Exp. 2

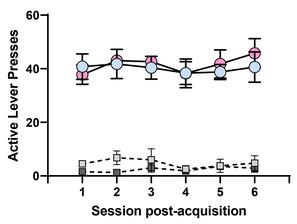


Microbiome knockdown does not affect lower-dose fentanyl intake at FR1

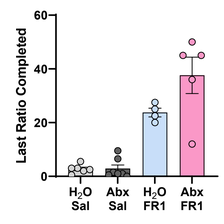
Acquisition



FR1 maintenance

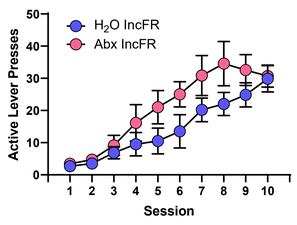


Prog. Ratio

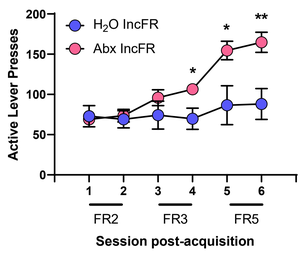


Rats on abx will work harder for fentanyl at higher fixed-ratios and during progressive ratio

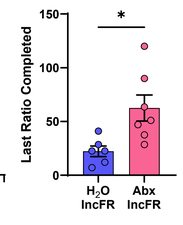
Acquisition



Increasing FR

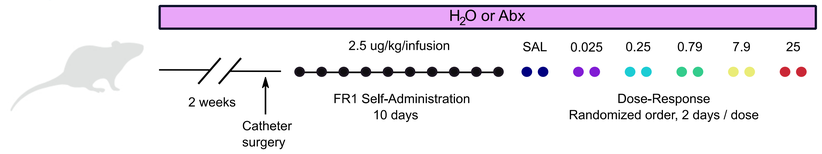


Prog. Ratio

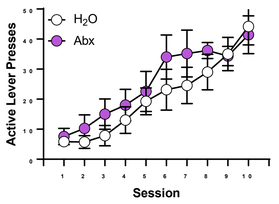


Abx shifts the fentanyl dose-response curve

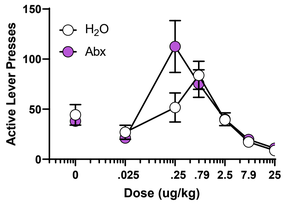
Exp. 3



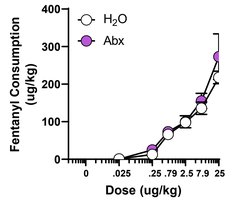
Acquisition



Dose-Response Lever Press

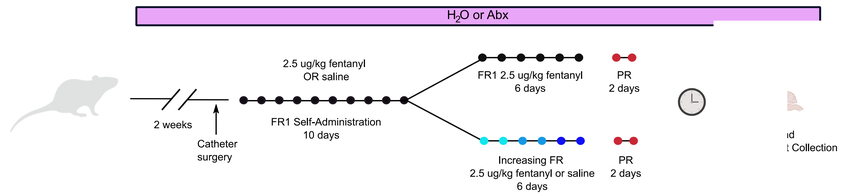


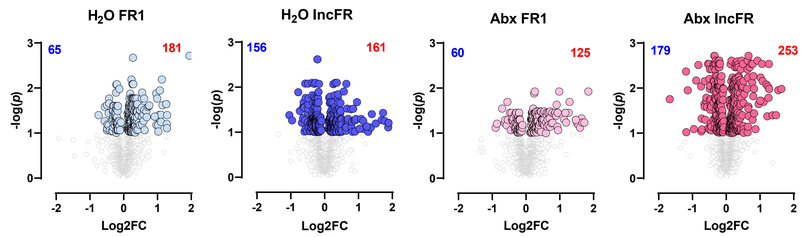
Dose-Response Consumption

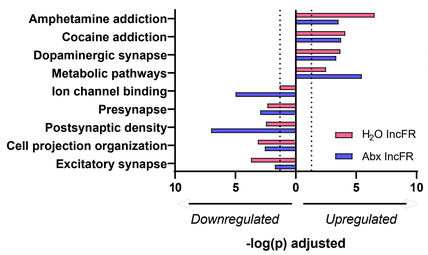


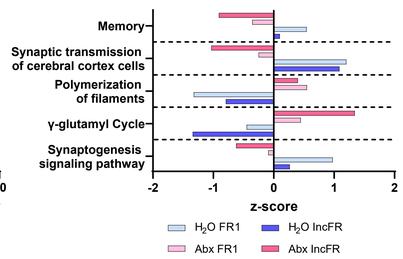
Proteomic analysis of NAc identifies unique pathways influenced by abx and fentanyl

NAc from Exp. 2



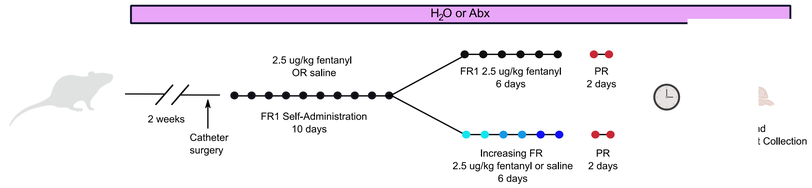




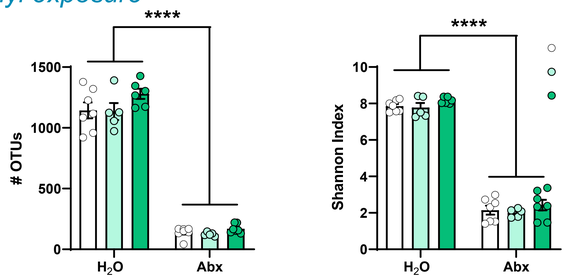


Abx, but not fentanyl, influences the gut microbiome

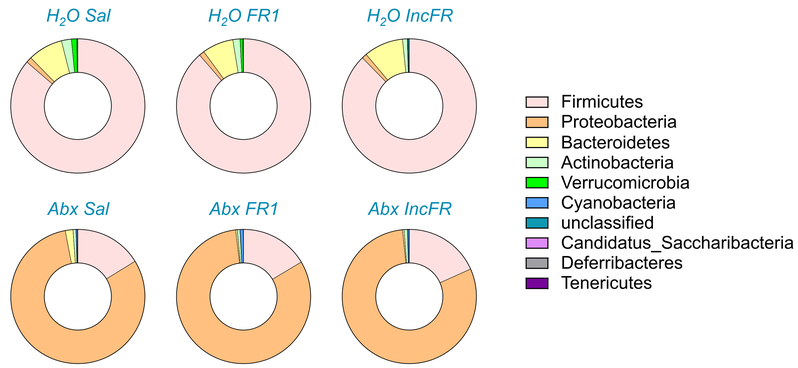
Cecal content from Exp. 2



Abx reduces the complexity of the microbiome regardless of fentanyl exposure



Abx shifts the dominant phyla of gut bacteria but fentanyl self-administration does not



Summary

- Abx reduced the complexity of the microbiome.
- Abx rats administered less high dose fentanyl, had more motivation for moderate dose fentanyl, and found lower doses of fentanyl more reinforcing than rats with an intact microbiome.
- Microbiome knockdown influenced protein expression in the NAc, specifically in pathways involved in memory formation and synaptogenesis.

Funding provided by: K01 DA050906 to RSH, K08 DA044308 to DDK, DP1 DA051551 to DDK, NARSAD to RSH and DDK, and pilot funds from Yale/NIDA Neuroproteomics Center Grant (DA018343) to RSH and DDK. Diagrams made using Biorender.com.