A role for casein kinase 1-epsilon in the motivational properties of opioids

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BACKGROUND

Casein kinase-1 (CK-1) is a family of serine/threonine-selective kinases that possess diverse molecular substrates and biological functions. Notably, CK-1 phosphorylates DARPP-32, a striatally abundant protein that integrates dopaminergic signaling in response to drugs of abuse. Recent studies demonstrate that the epsilon isoform of CK-1, Csnk1e, contributes to the locomotor stimulant properties of fentanyl, a selective mu opioid receptor agonist. We previously found that selective pharmacological inhibition of Csnk1e enhanced the locomotor stimulant properties of fentanyl, indicating a negative regulatory role for Csnk1e in drug-induced behavioral responses. Because shared neurobiological mechanisms mediate drug-induced locomotor activity and drug reward, locomotor activity can frequently be used as a proxy for identifying targets that are important for drug reward. Here, we tested the hypothesis that Csnk1e negatively regulates the motivational properties of fentanyl.

MATERIALS AND METHODS

Csnk1e knockout, heterozygous, and wild-type mice were bred by heterozygote breeding. Twenty-four hours post-assessment of initial preference for the drug-paired side on Day 1, mice received fentanyl (0, 0.025, 0.05, 0.2 mg/kg, i.p.) on Days 2 and 4 on the drug-paired side, and saline (i.p.) on Days 3 and 5 on the other side (distinguished by floor textures). Seventy-two hours later (Day 8), mice were assessed for fentanyl CPP (Day 8-Day 1). Separate cohorts of mice were utilized for the hot plate assay. Mice were assessed for pain response (licking the hindpaw) on the hot plate (52.5°C) prior to drug exposure, and 10 minutes after fentanyl injection (0, 0.2, 0.4 mg/kg, i.p.).

RESULTS

Csnk1e knockout mice showed an enhanced fentanyl reward compared to wild-type mice at a low dose (0.05 mg/kg, i.p.). The knockout mice also exhibited a significant reduction in fentanyl reward at the highest dose (0.2 mg/kg, i.p.), suggesting an enhanced sensitivity to the aversive properties of opiates that are observed following high doses. Additionally, no differences were observed in fentanyl analgesia in the 52.5°C hot plate assay (0-0.4 mg/kg, i.p.).

SUMMARY

Csnk1e knockout mice showed a leftward shift in the inverted u-shaped curve for opioid reward, exhibiting enhanced reward at lower doses and significantly decreased reward at higher doses. No differences were observed in fentanyl analgesia, implicating a neural mechanism selective for dopaminergic reward circuitry. To gain further insight into the neural mechanism, we are testing the hypothesis that Csnk1e knockout mice show differential DARPP-32 signaling in response to fentanyl. Finally, we are using an unbiased transcriptome approach (mRNA sequencing) to generate novel hypotheses regarding the molecular mechanism that mediates Csnk1e-mediated inhibition of opioid reward.

REFERENCES

- Bryant CD, Graham ME, Distler MG, Munoz MB, Li D, Vezina P, Sokoloff G, Palmer AA (2009). A role for casein kinase 1 epsilon in the locomotor stimulant response to methamphetamine. *Psychopharmacology 203 (4): 703-11.*
- Bryant CD, Parker CC, Zhou L, Olker C, Chandrasekaran RY, Wager TT, Bolivar VJ, Loudon AS, Vitaterna MH, Turek FW, Palmer AA (2012). *Csnk1e* is a genetic regulator of sensitivity to psychostimulants and opioids. *Neuropsychopharmacology 37 (4): 1026-35.*

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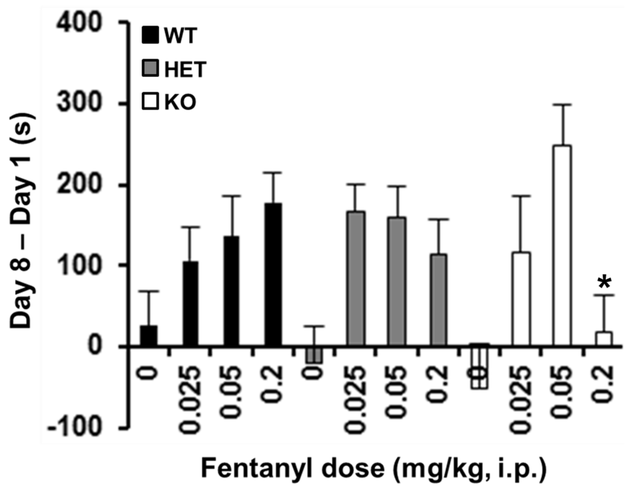
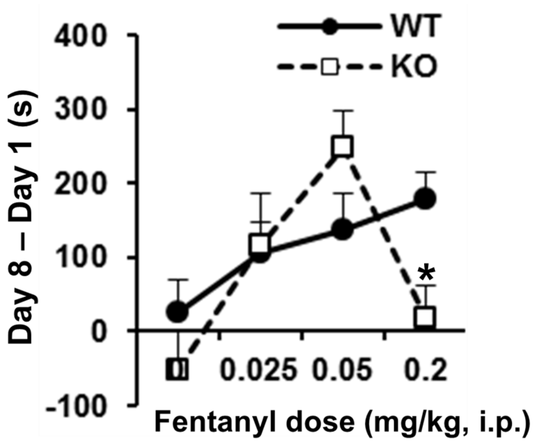
1. Enhanced sensitivity to opioid reward/aversion in Csnk1e knockout mice.

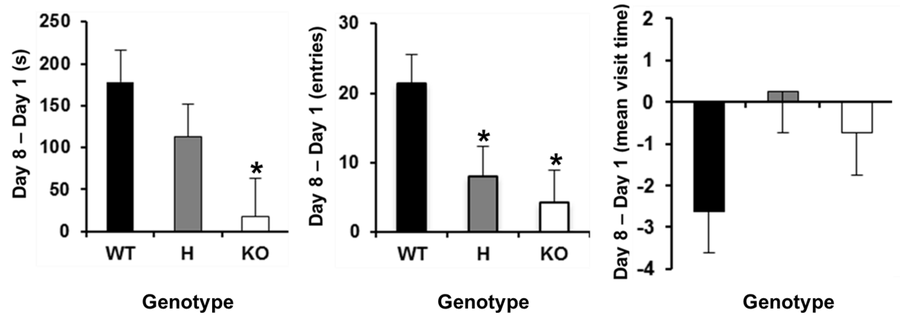
Day1	Day2 Day3 Day4 Day5	Day6 Day7	Day8
SAL	DRUG SAL DRUG SAL	- -	SAL
Initial pref.	Training	Consolid.	CPP



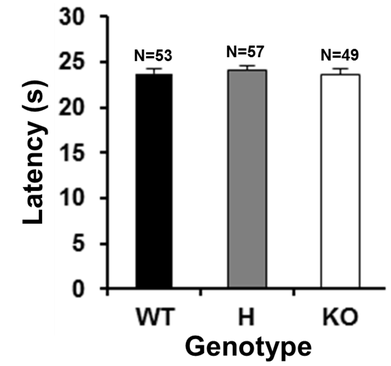
2. Altered dose-response relationship of opioid reward/aversion in Csnk1e knockout mice.



3. Dissection of conditioned opioid reward behavior in Csnk1e knockout mice.



4. Baseline pain sensitivity in Csnk1e knockout mice.



5. Opioid analgesia in Csnk1e knockout mice.