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Desta M. Pulley
Rowan University

Jessica J. Debski
Rowan University

Daniel Manvich
Rowan University

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Desta M. Pulley, Jessica J. Debski, Daniel F. Manvich

Department of Cell Biology and Neuroscience, Rowan University School of Osteopathic Medicine, Stratford, NJ

Rowan University Graduate School of Biomedical Sciences

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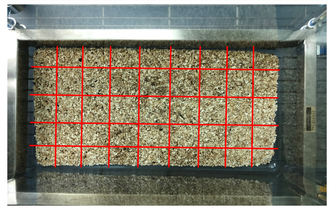
Introduction

In light of the increasing rates of opioid abuse in the US, the search for viable medications to treat opioid abuse disorder (OUD) has become ever more urgent. Opioids exert their abuse-related effects in part by indirectly increasing dopamine (DA) neurotransmission in the mesolimbic system, a dopaminergic projection arising in the ventral tegmental area and terminating in the nucleus accumbens. The DA D_3 receptor (D_3R), which belongs to the D2 family of dopamine receptors (D_2, D_3 , D_4 receptor subtypes), is highly expressed in these brain regions and has shown strong potential as a pharmacotherapeutic target for the treatment of OUD. More specifically, D_3R antagonists have been shown by us and others to attenuate the abuse-related behavioral effects of opioids without producing adverse side effects associated with nonselective D2-like receptor antagonists.

We previously examined the effects of the selective D_3R antagonist PG01037 (133-fold selectivity for D_3R vs. D_2R) using drug-induced hyperactivity as a behavioral proxy for DA release within the nucleus accumbens. Interestingly, we found that PG01037 enhances cocaine-induced hyperlocomotion while it attenuates morphine-induced hyperlocomotion in mice. The potentiation of psychostimulant effects could confound the potential use of D_3R antagonists for the treatment of OUD, since many opioid users co-abuse stimulants such as cocaine. However, recent studies with more selective D_3R antagonists found that they do not enhance certain effects of cocaine while still reducing opioid effects. It is currently unknown what impact these highly-selective D_3R antagonists will have on cocaine-induced hyperactivity and/or dopamine neurotransmission.

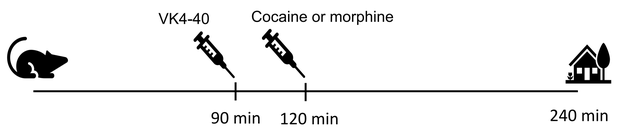
The purpose of this study was to examine the impact of pretreatment with the novel and highly selective D_3R antagonist VK4-40 (250-fold selectivity for D_3R vs. D_2R) on cocaine- and morphine-induced hyperlocomotion in mice.

Methods



16 locomotor activity chambers (above; left. San Diego Instruments; San Diego, California) were used to measure horizontal locomotion in mice. “Ambulations” were recorded when a mouse interrupted an infrared beam adjacent to a previously-interrupted beam in either the x- or y- plane of the chamber (above; right). Repeated disruptions of the same beam were not counted.

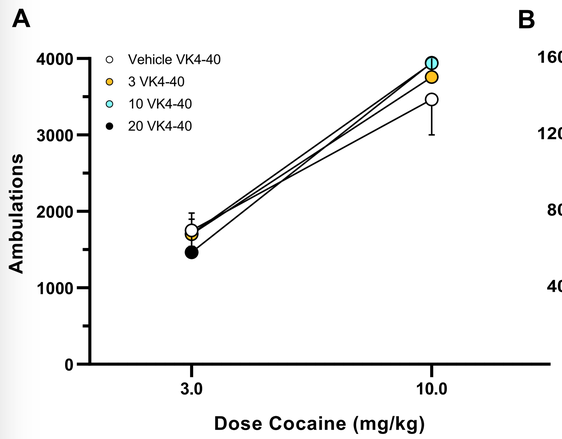
- 2 groups of 16 adult C57BL/6J mice (8 male; 8 female) were tested weekly
  - Group 1: VK4-40 (veh, 3, 10, 20 mg/kg) and cocaine (3, 10 mg/kg)
  - Group 2: VK4-40 (veh, 3, 10, 20 mg/kg) and morphine (0, 5.6, 18 mg/kg)
- 4-hour locomotor activity sessions
  - 90 min habituation prior to 1st injection
  - 1st injection (VK4-40) followed by 30 min
  - 2nd injection (cocaine or morphine) followed by120 min
  - All drugs administered i.p.



Ambulations were recorded for 4 h. Cocaine data were analyzed 60 min post-cocaine injection, whereas morphine was analyzed 120 min post-injection.

VK4-40 selectively attenuates morphine-induced hyperlocomotion

Cocaine dose-response



Morphine dose-response

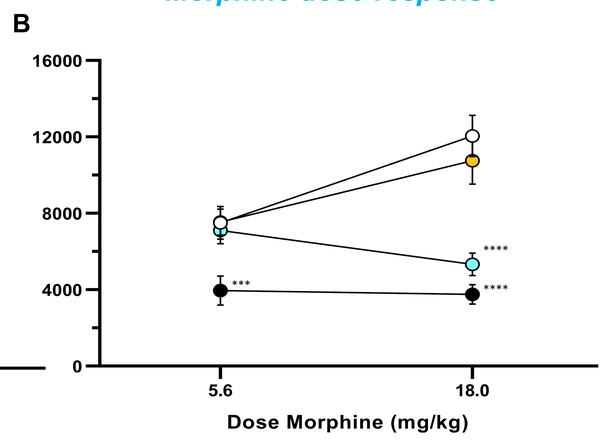


Figure 1. Dose-response showing effects of VK4-40 pretreatment on total ambulations **(A)** 60 minutes following cocaine injections (n=16) and **(B)** 120 minutes following morphine injections (n=16). ***p<0.001, VK4-40 compared to vehicle at 5.6 mg/kg morphine. ****p<0.0001, VK4-40 compared to vehicle at 18 mg/kg morphine. Each data point represents mean ±SEM total ambulations.

Time course: VK4-40 + Cocaine

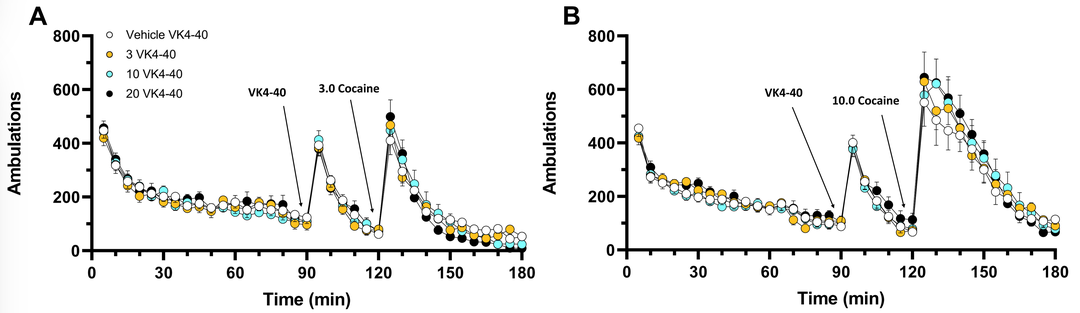


Figure 3. Time course effects of cocaine-induced locomotion following pretreatment with VK4-40. Vehicle, 3, 10, or 20 mg/kg of VK4-40 was administered 30 min prior to **(A)** 3 mg/kg cocaine, or **(B)** 10 mg/kg cocaine. Each data point represents mean ±SEM total ambulations recorded in 5-min bins.

Time course: VK4-40 + Morphine

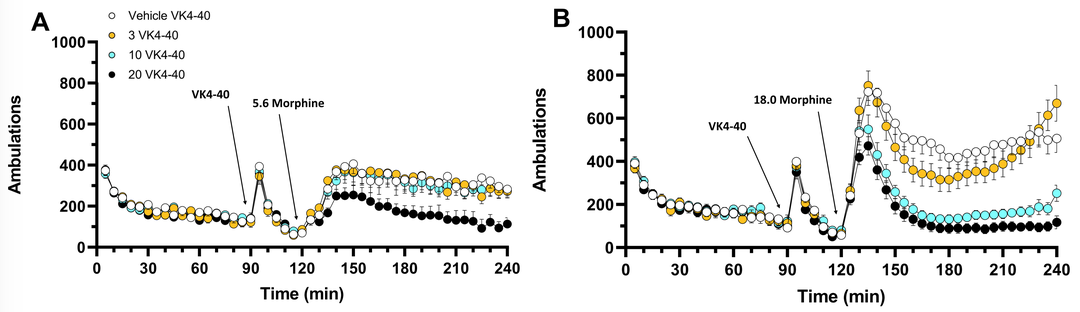


Figure 4. Time course effects of morphine-induced locomotion following pretreatment with VK4-40. Vehicle, 3, 10, or 20 mg/kg of VK4-40 was administered 30 min before **(A)** 5.6 mg/kg morphine, or **(B)** 18 mg/kg morphine. Each data point represents mean ±SEM total ambulations recorded in 5-min bins.

Effects of VK4-40 alone

VK4-40 dose-response (prior to saline)

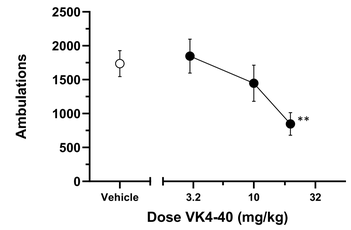


Figure 4. Effects of VK4-40 pretreatment on total ambulations over 120 min following saline i.p. (n=16). **p=0.001, VK4-40 compared to vehicle. Each data point represents mean ±SEM total ambulations.

VK4-40 attenuates locomotion only at the highest dose

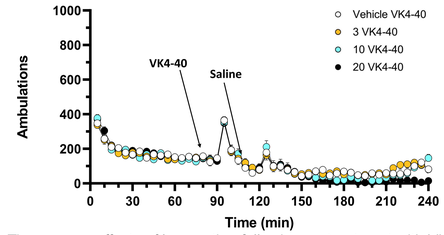


Figure 5. Time course effects of locomotion following pretreatment with VK4-40. Vehicle, 3, 10, or 20 mg/kg of VK4-40 was administered 30 min before saline. Each data point represents mean ±SEM total ambulations recorded in 5-min bins.

Summary

- ***VK4-40 dose-dependently attenuates morphine-induced hyperactivity, but not cocaine-induced hyperactivity***
- ***VK4-40 attenuates morphine-induced hyperactivity at doses that do not affect basal locomotion***
- ***Highly selective dopamine D_3 receptor antagonists have potential in treating opioid use disorder without enhancing effects of cocaine***

References

- Benyamin R, Trescot AM, Datta S, et al. Opioid complications and side effects. Pain Physician 2008;11:S105-20.
- Botz-Zapp CA, Foster SL, Pulley DM, et al. Effects of the selective dopamine D3 receptor antagonist PG01037 on morphine-induced hyperactivity and antinociception in mice. bioRxiv 2021;029918 [Preprint]: https://doi.org/10.1101/2020.04.07.029918
- Jordan CJ, Humburg B, Rice M, et al. The highly selective dopamine D3R antagonist, R-VK4-40 attenuates oxycodone reward and augments analgesia in rodents. Neuropharmacology 2019;158:107597.
- Manvich DF, Petko AK, Branco RC, et al. Selective D2 and D3 receptor antagonists oppositely modulate cocaine responses in mice via distinct postsynaptic mechanisms in nucleus accumbens. Neuropsychopharmacology 2019;44:1445-55.
- You ZB, Bi GH, Galaj E, et al. Dopamine D3R antagonist VK4-116 attenuates oxycodone self-administration and reinstatement without compromising its antinociceptive effects. Neuropsychopharmacology 2019;44:1415-24.

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