May 5th, 12:00 AM

Preferences for Support Resources Among Loved Ones of Adults Prescribed Opioid Medications

Ekrem Cetinkaya
Rowan University

Victoria Wong Murray
Rowan University

Ahmad Hussein
Rowan University

Danielle Arigo
Rowan University

Richard Jermyn
Rowan University

Morphine-induced hyperactivity is attenuated by intra-accumbens administration of the highly-selective dopamine D3 receptor antagonist VK4-40

Mansi Patel, Desta M. Pulley, Daniel F. Manvich PhD
Department of Cell Biology and Neuroscience, Rowan University School of Osteopathic Medicine, Stratford, NJ, USA

Introduction

Since the late 1990s, the opioid epidemic has claimed nearly 500,000 lives and continues to be the leading cause of drug-related deaths in the United States. Although there are treatments available for Opioid Use Disorder (OUD), their utility is hampered by adverse side effects, high rates of discontinuation, and only modest efficacy for relapse prevention[1]. To help combat the growing opioid crisis, the National Institute on Drug Abuse has recently launched several initiatives aimed at identifying new drug classes that may serve as safer and more effective OUD therapeutics.

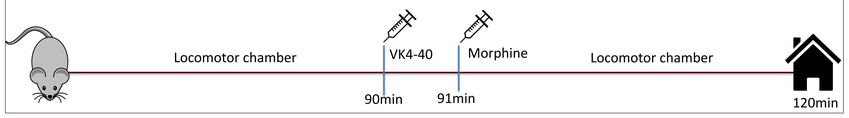
Opioids exert their rewarding effects by binding to mu opioid receptors (MOR) expressed by several populations of GABAergic neurons that normally provide inhibitory tone on dopamine (DA) neurons within the brain's mesolimbic DA reward system[2]. By inhibiting these GABAergic neurons in a MOR-dependent manner, opioids indirectly increasing DA levels via disinhibition of DAergic neurons. The mesolimbic DA system originates with DA neurons in the ventral tegmental area (VTA) that project to the nucleus accumbens (NAc)[2,3]. Importantly, several components of this reward systems express high levels of the dopamine D3 receptor (D3R) subtype, making it a promising pharmacological target for OUD treatment. It has previously been reported that pretreatment with highly-selective D3R antagonists attenuates the abuse-related effects of opioids, while advantageously enhancing their beneficial analgesic properties [3,4,5]. While promising, these results were acquired following systemic administration of VK4-40, leaving unresolved the precise neuroanatomical locations in which D3R antagonism exerts its modulatory effects on opioid reward.

The overall goal of this project is to determine the site(s) of action within the mesolimbic DA system where D3R antagonists exert their anti-opioid behavioral effects. To address this question, in the present study we assessed whether intra-NAc administration of a highly-selective D3R antagonist, VK4-40, alters morphine-induced hyperactivity in mice, a behavioral marker of increased DA neurotransmission within the reward system.

Methods

8 adult C57BL/6 mice (5 males, 3 females; Jackson Laboratory, Bar Harbor, ME) were surgically implanted with bilateral guide cannulae targeting the NAc.
Prior to onset of behavioral testing, mice were habituated to i.p. injections (saline, 10 ml/kg) and to locomotor chambers (30 min/day, 3 days). Horizontal locomotor activity was monitored and recorded via disruption of infrared beams that traveled through the test cage (San Diego Instruments, San Diego, CA).

Next, mice were tested once per week for effects of VK4-40 microinfusions on morphine-induced hyperactivity in 3.5-hr test sessions. Each session began by placing the mouse in the locomotor chamber and locomotion was recorded for 90 min. Next, the mouse was removed from the testing chamber and bilateral injectors were inserted into the guide cannula. 0.3 microL of VK4-40 (0, 100, 1000 ng/side) was infused over approximately one minute and injectors were left in place for one additional minute post-infusion to allow adequate diffusion prior to removal. Animals were then immediately injected with morphine (18 mg/kg, i.p.) and returned to the locomotor test cage. Locomotion was then measured for 120 min post-morphine administration. VK4-40 dose order was randomized for each subject.



Intra-NAc VK4-40 Attenuates Morphine-Induced Hyperactivity

Time course

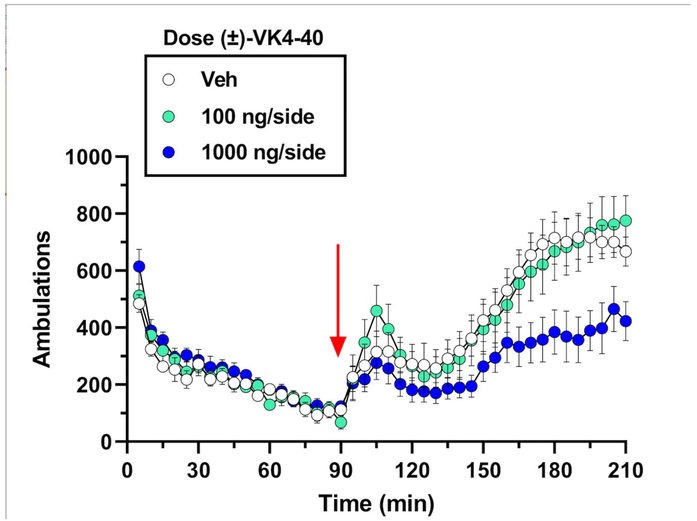


Figure 1. Time course of ambulations during habituation phase (0-90 min) and post intra-NAc infusion of VK4-40 (0, 100, 1000 ng/side) and 18 mg/kg morphine (90-210 min). Arrow indicates time of VK4-40 microinfusion followed immediately by morphine injection. Data represent mean ± SEM ambulations. n=8.

Total ambulations in 2 hr post-morphine administration

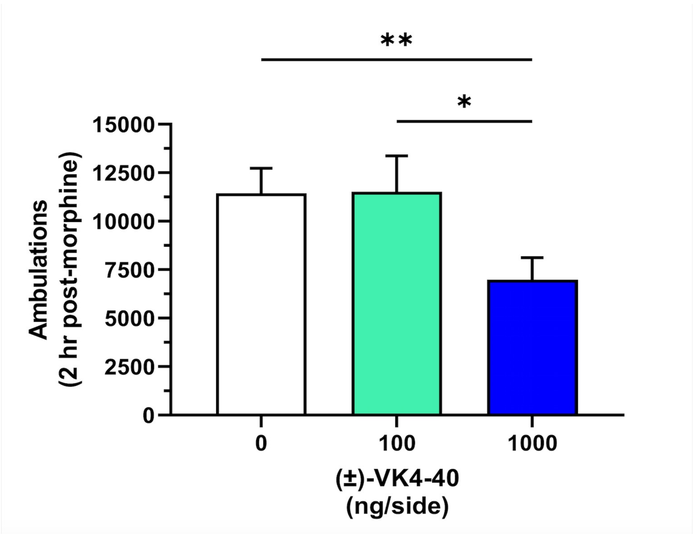


Figure 2. Total ambulations in the 2 hr following morphine injection (18 mg/kg i.p.). Morphine injection was immediately preceded by bilateral intra-NAc infusion of VK4-40 (0, 100, 1000 ng/side). Data represent mean ± SEM ambulations. * $p < 0.05$, ** $p < 0.01$ (pairwise comparisons indicated by horizontal lines). n=8.

Conclusions

- **Intra-NAc administration of VK4-40 attenuated morphine-induced hyperactivity at the highest concentration test (1000ng/side)**
- **These results preliminarily suggest that the NAc may be one brain region in which D3R antagonists act to reduce the abuse-related effects of opioids**

Future Directions

Next phases of this ongoing research project include:

- Determining whether intra-NAc VK4-40 administration perturbs basal locomotor activity
- Studying the effects of VK4-40 infusion in other nodes of the mesolimbic dopamine system
- Examining whether VK4-40 disrupts opioid-induced increases in the activity of VTA DA neurons and/or opioid-induced increases in NAc DA levels.
- **Collectively, these studies are poised to reveal the neurobiological mechanisms by which selective D3R antagonism disrupts the abuse-related effects of opioids.**

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Support

This work was supported by Rowan University SOM, HCOP CREATE, and NIH grant DA039991 to DFM.