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Intra-accumbens Microinfusion of the Dopamine D3 Receptor Partial Agonist (±)VK4-40 Does Not Affect Basal Locomotion in Mice

Yeonwoo Sim
Rowan University

Nicole M. Hinds
Rowan University

Amy Hauck Newman
National Institute on Drug Abuse

Daniel F. Manvich
Rowan University

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Yeonwoo Sim[1], Nicole M. Hinds[2], Amy Hauck Newman[3], Daniel F. Manvich[1,2]
[1]Rowan-Virtua School of Osteopathic Medicine, Stratford, NJ 08084
[2]Department of Cell Biology and Neuroscience, Rowan-Virtua School of Translational Biomedical Engineering & Sciences, Stratford, NJ 08084
[3]Molecular Targets and Medications Discovery Branch, National Institute on Drug Abuse-Intramural Research Program, NIH, DHHS, Baltimore, MD 21224

Introduction

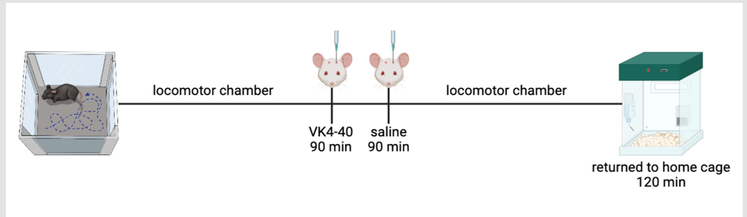
The current opioid epidemic is among the most severe public health crises in US history, with a reported 80,411 deaths in 2021 (National Institute of Drug Abuse, 2023). Opioids exert their rewarding effects by binding to mu opioid receptors (MORs) located in the ventral tegmental area, rostromedial tegmental nucleus, and nucleus accumbens (NAc), components of the brain's mesolimbic dopamine (DA) reward system. Many of the current medications used to reverse opioid overdose or treat Opioid Use Disorder (OUD) exert their effects by binding to MORs. However, the utility of these drugs is limited by their adverse side effects including risk of misuse, poor compliance, and their somewhat moderate efficacy for preventing relapse (National Institute of Drug Abuse, 2022; Kosten & George, 2002). Therefore, novel treatments with alternative pharmacological profiles to combat OUD could prove beneficial.

One promising target for OUD pharmacotherapeutic intervention is the dopamine D3 receptor (D3R). The D3R subtype is primarily expressed in areas of the brain associated with reward and motivation, including the NAc and ventral tegmental area (Galaj et al., 2020). Studies have shown that selective D3R antagonists and partial agonists can modulate opioid reinforcement and opioid-seeking behaviors (Galaj et al., 2020), including the recently-synthesized and highly-selective D3R partial agonist, (±)VK4-40 (VK4-40; Jordan et al., 2019; Woodlief et al., 2023). These findings have sparked enthusiasm for further investigation into VK4-40 and related D3R- selective compounds, however it remains unknown what brain region(s) within the mesolimbic DA system mediate the therapeutic effects of VK4-40. We previously demonstrated that site-directed administration of VK4-40 directly into the NAc decreases opioid-induced hyperactivity in mice (Patel et al., 2022), a behavioral proxy measure for the abuse-related effects of opioids and their dopamine-increasing effects within the mesolimbic DA system. The goal of this project was to extend these previous findings by assessing whether intra-NAc microinfusion of VK4-40 alters basal locomotion in the absence of opioid administration.

Methodology

Subjects: 9 adult C57Bl/6J mice (5 males and 4 females; Jackson Laboratories, Bar Harbor, ME) were surgically implanted with bilateral guide cannulae targeting the NAc core/shell junction and allowed to recover for 1 week. Mice were habituated to i.p. saline injections (0.2 µL) and were also habituated to locomotor test chambers for 30 min/d over 3 d prior to onset of behavioral experiments.

Locomotor assessment: Mice were tested once per week for effects of VK4-40 microinfusions on basal locomotion 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. VK4-40 (veh or 1 µg/side in 0.3 µL) 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 saline (10 µL/kg, i.p.) and returned to the locomotor test cage. Locomotion was then measured for an additional 120 min. The dose order for VK4-40 and vehicle administration was randomized for each subject. Each mouse received both treatments, separated by at least one week. The active dose of VK4-40 (1 µg/side) was determined from prior experiments.



Results

Time Course

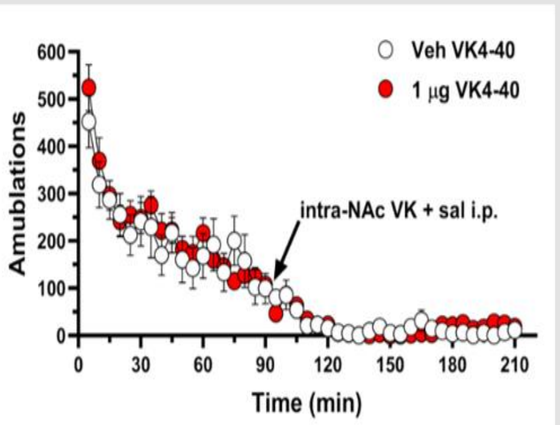


Figure 1. Time course of horizontal locomotor activity (ambulations) during habituation phase (0-90 min) and post intra-NAc infusion of VK4-40 (veh, 1 µg/side; 90-210 min). Arrow indicates time of intra-NAc infusion and saline injection. Data are depicted as mean ± SEM ambulations. n=9.

Total ambulations in 2 hr post-saline administration

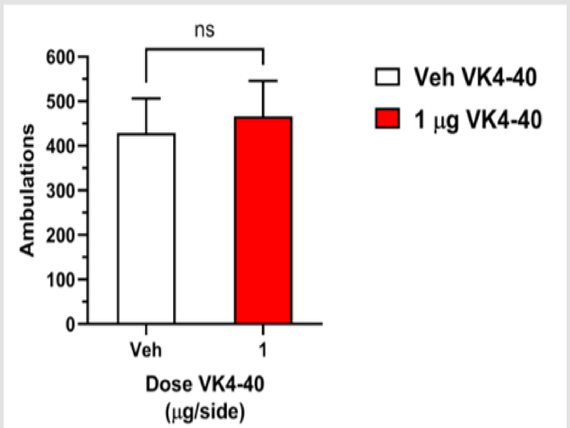


Figure 2. Total horizontal locomotor activity (ambulations) in the 120-min period following intra-NAc infusion of VK4-40 and i.p. saline administration. Data are depicted as mean ± SEM ambulations. Arrow indicates time of intra-NAc infusion and saline injection. n=9. "ns", not significant.

Summary

- **VK4-40 did not appreciably alter basal locomotion in mice**
- **Intra-NAc VK4-40 likely does not reduce opioid-induced hyperactivity via disruptions in generalized motor function**
- **The NAc may be one brain region in which D3R partial agonists and antagonists act to reduce the abuse-related effects of opioids**

Future Directions

The next phase of this project is to determine whether intra-NAc VK4-40 microinfusions may similarly affect psychostimulant-induced hyperlocomotion and to identify the neuropharmacological mechanisms by which VK4-40 exerts its therapeutic effects.

We also plan to examine a potential role for other brain regions in mediating the inhibitory actions of VK4-40 on opioids.

Acknowledgements

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References