The direct link between adult hippocampal neurogenesis and mouse's enhanced vulnerability to drug addiction

Helen Wang

Abstract

Drug addiction has long been a problem in human history, causing a series of physiological and mental issues. Among them, cocaine is known for its relatively strong damage to the human body, and many studies have been done on its addictive features. Throughout the past decade, researchers have been perpetually searching for ways to improve the treatment for drug addiction, especially cocaine addiction. By testing the effect of reduced adult hippocampal neurogenesis on mice, researchers in previous studies have found that there exists either a direct or indirect relationship between adult hippocampal neurogenesis (AHN) and cocaine addiction. This article examines previous studies that used cocaine to test the relationship between reduced AHN and the vulnerability to addiction in mice and compares cocaine with other types of strong drugs to analyze whether the same relationship with AHN exists for those drugs as well.

Keywords: Adult hippocampal neurogenesis (AHN), Drug addiction, Brain reward pathway

1. Introduction

Addictive drugs can be classified into four categories: stimulants, depressants, hallucinogens, and opioids. As the name implies, stimulants stimulate brain activity, causing wakefulness and a sudden euphoria. Caffeine is a type of stimulant. Some commonly known illegal stimulants are cocaine, methamphetamine, MDMA, and Cathonine. Depressants, also implied in the name, calm people down. Doctors would prescribe some of them to patients with sleep disorders or anxiety issues. The most common depressant in the world is alcohol. Hallucinogens cause hallucinations. Some examples of non-dissociative hallucinogens are mescaline, DMT, LSD, and psilocybin, and some examples of dissociative hallucinogens are ketamine and PCP. Lastly, opioids cause intense euphoria and sedation and are often prescribed by doctors to patients with severe pain. Opioids are also classified into two categories: natural opioids and synthetic opioids. Natural opioids are made from the opioid poppy plant. Morphine, heroin, and opium are some commonly known natural opioids. On the other hand, synthetic opioids, such as Fentanyl, are created through chemical processes in laboratories (Rehab Spot).

Drug addiction has long been a problem in human history, causing a series of physiological and mental issues. Data shows that from March 2020 to March 2021, at least 96,779 people in the United States died from drug abuse. This data on drug overdose deaths increases by 30% every single year (Drug Abuse Statistics). Other data demonstrates that approximately 80,411 people died from opioid overdose in 2021 (CDC Wonder). To lower the death rate and improve drug addicts' health status, scientists have been developing methods to refine reinstatement treatments. For instance, exercise as part of the treatment can activate the brain's reward pathway, decrease glutamate in the striatum, influence the brain's plasticity, and increase adult hippocampal neurogenesis (Lynch et al., 2013). This article mainly discusses the relationship between AHN and addiction to different drugs. Considering the multiple negative effects exhibited by different types of drugs, this article will focus mainly on cocaine, methamphetamine, heroin, Fentanyl, and morphine.

2. Drugs and the brain reward pathways

Drugs affect the limbic system, the part of the brain that processes emotions, in the brain's temporal lobe by altering the dopaminergic synapses in the nucleus accumbens (NAc). They elevate dopamine levels to evoke pleasurable effects in organisms' bodies (Gardner, 2011).

2.1 The brain reward pathway

A brain reward pathway that facilitates reward-seeking behaviors is called the mesolimbic pathway. This pathway involves projecting midbrain dopamine neurons from the ventral tegmental area (VTA) to the nucleus accumbens (NAc). The prefrontal cortex (PFC), amygdala, hippocampus, and other parts of the limbic system are also involved in this mesolimbic pathway (Figure 1) (Lewis et al., 2021). Without drugs, dopamine neurons would release dopamine into the synapses to let the dopamine bind to dopamine receptors, and the dopamine receptors

would spread the message between neurons to evoke a pleasurable effect on the body. The transporter protein would then remove dopamine to recycle it for further use.

The VTA is one of the main activation sites in the mesolimbic pathway. The VTA dopamine, GABA, and glutaminergic neurons are found to be critical for reward processing. According to Cooper's paper, the VTA is heterogeneous and has 60-65% dopamine neurons, 30-35% GABA neurons, and 2-3% glutaminergic neurons. The VTA projects dopamine neurons to the NAc, PFC, and sometimes the amygdala and hippocampus. These dopamine neurons also receive a large amount of glutamatergic input from the PFC, ventral hippocampus (Hipp), and basolateral amygdala (BLA).

The NAc is also one of the main activation sites in the mesolimbic pathway. It is composed mainly of medium spiny neurons (MSNs), which are GABAergic projection neurons and express D1- or D2-like DA receptors. While only NAc D1 MSNs project to the VTA, D1 MSNs and D2 MSNs project to the ventral pallidum (VP).

The PFC plays an important role in the brain reward pathway. It integrates cognitive control and motivation during decision-making. Within the PFC, the infralimbic (IL) medial prefrontal cortex (mPFC) primarily projects to the NAc shell, and the prelimbic mPFC (PrL) projects to the NAc core. While the VTA projects dopamine to the mPFC, the mPFC also sends glutamatergic projections to both the VTA and the NAc (Kim et al., 2016).

As mentioned previously, the vHIPP also projects glutamatergic input to NAc. Moreover, vHIPP is thought to integrate emotional information from the BLA and the locus coeruleus and spatial or contextual information from the dorsal hippocampus. Consequently, the vHIPP-NAc connection influences goal-directed behavior, locomotor responses to addictive drugs, and cue-induced drug-seeking behavior by providing contextually relevant emotional information. The role of the hippocampus in the mesolimbic pathway is the focus of discussion in this article.

The BLA also plays a role in the brain reward circuitry. Previous studies have found that activating BLA-NAc projections can facilitate reward-seeking behavior. The BLA particularly mediates fear- and anxiety behaviors (Cooper et al., 2017). Anxiety is one of the reasons why drugs can be so addictive, so the BLA is often a focus of many researchers.

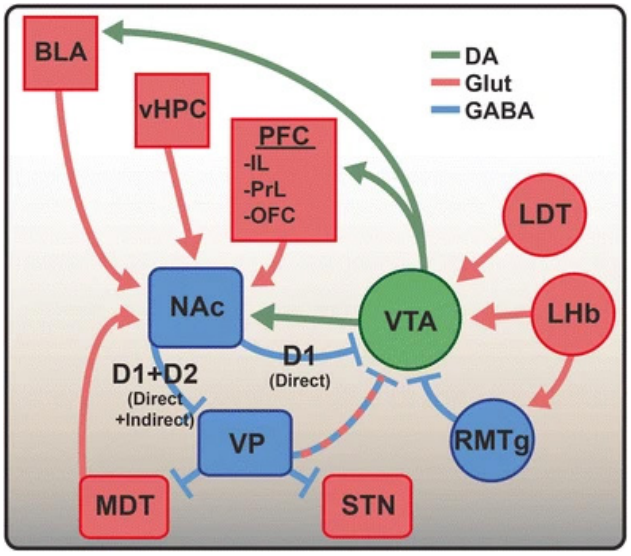

Figure 1. A visual graph that marks neural transmission between the ventral tegmental area (VTA), the nucleus accumbens (NAc), the ventral pallidum (VP), the rostral medial tegmentum (RMTg), the prefrontal cortex (PFC), which includes the infralimbic (IL) medial prefrontal cortex, the prelimbic (PrL) prefrontal cortex, and the orbitofrontal cortex (OFC), the bastrolateral amygdala (BLA), the ventral hippocampus (vHPC), the laterodorsal tegmentum (LDT), the lateral habenula (LHb), the mediodorsal thalamus (MDT), and the subthalamic nucleus (STN). Furthermore, D1 and D2 stand for dopamine type 1 receptor and dopamine type 2 receptor, respectively (Cooper et al., 2017).

2.2 Cocaine brain reward pathway

When cocaine is consumed and enters the brain, it blocks the presynaptic transporters that recycle serotonin, noradrenaline, and dopamine, causing an accumulation of these neurotransmitters. The accumulation of serotonin influences serotoninergic activity, which might induce seizures; the accumulation of noradrenaline, a neurotransmitter that activates the alpha- and beta-adrenergic receptors, enhances adrenergic response; the accumulation of dopamine leads to a release of an abnormally large number of natural neurotransmitters and a sudden evoke of pleasurable effects. Cocaine can also act directly over adrenergic, N-methyl-D-aspartate (NMDA), and sigma and kappa opioid receptors (Roque Bravo et al., 2022). Though cocaine causes the brain reward pathway to function abnormally, the activated brain regions are similar to that of a normal reward pathway: the VTA, NAc, and PFC.

2.3 Methamphetamine brain reward pathway

Similar to cocaine, methamphetamine is also a stimulant, so it also blocks dopamine from re-entering the presynaptic transmitters, causing dopamine to accumulate and evoking a strong feeling of pleasure (The reward circuit: How the brain responds to methamphetamine). The activated brain regions are the same as well.

2.4 Heroin brain reward pathway

Heroin impacts the brain's reward pathway by having a chemical structure mimicking a natural neurotransmitter. This way, heroin could attach to the neurons and activate them. Animals have heroin-seeking behavior when the neural switch in the ventromedial prefrontal cortex (vmPFC) is turned on. Different from cocaine-seeking brain circuitry, in which information is processed in series, heroin-seeking brain circuitry has information processed in parallel. For cocaine seeking, the dorsal-ventral circuits connected through Haber's loops are interdependent, but for heroin seeking, the circuits are independent, as in "parallel" (Figure 2) (Peters et al., 2013). This is one significant difference between stimulants and opioids, but research shows that the hippocampus still plays an important role in both brain reward pathways. Moreover, the frontostriatal circuitry that connects the dorsal-ventral circuits in heroin addicts is dysfunctional, as is evident from the fact that compared with normal people, heroin addicts have significantly smaller vmPFC and NAc volumes (Husain, 2023).

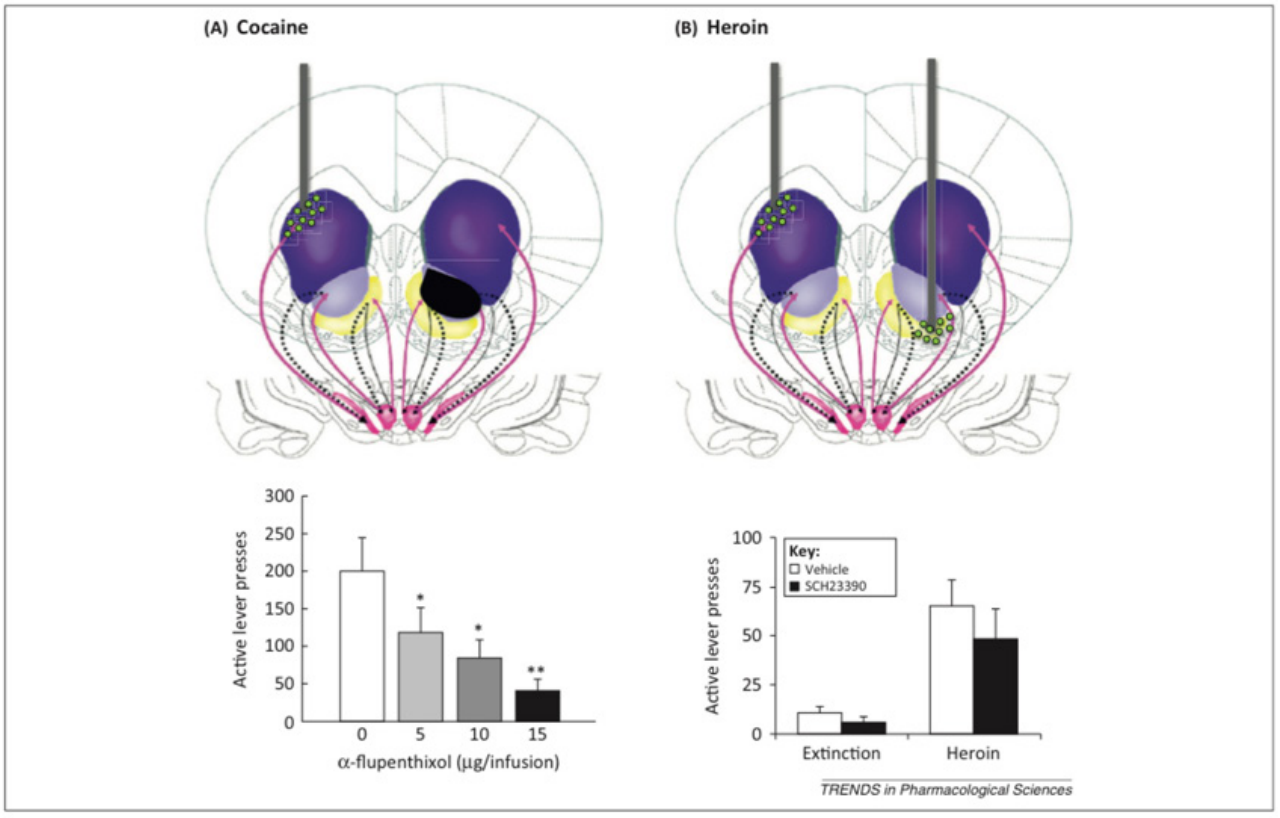

Figure 2. Difference between the dorsal-ventral circuits of cocaine-seeking and heroin-seeking. For cocaine-seeking, the circuits are interdependent, but for heroin-seeking, they are independent (Peters et al., 2013).

2.5 Fentanyl brain reward pathway

Like heroin, Fentanyl is also an opioid that binds to opioid receptors in the limbic system and elevates dopamine levels significantly. Fentanyl enhances the activity of MSNs in the striatum (Neuroscience News, 2023). The brain reward pathway for fentanyl addiction is similar to that of heroin addiction.

2.6 Morphine brain reward pathway

Morphine is also an opioid, so its brain reward circuitry is similar to that of Fentanyl and heroin. It also has the mu-opioid receptor (MOR) as the key to the circuitry. In some studies, the ventral tegmental area-medial prefrontal cortex (VTA-mPFC) circuit is involved in morphine reward (Kim et al., 2016). Previous studies show that the

VTA-hippocampus circuit plays a role in the acquisition of morphine-induced conditioned place preference (CPP), suggesting that the hippocampus does play a role in impacting the brain reward circuitry.

3. Adult hippocampal neurogenesis and drug abuse

In Noonan's paper, reduced AHN through cranial irradiation (IRR) was found to influence mice's cocaine self-administration behavior (Figure 3) (Noonan et al., 2010). In Castilla-Ortega's study and Rivera's study, reduced AHN through either TMZ treatment (temozolomide dissolved in dimethylsulfoxide, or DMSO) or IRR enhanced mice's vulnerability to drug addiction as well (Castilla-Ortega et al., 2015; Rivera et al., 2019). Reduced AHN was shown to influence the reaction to cocaine administration of the following brain regions: supra pyramidal (SupraDG) and infrapyramidal (InfraDG) blades of the DG, hippocampal *Cornu ammonis* (CA) in the CA3 and CA1 areas, PrL, IL, accumbent nucleus (Acb) in its core (AcbC) and shell (AcbSh), dorsomedial striatum (dmCPU), dorsolateral striatum (dlCPU), central amygdala (Ce), BLA, medial septum (MS), lateral septum (LS), and the paraventricular hypothalamic nucleus (PVN). Castilla-Ortega detected that, except for CA3, CA1, and BLA, cocaine treatment significantly affected all the assessed brain areas (Figure 4&5) (Castilla-Ortega et al., 2015). Such findings suggest that reduced AHN can largely alter the brain reward pathway, making it function abnormally as some regions are not as active while some are more active than usual. Castilla-Ortega explains in her paper that the TMZ treatment could damage the functional connectivity of the dentate gyrus, thus prohibiting the motivation of drug seeking. This also explains why the involvement of the IL, Acb, and PVN areas increased when mice underwent the TMZ treatment.

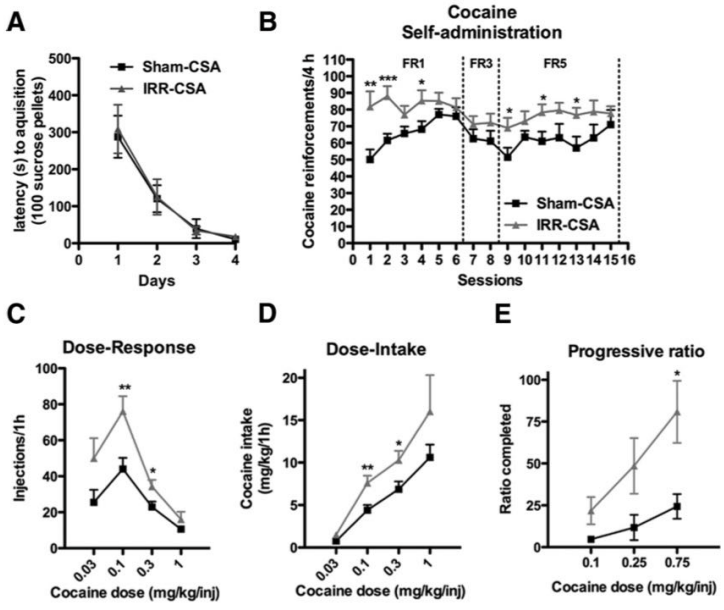

Figure 3. Cranial irradiated mice are shown to be self-administrating more cocaine, especially during the 24-hour reinforcement period (Noonan et al., 2010).

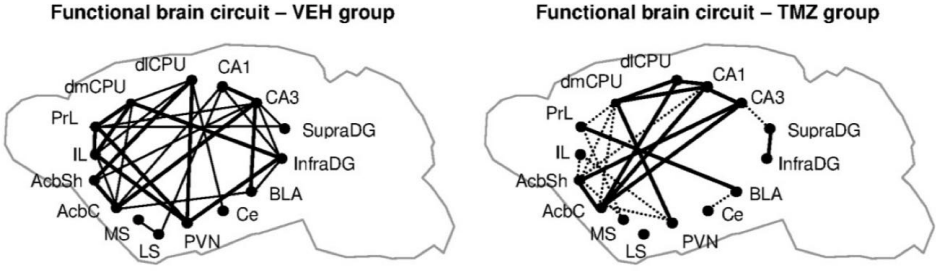

Figure 4. The brain reward pathway is significantly altered after treating the rats with TMZ (Castilla-Ortega et al., 2015).

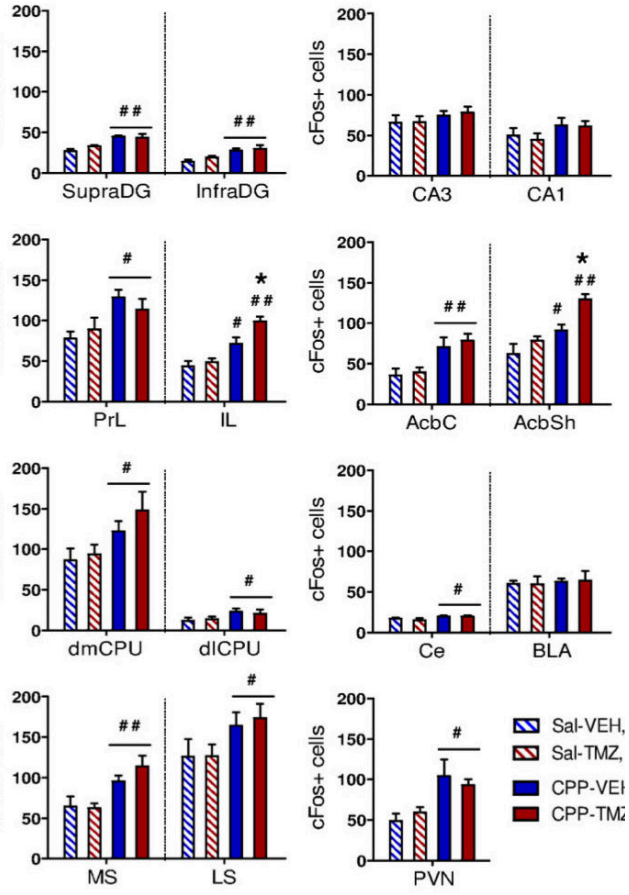

Figure 5. C-Fos expression shows that different brain regions' activities are altered after treating rats with TMZ (Castilla-Ortega et al., 2015).

As mentioned previously, opioids (heroin, Fentanyl, morphine) function and alter the brain reward pathway differently compared with stimulants (cocaine and methamphetamine). The dorsal-ventral circuits connected by Haber's loops are interdependent for stimulants, but for opioids, the circuits are independent. However, since the brain regions involved in both brain reward pathways are similar (both involve the activation of the VTA, the NAc, the PFC, the hippocampus, and other previously mentioned brain regions), the reduced AHN will possibly also affect opioid-seeking behaviors and enhance mice's vulnerability to opioids. Both types of drugs go through the mesolimbic pathway (VTA-NAc) and involve the PFC, CA, and MSN areas, which are areas influenced by reduced AHN. Therefore, the effect of reduced adult hippocampal neurogenesis should be similar for both stimulants and opioids.

4. Conclusion

Reduced adult hippocampal neurogenesis is shown to enhance a mouse's vulnerability to drug addiction by altering the brain reward circuitry or the mesolimbic pathway. When AHN is reduced, particular brain regions, such as the IL, Acb, and PVN, show increased involvement in the reward pathway. Currently, there has not been clear evidence of the direct link between reduced AHN and the increased mouse's drug-seeking behavior. However, if there is one, then reduced AHN should lead to similar impacts on stimulants and opioids, at least all strong drugs. Further research could be done to discover the mechanism of this phenomenon and certify whether a direct link exists. There have already been some researchers developing treatments, like exercise, to improve drug rehabilitation using this novel discovery of the relationship between reduced AHN and drug abuse or drug-seeking behavior. Henceforth, if a direct link between AHN and drug addiction is proven its existence, then researchers could develop better methods to treat the drug abuse problem in the world.

5. References

Adinoff, B. (2004). Neurobiological processes in drug reward and addiction. *Harvard Review of Psychiatry, 12*(6), 305–320. https://doi.org/10.1080/10673220490910844

Bulin, S. E., Mendoza, M. L., Richardson, D. R., Song, K. H., Solberg, T. D., Yun, S., & Eisch, A. J. (2017). Dentate gyrus neurogenesis ablation via cranial irradiation enhances morphine self-administration and locomotor sensitization. *Addiction Biology*, *23*(2), 665–675. https://doi.org/10.1111/adb.12524

Castilla-Ortega, E., & Santín, L. J. (2020). Adult hippocampal neurogenesis as a target for cocaine addiction: A review of recent developments. *Current Opinion in Pharmacology*, *50*, 109–116. https://doi.org/10.1016/j.coph.2019.10.002

Castilla-Ortega, E., Blanco, E., Serrano, A., Ladrón de Guevara-Miranda, D., Pedraz, M., Estivill-Torrús, G., Pavón, F. J., Rodríguez de Fonseca, F., & Santín, L. J. (2015). Pharmacological reduction of adult hippocampal neurogenesis modifies functional brain circuits in mice exposed to a cocaine conditioned place preference paradigm. *Addiction Biology*, *21*(3), 575–588. https://doi.org/10.1111/adb.12248

Centers for Disease Control and Prevention. (n.d.). *Multiple cause of death data on CDC Wonder*. Centers for Disease Control and Prevention. https://wonder.cdc.gov/mcd.html

Cooper, S., Robison, A. J., & Mazei-Robison, M. S. (2017). Reward circuitry in addiction. *Neurotherapeutics, 14*(3), 687–697. https://doi.org/10.1007/s13311-017-0525-z

Deschaux, O., Vendruscolo, L. F., Schlosburg, J. E., Diaz-Aguilar, L., Yuan, C. J., Sobieraj, J. C., George, O., Koob, G. F., & Mandyam, C. D. (2012). Hippocampal neurogenesis protects against cocaine-primed relapse. *Addiction Biology*, *19*(4), 562–574. https://doi.org/10.1111/adb.12019

Drug overdose death statistics [2023]: Opioids, Fentanyl & more. NCDAS. (2023, January 1). https://drugabusestatistics.

org/drug-overdose-deaths/

Gardner, E. L. (2011). Addiction and brain reward and Antireward Pathways. *Chronic Pain and Addiction*, 22–60. https://doi.org/10.1159/000324065

Husain, M. (2023). The Addicted Brain: Differences between heroin and cocaine? *Brain*, *146*(4), 1227–1227. https://doi.org/10.1093/brain/awad065

Jasinska, A. J., Stein, E. A., Kaiser, J., Naumer, M. J., & Yalachkov, Y. (2014). Factors modulating neural reactivity to drug cues in addiction: A survey of human neuroimaging studies. *Neuroscience & Biobehavioral Reviews*, *38*, 1–16. https://doi.org/10.1016/j.neubiorev.2013.10.013

Kavanagh, O. N., & Machado, T. C. (2023). A method of diamorphine (heroin) administration for harm reduction. *Harm Reduction Journal, 20*(1). https://doi.org/10.1186/s12954-023-00758-1

Kim, J., Ham, S., Hong, H., Moon, C., & Im, H.-I. (2016a). Brain reward circuits in morphine addiction. *Molecules and Cells, 39*(9), 645–653. https://doi.org/10.14348/molcells.2016.0137

Kiyatkin, E. A. (2019). Respiratory depression and brain hypoxia induced by opioid drugs: Morphine, oxycodone, heroin, and Fentanyl. *Neuropharmacology, 151*, 219–226. https://doi.org/10.1016/j.neuropharm.2019.02.008

Koob, G. F., & Volkow, N. D. (2016). Neurobiology of addiction: A neurocircuitry analysis. *The Lancet Psychiatry*, *3*(8), 760–773. https://doi.org/10.1016/s2215-0366(16)00104-8

Kramer, J., Dick, D. M., King, A., Ray, L. A., Sher, K. J., Vena, A., Vendruscolo, L. F., & Acion, L. (2020). Mechanisms of alcohol addiction: Bridging Human and Animal Studies. *Alcohol and Alcoholism, 55*(6), 603–607. https://doi.org/10.1093/alcalc/agaa068

Lewis, R. G., Florio, E., Punzo, D., & Borrelli, E. (2021). The Brain's reward system in health and disease. *Circadian Clock in Brain Health and Disease*, 57–69. https://doi.org/10.1007/978-3-030-81147-1_4

Lynch, W. J., Peterson, A. B., Sanchez, V., Abel, J., & Smith, M. A. (2013). Exercise as a novel treatment for drug addiction: A neurobiological and stage-dependent hypothesis. *Neuroscience & Biobehavioral Reviews, 37*(8), 1622–1644. https://doi.org/10.1016/j.neubiorev.2013.06.011

Neuroscience News. (2023, February 21). *Brain circuit involved in fentanyl abuse and relapse identified*. https://neurosciencenews.com/brain-circuit-fentanyl-addiction-22538/

Niibori, Y., Yu, T.-S., Epp, J. R., Akers, K. G., Josselyn, S. A., & Frankland, P. W. (2012). Suppression of adult neurogenesis impairs population coding of similar contexts in hippocampal CA3 region. *Nature Communications*, *3*(1). https://doi.org/10.1038/ncomms2261

Noonan, M. A., Bulin, S. E., Fuller, D. C., & Eisch, A. J. (2010). Reduction of adult hippocampal neurogenesis confers vulnerability in an animal model of cocaine addiction. *The Journal of Neuroscience*, *30*(1), 304–315. https://doi.org/10.1523/jneurosci.4256-09.2010

Peters, J., Pattij, T., & De Vries, T. J. (2013). Targeting cocaine versus heroin memories: Divergent roles within ventromedial prefrontal cortex. *Trends in Pharmacological Sciences*, *34*(12), 689–695. https://doi.org/10.1016/j.tips.2013.10.004

Rivera, P. D., Simmons, S. J., Reynolds, R. P., Just, A. L., Birnbaum, S. G., & Eisch, A. J. (2019). Image-guided cranial irradiation-induced ablation of dentate gyrus neurogenesis impairs extinction of recent morphine reward memories. *Hippocampus*, *29*(8), 726–735. https://doi.org/10.1002/hipo.23071

U.S. Department of Health and Human Services. (n.d.). *The reward circuit: How the brain responds to methamphetamine*. National Institutes of Health. https://nida.nih.gov/videos/reward-circuit-how-brain-responds-to-methamphetamine

Sartor, G. C., & Aston-Jones, G. (2013). Post-retrieval extinction attenuates cocaine memories. *Neuropsychopharmacology*, *39*(5), 1059–1065. https://doi.org/10.1038/npp.2013.323

Zhang, J., Song, C., Dai, J., Li, L., Yang, X., & Chen, Z. (2022). Mechanism of opioid addiction and its intervention therapy: Focusing on the reward circuitry and mu-opioid receptor. *MedComm, 3*(3). https://doi.org/10.1002/mco2.148

Zhang, L., & Yuan, T.-F. (2019). Exercise and substance abuse. *International Review of Neurobiology*, 269–280. https://doi.org/10.1016/bs.irn.2019.07.007