Roles of Extracellular Vesicles in Opioid Addiction: Potential Applications

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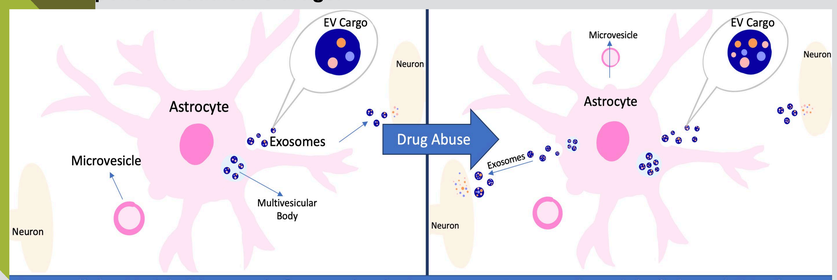
Abstract

Extracellular Vesicles (EVs) are lipid-bilayer membranous vesicles that facilitate intercellular communication via their secretion. EVs contain a variety of cargoes that reflect the intracellular environment of their host cells, and these cargoes can induce functional changes in recipient cells. A wide body of previous research has demonstrated that EVs play a role in a diverse range of disease pathologies as well as regular function and have emerged as promising vehicles for therapeutics and drug-delivery systems. Unsurprisingly, some work has recently been published implicating EVs in drug addiction pathways and therapeutics. Given the pressing scope of the opioid misuse and abuse in the U.S., it is necessary to consider the role of EVs in the development of opioid dependence and tolerance, as well as their role in potential therapeutics. The current review seeks to identify work investigating the role of EVs in opioid addiction and identify gaps and future directions in the literature.

Background

- **Misuse of prescription opioids and non-prescription heroin accounted for two-thirds of drug-overdose related deaths in 2017.[1]**
- **Understanding the mechanisms underlying opioid addiction and potential treatments for opioid dependency has become an increasingly urgent topic of investigating.**
- **Extracellular Vesicles are a heterogenous class of lipid-bilayer vesicles that are key players in cell-to-cell communication and cargo transmission.**
- **EV cargoes are reflective of the intracellular conditions of the host cell and can be transmitted from host to recipient cells to induce functional changes in the recipient cell.[2] Cargoes include:**
  - ***Lipids***
  - ***Proteins***
  - ***Small non-coding RNAs***
- **EV subclasses:**
  - ***Exosomes (30 nm – 150 nm)***
  - ***Microvesicles (100 nm – 500 nm)***
  - ***Apoptotic Bodies (500 nm – 5000 nm)***
- **EVs have been implicated neurodegenerative diseases, cardiovascular disease, HIV, and many cancers.[3] EVs also play a role in regular physiological processes, including immune response, exercise, and stem-cell communication.**
- **EV cargo (miRNA) has been implicated in the body's response to addictive substances and select studies have demonstrated elevated EV release in response to addictive drugs.[4]**



Extracellular Vesicle biogenesis & secretion in Astrocytes. Proposed model of altered EV release following chronic drug abuse. Drug abuse enhances EV secretion and alters EV cargoes, specifically miRNA, which may impact gene expression in receiving cells.

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Hypothesis

Extracellular Vesicle-associated cargoes play a critical role in exacerbating opioid addiction and dependency. EVs have the potential to serve as vehicles for therapeutics in opioid addiction.

Methods

Search Database: PubMed

Search Terms: *extracellular vesicles, exosomes, microvesicles, opioids, addiction, opioid dependence*

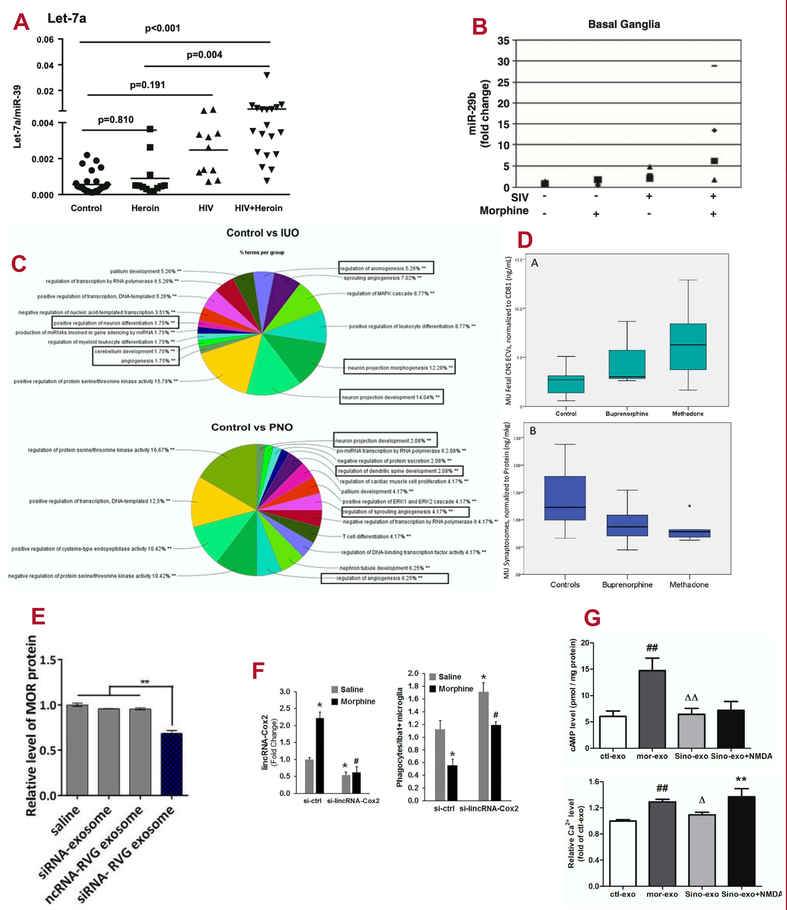
Drugs Considered: All Opioid Analgesics, including prescription opioids & illicit Heroin

Excluded studies that did not investigate the role of EVs in opioid dependence and addiction or therapeutics

Results

Opioid(s) Investigated	Context	Findings	Source
Heroin	Opioids & HIV-related Neuronal Disfunction	Interaction of HIV and heroin leads to increased levels of inflammatory exosomal miRNAs not displayed by subjects exposed to HIV or heroin alone.	Wang et. al (2019).[5] **A**
Morphine	Opioids & HIV-related Neuronal Disfunction	Morphine exposure increased exosomal miRNA-29b secretion from astrocytes. Increased miRNA-29b presentation decreased cell-viability via decreased PDGF-B expression.	Hu et. al (2012).[6] **B**
Oxycodone	Maternal Opioid Use	Significant alternation of In-Utero Oxycodone (IUO) Exposed BDE Cargo, including miRNAs associated with brain development. Significant reduction in spine density of IUO offspring compared with PNO and controls.	Shahjin et. al (2019).[7] **C**
Methadone & Buprenorphine	Maternal Opioid Use	Fetal nervous system derived EVs from maternal blood revealed upregulated Mu Opioid Receptor (MOR) protein levels. EVs signatures signaled crosstalk between cannabinoid and opioid receptors.	Goetzl et. al (2019).[8] **D**
Morphine	Cargo Delivery Vehicles	Exosomal delivery of MOR-siRNA reduced the expression of MORs in target recipient cells	Liu et. al (2015).[9] **E**
Morphine	Cargo Delivery Vehicles	Uptake of morphine-exposed astrocyte-derived extracellular vesicles (ADEVs) by microglia led to impaired microglial phagocytosis. Intranasally delivered lincRNA-Cox2 siRNA-loaded ADEVs in morphine exposed mice microglia restored microglial phagocytic activity.	Hu et. al (2018).[10] **F**
Morphine	Cargo Delivery Vehicles	Chronic morphine upregulated activation of CaMKII and CREB (hippocampal signaling pathway associated with addiction memory). ADEV delivered sinomenine attenuated morphine dependence.	Ou et. al (2018).[11] **G**

Results



Conclusion and Future Directions

Extracellular Vesicles and their associated cargos likely play a significant role in mediating the body's response to opioids. Research evaluated in this review has demonstrated that EVs may play a crucial role in opioid-mediated neuroinflammation. Further, EVs have a promising future in therapeutics as cargo delivery systems. Future study is necessary to fully understand the role of EVs in mediating the response to opioids and to harness the potential of EVs as therapeutic delivery systems to fight opioid addiction and dependence. This study will be incorporated into a forthcoming, more comprehensive review of extracellular vesicles.

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