EVs, Substance Abuse, and HIV

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While extracellular vesicles (EVs) have been shown to play a role in CNS disorders, the intersection of EVs, drug use, and HIV is of particular interest. The interactions of HIV and drugs of abuse are a growing concern given the increasing incidence of HIV transmission via shared needles in illicit drug use. As a drug commonly taken through shared needles, METH is being investigated due to its role in exacerbating HIV-mediated inflammation through both increased vesicular shedding and extracellular release. *In vivo* experiments have shown that cocaine-induced EV release impacts synaptic plasticity through noncoding RNA. Nicotine studies have also highlighted how the differential packaging of antioxidant enzyme cargoes into EVs affects nicotine-mediated HIV pathogenesis. Additionally, studies of both morphine and heroin have demonstrated differences in the miRNA cargoes of EVs, potentially impacting gene expression and exacerbating HIV. Studies of alcohol use in combination with HIV have shown that EV cargoes such as cytokines are affected in HIV-infected subjects who use alcohol. Investigating EV cargo alterations in all forms of substance abuse studies may allow the EV, HIV, and addiction fields to progress towards diagnosis and remedies for substance-abuse-induced toxicity in HIV patients.

Extracellular vesicles (EVs) substance abuse HIV cocaine methamphetamine (METH) alcohol heroin nicotine

1. Introduction

1.1. Extracellular Vesicles

Extracellular vesicles (EVs) are a broad, heterogeneous class of membranous lipid-bilayer vesicles that facilitate intercellular communication throughout the body. Secreted from all cell types, these cargo carriers have become important targets of investigation in various fields of study for their potential role in disease pathologies, drug-delivery systems, and therapeutics [1][2]. For the purpose of this review, all three classes of EVs—exosomes (30–150 nm), microvesicles (100–500 nm), and apoptotic bodies (500–5000 nm)—are collectively referred to as EVs, as endorsed by the International Society for Extracellular Vesicles [3]. EVs carry a variety of cargo types, including proteins, lipids, DNA fragments, and a variety of small noncoding RNAs, including miRNAs, mRNAs, and siRNAs [4][5]. The contents of EVs are reflective of the intracellular environments of their host cells, and EVs are released by both healthy and diseased cells [6]. EVs can transfer these cargoes from host cells to recipient cells, inducing functional transformations within recipient cells [7][8][9]. Regulation of EV secretion remains an active area of study,

although certain stimuli and cellular conditions have been implicated in triggering EV release from different cell types [10].

EVs play a role in various aspects of healthy physiology, including immune responses [11][12], embryonic stem-cell communication during embryo implantation [13], and exercise [14][15]. EVs also shuttle essential biomolecules between cells that are critical for intercellular communication [16], antigen presentation [17], and signal transduction [18]. Moreover, EVs derived from mesenchymal stem cells have garnered interest in the fields of tissue repair, inflammation, anticancer therapy [19], and stroke [20][21]. Further, compelling evidence marks EVs as a potential drug-delivery system [1][22][23][24]; indeed, engineered EVs are capable of passing through the blood–brain barrier (BBB) [25], which has traditionally been a roadblock for efficient drug delivery to the brain [26][27][28][29].

Besides their beneficial role in the maintenance of physiological homeostasis and potentially therapeutic, diagnostic, and drug-delivery capabilities, EVs have been implicated in many pathogenies, including cardiovascular disease [30], neurodegenerative disorders [31][32][33][34], traumatic brain injury [35][36], HIV [37][38], and a wide range of cancers [39][40][41][42][43]. For instance, EVs may contribute to cancerous proliferation through angiogenesis, migratory and invasive capacities, and formation of metastatic lesions [44]. Dissecting the role and effects of EVs in these disease pathologies presents an ongoing challenge and an opportunity to progress understanding of the mechanisms underlying a diverse array of pressing health issues. Specifically, EV contents may indicate pathological changes in the body, and analysis of the molecular cargoes of the EVs may contribute to the advancement of diagnostic and treatment methods for these diseases.

1.2. Extracellular Vesicles in CNS Disorders and Addiction

1.2.1. EVs and CNS Disorders

Central nervous system (CNS) cells like neurons, microglia, astrocytes, oligodendrocytes, ependymal, and brain endothelial cells communicate by releasing EVs containing signaling molecules [45][46]. EVs aid in the signal transmission between neurons and glial cells, along with communication between CNS and peripheral body systems [47][48][49]. EVs maintain cellular homeostasis and clear abnormal aggregates; however, they also contribute to pathogenesis by delivering toxic substances to healthy cells, leading to inflammation and neurodegeneration [50] and thereby perpetuating CNS-associated neurodegenerative disorders [51][52]. Such CNS disorders include lysosomal storage disorders, Parkinson's disease (PD) [53], Alzheimer's disease (AD) [54][55][56][57], Huntington's disease, amyotrophic lateral sclerosis [58], epilepsy, and multiple sclerosis [59][60][61][62][63]. EVs exacerbate disease pathogenesis by providing transportation to abnormally folded proteins and disease factors like α-synuclein [64], amyloid beta (Aβ) and Tau [65][66], huntingtin, and superoxide dismutase 1 [52][58].

EVs in diseased states differ significantly in their morphology and function, making them ideal biomarker candidates [67] as they contain unique proteins depending on the healthy or diseased microenvironment conditions [68][69]. The ability of EVs to cross the BBB, combined with their prevalence in bodily fluids, makes it possible to detect certain biomarkers found in difficult-to-assess regions like the CNS and spleen [70]. EVs may also contribute to neuroprotection; in AD, EVs sequester Aβ in vitro and promote its clearance, thus reducing neurotoxicity [71][72]

[73]. Moreover, neuronal EVs carry extracellular RNAs [74][75], including disease miRNA signatures that could be used as biomarkers to diagnose CNS disorders [58][76][77][78].

Additionally, EVs are potential candidates as therapeutic delivery agents as they can be easily loaded with therapeutic drugs, are minimally degraded, maintain their morphology and function, and can cross the BBB [2][79][80][81][82]. Due to their ability to carry functional small miRNA, tRNAs, lipids, and proteins [83], EVs are excellent carriers of the therapeutic agents. Besides acting as protective barriers against degradation and immunoreactivity, EVs can also increase the efficiency of delivery to targets, further aiding drug delivery and therapy for CNS diseases.

1.2.2. EVs and Substance Abuse

Investigations into the role of EVs in drug addiction and as future therapeutics for addiction are currently represented by a small but developing body of work [84]. Recent evidence points to a role of EV cargoes, specifically noncoding regulatory miRNAs [85], in mediating the body's response to a variety of addictive substances, including cocaine [86][87], cannabinoids [88], nicotine [89], alcohol [90], and opioids [91][92]. These studies indicate that EVs and their cargoes may play a significant role in modulating addiction to a variety of substances, but further investigation is required to understand the full impact of EVs on addictive pathways and of addictive substances on EV secretion, uptake, and cargo content. There is a significant gap in the knowledge connecting substance abuse and our understanding of EVs and their cargoes in those addiction pathologies, although many investigators are currently working to close that gap.

2. EVs, Substance Abuse, and HIV

The Centers for Disease Control and Prevention (CDC) reports that out of 38,739 HIV infected individuals in the United States, 9% (3641) are individuals who inject drugs (http://www.cdc.gov/hiv/group/hiv-idu.html). As EVs can cross the BBB, the presence of HIV components in EVs can contribute to neuroinflammation [93] and neurodegeneration [6]. The interactions of HIV and drugs of abuse are of growing interest given the growing incidence of HIV transmission via shared needles during illicit drug use [94][95][96]. HIV exposure may also perpetuate addiction to stimulants [97]. Studies of HIV suggest that neuropathologies and substance abuse disorders often have a complex relationship that cannot be classified in one direction [98][99][100]; HIV and substance use together frequently result in the exacerbation of CNS disorders [101]. EVs are likely a key communication factor causing this exacerbation and interrelationship between HIV and substance abuse [102], however further research needs to be performed.

HIV is particularly hard to treat due to its ability to amass beyond the blood–brain barrier; it has a wide variety of impacts on the brain, including increased EV release [103][104]. Recently, research has investigated the role EVs play in the progression of microglia-mediated inflammation of HIV-infected subjects [93][103][105]. This inflammatory state is not resolved by combination antiretroviral therapy (cART) and remains a persisting issue [93]. Currently, METH is being investigated for its potential role in exacerbating HIV-mediated inflammation due to its ability to

increase vesicular shedding and extracellular release [106][101][107][108]. Additionally, macrophage-derived EVs from primary human pulmonary arterial smooth muscle cells have been shown to be critically regulated by cocaine addiction and HIV infection [109].

Much like cocaine and METH, nicotine exacerbates HIV pathogenesis through the oxidative stress pathway [94][110]. Interestingly, EVs have revealed a strong correlation between cigarette smoking and HIV [110]. A recent study found that cigarette smoke condensate (CSC) reduced the total protein and antioxidant capacity in EVs isolated from HIV-infected and uninfected macrophages [111]. The EVs isolated from CSC-treated uninfected cells exhibited a protective property against cytotoxicity and viral replication in HIV-infected macrophages. Intriguingly, EVs isolated from HIV-infected cells lost their protective capacity. Further, levels of catalase and PRDX6, antioxidant enzyme cargoes, were decreased in EVs derived from HIV-infected cells. These results highlight the role of antioxidant enzymes in HIV replication and how the differential packaging of these cargoes into EVs affects nicotine-mediated HIV pathogenesis [111]. Indeed, Ranjit et al. suggest that because neurons have a weak antioxidant defense capacity and therefore rely on astrocytes to supply antioxidants, synthetically developed EVs loaded with antioxidant cargoes may be an efficient strategy for offsetting smoking-induced oxidative stress and HIV replication in the CNS [112].

Previous studies suggest that opioids may also play a role in exacerbating HIV-related neurological dysfunction and neuropathogenesis [113]. In simian immunodeficiency virus (SIV)-infected macaque monkeys, a model of HIV, opioid dependency has been demonstrated to increase mortality and exacerbate viral replication [114]. A 2012 study built upon previous studies of the consequences of HIV infection and opioid use by investigating the role of EV-delivered miR-29b in the regulation of PDGF-B gene expression in opioid-dependent SIV-infected macaques [115]. PDGF-B plays a crucial role in neuronal homeostasis, primarily via the protection of hippocampal neurons from glutamate-induced damage. The results of this study indicated that morphine exposure led to increased miR-29b secretion from astrocytes via EVs and demonstrated that increased miR-29b presentation decreased cell viability via decreased PDGF-B expression. This early study was the first to demonstrate that ADEVs can deliver miRNA cargoes to neurons and, in turn, these cargoes can induce functional changes in gene expression in the recipient neurons.

Similarly, a 2019 study investigated the effects of HIV infection and heroin use on inflammation-associated EV miRNA [116]. This study found that HIV-infected heroin users had significantly upregulated levels of miR-146a, miR-126, miR-21, and miR-let-7a, all of which are implicated in neuroinflammation. Interestingly, only the HIV-infected heroin-using group displayed this upregulation; neither uninfected heroin users nor heroin-free HIV-infected patients displayed significant levels of these miRNAs. Further, several members of the let-7 family of miRNA were significantly upregulated within the group of heroin users without HIV infection, namely miRNA-let-7a, -7d, -7e, -7f, -7g, and -7i. The let-7 family is highly conserved across animal species, including humans and mice, and is known to promote cell differentiation [117]. Interestingly, another group noted that morphine significantly increased expression levels of miRNA-let-7a, 7c, and 7g [91]. These results further indicate the importance of understanding the implications of the combination of HIV infection and opioid use as it relates to EV miRNA cargo.

As opioids and needle-sharing are associated with increased risk of HIV infection, alcohol also increases the risk of infection and aggravates HIV replication. Further, alcohol diminishes the adherence to and the efficiency of antiretroviral therapy (ART), which may further enhance HIV replication. HIV infection is correlated with enhanced expression of pro-inflammatory cytokines and chemokines, consequently promoting the pathogenesis of HIV [118]. In the search for a prospective biomarker for alcohol-stimulated toxicity in HIV patients, Kodidela et al. found that HIV-positive alcohol users had substantially lower levels of EV IL-1ra compared to HIV-negative alcohol drinkers. Additionally, no change in the levels of EV IL-1ra was found in the nondrinker HIV-positive subjects. IL-10 was also present in EVs of HIV-positive drinkers. Furthermore, compared to plasma, the percentages of TNF-α, IL-8, and IL-1ra packaged in the EVs isolated from HIV-positive alcohol users were 15%, 10%, and 10%, respectively [118].

In addition to cytokine EV cargo changes, hemopexin (HPX), a protein that binds to free heme, was found in reduced concentrations in the EVs of HIV-positive drinkers, possibly aggravating or contributing to neuroAIDS in those patients [119]. Although unchanged in alcohol drinkers and HIV patients, HPX was substantially downregulated in alcohol users with HIV. HPX may possess an anti-inflammatory function through the negative regulation of TNF-α and IL-6 secretion by macrophages. Additionally, HPX is an extracellular antioxidant, and its diminished level in the EVs of HIV-positive drinkers is consistent with its protective role against alcohol-induced oxidative stress. Additionally, Kodidela et al. found that GFAP expression was significantly enhanced in plasma EVs obtained from HIV-positive subjects and alcohol users, suggesting increased astrocyte activation in those subjects [120]. Exploring EV cargo alterations, such as those listed in Table 1, may allow the field to progress towards diagnosis of and remedies for alcohol-induced toxicity in HIV patients.

Table 1. Differentially regulated EV cargoes identified in studies of substance abuse and HIV.

Cargo		Condition	EV Source	Model	Up/Down	Reference
miRNA	29b	Morphine + HIV	Astrocyte	Rat primary cultures	Up	[115]
	21	Heroin + HIV	Plasma	Human	Up	[116]
	146a	Heroin + HIV	Plasma	Human	Up	[116][121]
	126	Heroin + HIV	Plasma	Human	Up	[116]
	let-7a	Heroin + HIV	Plasma	Human	Up	[116]
	let-7b	Alcohol	Microglia	BV2 cell line	Up	[122]
	276	Methamphetamine (METH)	Plasma	Rat	Up	[123]
	218b	METH	Plasma	Rat	Up	[123]
	194-5p	METH	Plasma	Rat	Up	[123]

Cargo		Condition	EV Source	Model	Up/Down	Reference
	152-3p	METH	Plasma	Rat	Up	[123]
	25	METH	Plasma	Rat	Down	[123]
	276	Ketamine	Plasma	Rat	Down	[123]
	22-3p	METH/Bipolar	Plasma	Rat	Up	[123][124]
	107	Nicotine	Bronchoalveolar lavage fluid (BLF)	Human	Up	[125]
	126	Nicotine	BLF	Human	Up	[125]
	19a-3p	Nicotine	BLF	Human	Up	[125]
	200a-3p	Nicotine	BLF	Human	Up	[125]
	21-3p	Nicotine	Macrophage	RAW264.7 cell line	Up	[126]
	21	SIV	Brain	Monkey	Up	[102]
	182	Alcohol	Astrocyte	Mouse primary culture	Up	[121]
	200b	Alcohol	Astrocyte	Mouse primary culture	Down	[121]
	155	Alcohol	Microglia	BV2 cell line	Up	[122]
	140-3p	Alcohol	Fetal neural stem cells (fNSC)	Mouse	Up	[127]
	15b-3p	Alcohol	fNSC	Mouse	Up	[127]
	340-5p	Alcohol	fNSC	Mouse	Up	[127]
	674-5p	Alcohol	fNSC	Mouse	Up	[127]
	130a	HIV/Cocaine	Monocytes	Monomac-1 cell line	Up	[109]
lncRNA	MALAT1	Nicotine	BLF	Human	Up	[125]
	HOTAIR	Nicotine	BLF	Human	Up	[125]
	HOTTIP	Nicotine	BLF	Human	Up	[125]

Cargo		Condition	EV Source	Model	Up/Down	Reference
	AGAP-AS1	Nicotine	BLF	Human	Up	[125]
	ATB	Nicotine	BLF	Human	Up	[125]
	TCF7	Nicotine	BLF	Human	Up	[125]
	FOXD2-AS1	Nicotine	BLF	Human	Up	[125]
	HOXA11-AS	Nicotine	BLF	Human	Up	[125]
	PCAF1	Nicotine	BLF	Human	Up	[125]
	BCAR4	Nicotine	BLF	Human	Up	[125]
	EGFR	Nicotine	BLF	Human	Up	[125]
	KRAS	Nicotine	BLF	Human	Up	[125]
mRNA	ALK	Nicotine	BLF	Human	Up	[125]
	MET	Nicotine	BLF	Human	Up	[125]
	LKB1	Nicotine	BLF	Human	Up	[125]
	BRAF	Nicotine	BLF	Human	Up	[125]
	PIK3CA	Nicotine	BLF	Human	Up	[125]
	RET	Nicotine	BLF	Human	Up	[125]
	ROS1	Nicotine	BLF	Human	Up	[125]
	130a	HIV/Cocaine	Monocytes; Plasma	Monomac-1 cell line; Human	Up	[109][118]
	IL6/IL-8	Smoking + HIV	Plasma	Human	Up	[118]
Cytokines	IL-6	Smoking + HIV	Plasma	Human	Up	[118]
	IL-1ra	Alcohol/ Nicotine + HIV	Plasma	Human	Up	[118]
	IL-10	Alcohol/Nicotine HIV	Plasma	Human	Up	[118]

Cargo		Condition	EV Source	Model	Up/Down	Reference
Proteins	Amyloid beta (Aβ)	HIV	Brain	Human	Up	[103]
	GFAP	HIV + Alcohol	Plasma	Human	Up	[120]
	L1CAM	Nicotine	Plasma	Human	Up	[120]
	α-synuclein	METH	Neuroblastoma cells	SH-SY5Y cell line	Up	[128]
	TLR4	Alcohol	Astrocyte	Mouse primary culture	Up	[121]
	NFκB-p65	Alcohol	Astrocyte	Mouse primary culture	Up	[121]
	IL-1R	Alcohol	Astrocyte	Mouse primary culture	Up	[121]
	Caspase-1	Alcohol	Astrocyte	Mouse primary culture	Up	[121]
	CPM	HIV	Plasma	Human	Up	[129]
	CDH3	HIV	Plasma	Human	Up	[129]
	HPX	HIV + alcohol	Plasma	Human	Down	[119]
	BAGE	Nicotine	Lung	Human	Up	[125]
	PD-L1	Nicotine	Lung	Human	Up	[125]
	PRDX6	HIV + Nicotine	Macrophage	U937 cells	Down	[111]
	Catalase	HIV + Nicotine	Macrophage	U937 cells	Down	[111]
	CSF2RA	HIV	Plasma	Human	Up	[129]
	MANF	HIV	Plasma	Human	Up	[129]

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