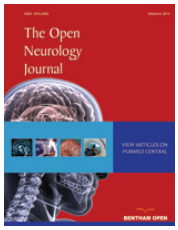

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REVIEW ARTICLE

Exosomes and their Cargo as a New Avenue for Brain and Treatment of CNS-Related Diseases

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Abstract:

Extracellular Vesicles (EVs), which belong to nanoscale vesicles, including microvesicles (MVs) and exosomes, are now considered a new important tool for intercellular neuronal communication in the Central Nervous System (CNS) under physiological and pathological conditions. EVs are shed into blood, peripheral body fluids and cerebrospinal fluid (CSF) by a large variety of cells.

EVs can act locally on neighboring and distant cells. EVs represent the fingerprints of the originating cells and can carry a variety of molecular constituents of their cell of origin, including protein, lipids, DNA and microRNAs (miRNAs).

The most studied EVs are the exosomes because they are ubiquitous and have the capacity to transfer cell-derived components and bioactive molecules to target cells. In this minireview, we focused on cell-cell communication in CNS mediated by exosomes and their important cargo as an innovative way to treat or follow up with CNS diseases.

Keywords: Exosomes, Extracellular vesicles, Cellular communication, Biomarkers, MiRNAs, CNS.

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1. INTRODUCTION

The central nervous system (CNS) is characterized by two-way communication between its various cellular components [1]. Recent studies have shown that the pathogenesis of several neurodegenerative diseases involves an impaired communication between the different cell types in the nervous system [2 - 5].

It is well documented that intercellular communication is mediated by direct cell-cell contact and cell secretome [6, 7]. The main components of the cell secretome are EVs, which can be divided into three subtypes: microvesicles, exosomes, and apoptotic bodies. EVs are heterogeneous membrane structures that circulate in the extracellular body and are involved in cell-to-cell signalling. In the CNS, all cell types release EVs, which can be either taken up by neighbouring cells or released into the cerebrospinal fluid (CSF) and blood. Moreover, the exosomes can cross the Blood-Brain Barrier (BBB) [8, 9].

Cells release EVs, either as a part of normal physiological conditions or in response to precise stimuli. In addition, EVs may exert their role in communication by delivering their cargo molecules implicated in both physiological and pathological processes, from the parent cells to the target cells. Due to their small size, EVs can be diffused from the release site to reach multiple biological fluids [10, 11].

In this minireview, we have summarized the current state of knowledge on the contribution of exosomes and their material to the pathogenesis of CNS disorders, as well as their involvement in the maintenance of healthy physiological conditions.

2. EXTRACELLULAR VESICLES (EVs)

EVs represent a new emerging mode of cellular communication. They circulate in the extracellular body fluid and have the ability to modulate the different biological processes and pathways, including neuroinflammation and a large number of diverse diseases, including neurological disorders [12 - 15]. Prokaryotic and eukaryotic cell types secrete EVs, and in response to specific external signals, the level and the composition of EVs are in a dynamic state reflecting the parental cells.

Moreover, EVs are isolated from the main human body fluids by centrifugation. Cells produce different classes of EVs

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with a diameter of 1-1000 nm: Exosomes (10 –100 nm), microvesicles (MVs) (100 – 1000 nm), and apoptotic bodies (1– 5 nm) [16 - 21]. However, it is evident that this classification is defective, as these size ranges overlap, suggesting that microvesicles in size ranges of exosomes can also bud directly from the cell membrane. Two common pathways are known for the production of EVs: the first pathway, the endosomal sorting complexes required for transport (ESCRT)‐dependent pathway with sphingolipids and the second pathway is an ESCRT-independent route in which tetraspanins are involved [22 - 32].

Certainly, these two different pathways that are generated from the same cell have different EVs with different cargo acting on different target cells [32]. EVs consist of heterogeneous membranous structures and are formed by a phospholipid bilayer that contains active biological molecular components of the parental cell, including proteins, lipids, DNAs, mRNAs, miRNAs, non‐coding RNAs, and organelles [33].

Various protein classes are present in the vesicles, including histones in apoptotic vesicles and exosomal tetraspanins, (CD9, CD63, and CD81) [33, 34]. The most important protein markers that are isolated from MVs are surface receptors, integral membrane proteins, cytosolic proteins. RNAs molecules such as: mRNAs and miRNAs have also been isolated from exosomes and can be used as diagnostic biomarkers [35].

However, various RNA species have been found in EVs, mainly mRNAs and miRNAs. Cells appear to take up EVs through endocytic routes, including endocytosis as the preferred route [36]. However, the penetration of EVs into the cells involves various mechanisms, such as clathrin‐dependent [37] or‐independent endocytosis [38], phagocytosis [39], caveolin‐mediated uptake [40], and lipid‐raft‐mediated absorption [41]. In addition, the presence of proteins and glycoproteins on the EVs surface can influence their mode of entry [42, 43]. In the host cell, EVs can influence their biological messengers in distinct ways, for example, by delivering receptors and/or exchanging phospholipids between cells, consigning intracellular proteins or transferring mRNA, which act as signaling complexes and stimulate target cells directly [44]. Anyway, the principal way utilized by EVs, *i.e*., to stimulate host cells, remains unclear. Various methods and technologies have been developed to detect and isolate EVs from biological fluids based on their physic-chemical properties. Another important parameter used to study EVs is their density. Moreover, different classes of EVs can be isolated by differential ultracentrifugation. Indeed, exosomes [45] and exosome-like vesicles [46] can be isolated with centrifugation at 100, 000 × g or more [47], while Microparticles(MPs)/Microvesicles (MVs) [48] can be isolated with centrifugation at 10,000 × g [16]. The most common used techniques to characterize EVs, which provide the necessary details required regarding the structure of EVs are: atomic force microscopy, procoagulant assays, flow cytometry, and ELISA-based solid-phase capture assays [49, 50]. In addition to electron microscopy, other imaging techniques, including scanning electron microscope (SEM) and the transmission electron microscope (TEM) are also used to analyse all EVs [51]. A large number of studies have reported that EVs in the CNS act as promising vectors in the pathogenesis of neurological diseases, or intercellular communication, or are used for vaccine and drug delivery. Furthermore, circulating EVs can also be used as biomarkers for diagnosis and therapeutic follow-up of CNS-associated diseases [52, 53].

3. EXOSOMES

Various studies have highlighted the great potential of exosomes in cell-to-cell exchanges in the CNS, which can act locally on neighbouring and distant cells [45, 54, 55]. Exosomes, the fingerprints of the cells of origin, can carry a variety of molecules derived from their parent cells, including miRNAs [56]. In fact, exosomes are highly enriched in miRNAs [57, 58].

Recent findings have provided further evidence for the emerging roles of miRNAs and exosomes in neural development, homeostasis, neuron-glia communications, CNS health, and a range of physiological functions [59 - 61]. In addition, we proposed a bidirectional communication model between neurons and glia in neuroprotection, indicating that miRNA from oligodendroglial exosomes contributes to neuroprotection and neuronal integrity [62]. Exosomes can transfer their cargo to the host cell and interact in different ways: receptor-ligand, a direct fusion of membranes, or internalization via endocytosis [63].

The exosomal biological molecules influence the host cells through the following mechanisms: (1) ligand-surface receptor binding and stimulation of target cells, (2) transfer of activated receptors to recipient cells, and (3) epigenetic reprogramming of recipient cells via the delivery of genetic material, RNA, phospholipids and functional proteins [64]. Among all the EVs, exosomes are the most studied EV because of their capacity to deliver natural cellular components. Inside exosomes, different biologically active compounds, including mRNAs, miRNAs and proteins, are present [33, 64, 65].

3.1. The Role of Exosomes miRNA in CNS Health and Diseases

Neurons are the most important cell types in the nervous system and have the ability to receive and transmit impulses through chemical or electrical signals to the periphery and glial cells. In the CNS, glial cells are represented by oligodendrocytes, astrocytes, ependymal and microglial cells, while in the peripheral nervous system (PNS), they are represented by Schwann cells and Satellite glial cells [66]. Exosomes are active actors in intercellular communication, whereas endosomes are released from all cell types, including neurons and glial cells, under healthy and pathophysiological conditions.

The existing literature has highlighted that both exosomes and EVs are used interchangeably and inaccurately to describe exosomes. These exosomes would be useful to investigate the method used in isolation and characterization. The composition of the exosomes not only reflects the content of their original cells, but also their original conditions. These include proteins, lipids, nucleic acids, such as non-coding RNA, rRNA

(ribosomal RNA), and miRNA [53]. This is in line with emerging data showing that exosomes derived from glial cells and mesenchymal stromal cells (MSC) regulate neuronal function by transferring their miRNAs [67, 68]. In fact, MSC-derived exosomes have been shown to transfer miR-17-92 clusters to the distal axons of many cortical neurons, thereby promoting axonal growth [68]. These results suggest that the internalization of exosomal miRNA by the distal axons can modulate axonal biological functions. Additional data have reported an abundance of miRNAs in the embryonic CSF-derived exosomes [69]. It was found that these exosomes enriched with various subsets of miRNAs in the embryonic CSF (eCSF), including miR-124, promote neurogenesis [70]. In addition, another subset of miRNAs such as miRNAs −124, −125b, and −320a/b were also highly enriched in exosomes derived from human eCSF [69]. Interestingly, exposure of eNSCs to eCSF exosomes enriched with miRNAs resulted in NSC amplification. This implies exosomes in eCSF as essential determinants of eNSC development through the coordinated transfer of evolutionarily conserved molecules that are crucial for the regulation of eNSC during corticogenesis [69, 71]. The transfer of another set of exosome-derived miRNA, miR-132, released by neurons to endothelial cells, resulted in the maintenance of BBB integrity by modulating the expression of eukaryotic Elongation Factor 2 Kinase (Eef2k) and the vascular junction cadherin (Cdh5) [72]. This novel mechanism demonstrated the importance of the exosomal miRNA as an essential mediator for neurovascular communication, which is important for regulating the vascular integrity of the brain and maintaining its homeostatic functions. The regulatory effect of the exosomal miRNA is not limited to neurons only but is extended to the most important glial cells of the brain astrocytes and oligodendrocytes. These glial cells release miRNAs loaded exosomes to maintain homeostasis. Interestingly, Jovičić *et al*. found that the profile of miRNAs in exosomes secreted from cultured primary mouse astrocytes differs significantly from the profile of miRNAs detected in astrocytes, suggesting an underlying selective mechanism that certain exosomal miRNAs may include or exclude. The functions and targets of these miRNAs need to be further investigated [62]. More recent findings have shown that exosomal-containing miRNAs were enriched in the synaptodendritic compartment and generated in an activity-dependent manner [73, 74]. This has further provided support to the role of mRNA as a critical regulator of neural plasticity. In summary, the above-mentioned studies suggest that exosome-derived miRNAs may contribute to a variety of homeostatic and adaptive neuronal processes in the normal brain. However, a dysregulation of these mechanisms can lead to premature aging, neuronal damage, and/or neuropathological disorders. Table **1** illustrates the exosomal miRNAs and their various functions in brain cells of mice, rats, and humans in healthy individuals or those with CNS diseases.

Table 1. CNS exosomal miRNA and their various functions in health and diseases conditions.

Exosomal MiRNA Name	Exosomes Origin	Study Model	Target Pathways/CNS Component	Major Function	References
miR-124-3p	CSF-derived exosomes	SOD1G93A mice model of Amyotrophic Lateral Sclerosis (ALS)	Spinal neurons.	Potential use of CSF exosomal miR-124-3p as a disease stage indicator in ALS.	[90]
miR-124	Microglia	Cultured BV2 microglial cells	Targets PDE4B.	Reducing neuroinflammation and increasing neurite growth.	[91]
miR-223;	Dementia patients' serum	Human	AKT pathway through the gene PTEN.	Regulation of dementia-associated apoptosis . Promising biomarker for diagnosing and prognostic evaluation of dementia.	[92]
miR-223-3p highest level expression with other miRNAS	Human plasma	Older individuals (Human)	Various brain functional pathways.	Possible biomarkers in the assessment of age-related cognitive decline and/or in predicting blood-brain barrier dysfunctions.	[93, 94]
miR-140-5p, miR-197-3p, and miR-501-3p	Human serum	Machine learning models to determine whether miRNA can be utilized as a blood-based biomarker of cognitive aging.	Cognitive aging target brain components.	Prediction of multiple cognitive outcomes including in healthy older adults.	[95]
exosomal miRNAs derived fromhypothalamic NSC	Primary culture of NSC	Mouse model and *in vitr*o cultured NSC	Anti-aging speed controlling mechanisms and related hypothalamic pathways.	The anti-aging effect of hypothalamic Neural stem cells (NSC) is partially mediated by exosomal miRNAs secreted from these cells.	[96]

(Table 1) contd.....

Exosomal MiRNA Name	Exosomes Origin	Study Model	Target Pathways/CNS Component	Major Function	References
miR-501-3p	Mouse cerebral endothelial cells	Mouse model of Vascular Cognitive Impairment (VCI)	Cognition and aging processes related pathways.	Predicting BBB disruption and the development of vascular cognitive decline; synaptic plasticity. New avenue to develop optimal treatment for CNS disease with BBB disruption related neurological disorders including dementia. Potential biomarker of AD.	[97 - 99]
miR-127-3p	AD patient's serum	Human	Disease-specific mechanisms that could explain differences between AD and FTD.	Potential biomarker for differential diagnosis of Frontotemporal Dementia (FTD). To discriminate between FTD and Alzheimer disease (AD).	[100]
miR-141-3p	Serum plasma of AD patients	Human	Disease-specific mechanics	Exosomal miRNA as diagnostic biomarkers for neurodegenerative diseases (*e.g.* Alzheimer and Parkinson diseases).	[101 - 104]
miR-141-3p and miR-30d	Primary Human fetal astrocytes	Cultured primary astrocytes	Targets implicated in apoptosis, neuroinflammatory, and neurodegeneration showing possible roles of the selected miRNAs in these pathways.	Potential role in regulating the inflammatory response and oxidative stress induced by IL-1β . -serve as potential biomarkers of CNS neuroinflammation associated with neurological disorders and injuries.	[105]
miR-223;	Serum plasma of dementia patient	Human serum	Disease-specific signalling pathways.	Serum exosomal miR-223 is a promising biomarker for diagnosing dementia and evaluating the progression of disease.	[106]
miR-501-3p	Cultured hippocampal and cortical embryonic rats neuron	Embryonic rat model	Dendrites through the NMDAR subunit GluN2A, local regulation of AMPAR expression in dendrites.	Important roles of miR-501-3p, in NMDAR-dependent GluA1 expression and spine remodelling.	[98]
miR-191 and miR-135	Mouse hippocampus	Sprague Dawley rat embryos ; mouse models	Spine remodelling during development	Essential role for sustained spine remodelling associated with synaptic long-term depression.	[107]
miR-193b-3p	Cultured Bone marrow mesenchymal stem cells (BMSCs) isolated from mouse models	Plasma exosomes in subarachnoid haemorrhage patients and healthy controls.	Remodelling of inflammatory Reponses and neuroprotective effects via the inhibition of HDAC3/NF-κB signal pathway.	The transfer of miR-193b-3p into the brain after subarachnoid haemorrhage (SAH) attenuated neuroinflammation and reduced neuronal degeneration.	[108]
miR-361	Astrocytes-derived exosomal miR-361	Rat model of cerebral Ischemic(I)/Reperfusion (R) injury	miR-361 downregulate the AMPK/mTOR signalling pathway by targeting CTSB.	miR-361 increased OGD/R-inhibited PC12 cell activity and has anti-apoptotic effect. miR-361 targeted cathepsin B (CTSB). miR-361 reduced nerve damage in rats with cerebral I/R rats . Possible novel avenue for treating cerebral I/R injury.	[109]
miR-146a, miR-335-3p, miR-335-5p and miR-155	PD human serum	Idiopathic Parkinson Disease (iPD); patients with a mutation in the leucine-rich repeat kinase 2 (LRRK2) gene).	miRNAs regulate cellular mechanisms implicated in PD pathogenesis, such as inflammatory pathways.	miR-146a, miR-335-3p, and miR-335-5p downregulated in iPD and LRRK2-PD patients versus controls . miR-155 was upregulated in LRRK2-PD compared to iPD patients .	[110]
miR-21, miR-34	Significantly increased in substantia nigra compacta and amygdala respectively	Human PD brain tissue and human SH-SY5Y neuroblastoma cell line	Cell death pathway; pathways responsible for α-synuclein turnover.	While miR-21 and miR-34a are commonly associated with impaired cell death pathway; important role in P pathogenesis and as potentieal biomarkers for PD diagnosis.	[111]

3.2. The Role of Exosomal miRNAs in CNS Diseases, Therapeutics, and Diagnostic Biomarkers under Pathological Conditions

Jia *et al*. have shown that exosome cargo can have deleterious effects. Indeed, high-glucose (HG) stimulated exosomes have been shown to produce high levels of miR-28, -31a, and -130a compared to exosomes derived from non–high glucose- stimulated Schwann cells. In addition, *in vitro* treatment of distal axons with HG exosomes reduced axonal growth. These results demonstrate a functional role of exosomal miRNAs derived from HG- stimulated Schwann cells in promoting the development of diabetic peripheral neuropathy [75]. Functional recovery remains a real challenge after peripheral nerve injuries. This essentially depends on the reprogramming of differentiated Schwann cells (dSCs) into the repair phenotype (rSCs), which are heavily involved in axonal regeneration and neural tissue homeostasis. Interestingly, the repair phenotype releases exosomes that are internalized by the peripheral neurons, promoting axonal regeneration. The reprogramming mechanism of SCs is accompanied by the secretion of exosomes with regenerative potential. These exosomes are characterized by a repair-specific miRNA cargo that promotes neurite growth. Interestingly, an increased expression of miRNA-21, responsible for the regenerative capacity of rSC exosomes was shown. This activates PTEN and PI3-kinase, which are responsible for a large number of biological functions and homeostasis [76]. These results have reinforced our belief that the modification of exosomal miRNA cargo can be viewed as another important feature of the reparative and regenerative potential of SCs by improving the regeneration of axons and their functional recovery after nerve damage. Beyond their biological functions in brain development, health, and CNS homeostatic functions, several studies have demonstrated that exosomal miRNA are potential candidates of miRNA-based therapy against hypoxic-ischemic brain injury. Indeed, the investigation of the effect of non-ischemic and ischemic cerebral endothelial cells (CECs)-derived exosomes on axonal growth and changes of endogenous miRNA profiles within recipient neurons showed that both of these cell types significantly stimulate axonal growth. These observed effects were mediated by the modulation of axonal and stromal miRNAs and their target proteins which are involved in the mechanisms of axonal growth [77]. Exosomes and their cargo miRNAs were able to target key neuropathophysiological signaling pathways and modulate neuroinflammatory processes that are involved in a wide variety of neurological diseases.

This offers new strategies to prevent long-term disease development and progression [11]. Furthermore, exosomal miRNAs were considered as key regulators of gene expression in the CNS microenvironment and genes-related CNS diseases. Exosomal miRNA are considered as potential biomarkers for the diagnosis of CNS -associated diseases [78]. It was recently pointed out that miRNA networks have a regulatory function of cell- type-specific transcriptomes during human brain development [79]. The profiles of the exosomal miRNA derived from certain brain cells can not only influence brain development but also reflect brain damage [80]. It is well established that the BBB microenvironment is the protective structure of the CNS. Given the fact that exosomes can cross the BBB, they could serve as promising accessible diagnostic biomarkers of brain dysfunction. Recent studies have reported that the BBB microenvironment can be controlled by miRNA [81]. More interestingly and similar to BBB, the blood-tumor barrier (BTB) restricts paracellular diffusion. Ma *et al*. have shown that miR- 181a increases the permeability of the BTB by targeting Kruppel-like factor 6 (a transcription factor), suggesting the therapeutic potential of miR-181a against gliomas. In another set of experiments [82], findings have strengthened our convictions about the role of miRNA in therapeutics. Indeed, the authors have shown that exosomes derived from mesenchymal stem cells that overexpress microRNA-199a- have an inhibitory effect on glioma progression by downregulating ArfGAP with GTPase domain, ankyrin repeat, and PH domain 2 (AGAP2). In addition, the combination of miR-199a and hMSCs delivering miR-199a have enhanced the chemosensitivity of glioma cells to temozolomide (TMZ) and inhibited tumor growth *in vivo*. Interestingly, in line with the previously reported role of miR-199a-3p in suppressing the proliferation of glioma cells by regulating the AKT /mTOR signaling pathway [83], interestingly, it was found that the over-expression of miR-199a or the silencing of AGAP2 has led to the inhibition of glioma cell proliferation, migration, and invasion. A recent study has suggested the potential application of exosomal miR-210, miR-5194, and miR- 449 as promising novel non-invasive and highly sensitive diagnostic and prognostic biomarkers for glioma patients [84]. Moreover, the circulating miRNAs can be potentially used in the clinical management of gliomas with different histological grades in patients with a brain tumor [85], showing a correlation between the circulating levels of exosomal miRNA and the development of mental disorders.

CONCLUSION

The incidence of CNS disorders is increasing, and new treatment strategies can be very useful in improving patient management. Various researches in recent years have focused on the investigation of the mechanism involved in neuroprotection [86 - 89]. In addition, exosomes may be an important research topic as therapeutic agents and also as biomarkers in CNS disorders. Exosomes are released from brain cells and can pass through the BBB. In addition, they can be found in CFS, where they could be isolated and analysed to monitor the pathological progress of CNS diseases or treatment assessment and follow-up with the disease progression.

Despite the considerable growing interest in the regenerative ability to circulate exosomal-derived contents and particularly miRNA in CNS health and CNS-related diseases, further investigations are warranted to elucidate the mechanisms of the bi-directional transfer of exosomal miRNA across the BBB. Future perspectives exploring the exosomal miRNA in the various neurological contexts should focus on profiling changes in size or number of exosomes released and changes in cargo.

Taken together, these studies shed new light on the importance of developing new therapeutic strategies for CNS disorders and preventing further CNS damage.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

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