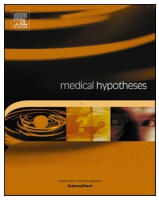
Medical Hypotheses 209 (2026) 111896



Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/ymehy



Neuro-entero-cardiac bridge: could gut-derived catecholamine-loaded extracellular vesicles synchronize the pathogenesis of Parkinson's disease, irritable bowel syndrome, and stress-triggered arrhythmias?

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ARTICLE INFO

Keywords:
Extracellular vesicles
Gut–brain axis
Parkinson's disease
Irritable bowel syndrome
Stress and arrhythmias

ABSTRACT

The gut–brain–heart axis is increasingly recognized as a clinically relevant interface in chronic and stress-responsive disorders. Parkinson's disease (PD), irritable bowel syndrome (IBS), and stress-triggered arrhythmias show epidemiologic and mechanistic convergence through autonomic dysregulation, mucosal immune activation, barrier dysfunction, and systemic inflammatory signaling. However, the molecular messengers that could help "couple" these organ systems over time remain incompletely defined. Extracellular vesicles (EVs) represent a plausible integrative mechanism because they can transport regulatory cargo (RNAs, proteins, lipids) and influence distant tissues, including during inflammation and stress responses. We hypothesize that stress-responsive gut-linked EVs originating from intestinal epithelial, immune, enteroendocrine, and enteric neural compartments may contribute to shared vulnerability across PD, IBS, and arrhythmias by distributing inflammatory and neuroactive regulatory signals (especially microRNAs) systemically. Importantly, direct evidence that gut-derived EVs are "highly enriched" with catecholamines (dopamine, norepinephrine) in PD, IBS, or arrhythmia contexts is currently lacking; therefore, EV-mediated catecholamine transport is presented here as a testable sub-hypothesis rather than an established driver of pathology. Even if EV-associated catecholamines are detectable, they may constitute a minor fraction relative to synaptic/autonomic catecholamine signaling and could represent an epiphenomenon of stress biology rather than a dominant transport route. We outline falsifiable predictions and a rigorous experimental strategy that explicitly addresses EV heterogeneity, contamination by non-EV particles, and causality controls. If supported, gut-linked EV cargo profiles could provide biomarkers that stratify tri-system risk and point toward adjunctive therapeutic approaches that complement established gut–brain–heart pathways (vagus/autonomic signaling and microbiota-derived metabolites, including TMAO-related pathways).

Introduction

Parkinson's disease (PD), irritable bowel syndrome (IBS) and stress-triggered arrhythmias are clinically distinct but share overlapping biology. Gastrointestinal dysfunction can precede motor symptoms in PD by years, and constipation and IBS-like complaints are frequently discussed as prodromal features [1,2]. IBS is characterized by stress-exacerbated abdominal pain, altered bowel habits, and mucosal immune activation with increased permeability in susceptible subsets [3,4]. Stress-triggered arrhythmias arise in predisposed individuals during sympathetic surges and dysautonomia, with inflammatory and neurohumoral factors contributing to arrhythmogenic vulnerability as demonstrated in Table 1 [5,6]. Existing mechanistic models already provide strong explanatory frameworks: (i) autonomic routes, including vagal and sympathetic signaling, connect gut and brain and are implicated in appetite regulation, mood, inflammation, and systemic responses [3,6,7]; (ii) microbiota–gut–brain signaling and microbial metabolites influence neurological and gastrointestinal physiology and

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https://doi.org/10.1016/j.mehy.2026.111896
Received 21 September 2025; Received in revised form 28 January 2026; Accepted 31 January 2026
Available online 7 February 2026
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may also shape cardiovascular risk via inflammatory and metabolic pathways, including TMAO-related mechanisms discussed in the gut-heart literature [7,8]. These models are not in conflict with EV biology. Rather, EVs may represent an additional systems-level layer of communication capable of stabilizing or prolonging molecular signals beyond transient neurotransmitter pulses. EVs are proposed as plausible cross-organ regulators primarily through miRNAs and inflammatory cargo, while catecholamine carriage is treated as an explicitly speculative, falsifiable sub-hypothesis that may be quantitatively minor compared with synaptic/autonomic catecholamine signaling.

The hypothesis

We propose that stress and gut dysfunction induce reproducible shifts in gut-linked EV populations and their regulatory cargo (notably microRNAs, inflammatory proteins, and lipids). These EVs can enter circulation and influence distal targets in the nervous system and myocardium, thereby contributing to a shared vulnerability state across PD progression, IBS symptom flares, and stress-triggered arrhythmias as shown in Table 2. This is conceptually consistent with EV-mediated systemic signaling during inflammation [8], established roles of circulating miRNAs as extracellular communicators and candidate biomarkers in cardiovascular disease [9–13], and stress-related gut changes mediated by corticotropin-releasing factor pathways and downstream immune/barrier effects [14–17].

Catecholamine sub-hypothesis

A narrower and higher-risk claim is that a subset of gut-linked EVs may carry catecholamines or catecholamine-pathway components (e.g., vesicular transport machinery, enzymes, or regulatory miRNAs that modulate adrenergic signaling) [18]. If present at functionally meaningful levels, EV-associated catecholamines could, in theory, alter the duration or spatial distribution of catecholaminergic effects compared with rapidly cleared free catecholamines [19]. However, we do not assume this occurs, and we do not claim catecholamine-loaded gut EVs have been demonstrated in PD/IBS/arrhythmias [20]. Moreover, even if detectable, EV-associated catecholamines may represent a small fraction of total catecholaminergic signaling, which remains dominated by synaptic and autonomic pathways [3,4,18]. This sub-hypothesis therefore requires direct quantification and can be falsified.

Rationale and link to the three conditions

(1) Parkinson's disease

Gastrointestinal α-synuclein pathology and gut involvement have been reported in early PD, with evidence supporting propagation from the gastrointestinal tract to the brain in animal models and discussion of vagal routes as a key pathway [2,14]. We propose that gut-linked EVs may act as adjunctive modulators of PD vulnerability by transporting inflammatory miRNAs/proteins that affect microglial activation, neuronal proteostasis, and oxidative stress responses. This complements (not replaces) established gut–brain mechanisms [6,7,10,11,14,15]. Catecholamine toxicity and monoamine oxidase-linked mechanisms have been proposed to contribute to dopaminergic vulnerability [5], but we do not claim EV catecholamine delivery triggers α-synuclein aggregation. Instead, catecholamines are treated as part of a stress-responsive milieu that may interact with EV-mediated regulatory cargo and autonomic signaling.

(2) Irritable bowel syndrome

IBS is strongly shaped by stress responses, corticotropin-releasing factor signaling, immune activation, and altered barrier function [16,17,20]. In this framework, gut-linked EVs could plausibly sustain or amplify mucosal immune activation and permeability through microRNA-mediated pathways. The mechanistic plausibility of circulating miRNAs as extracellular communicators supports this direction [12,13]. We do not assert catecholamines are validated EV cargo in IBS; rather, stress-related catecholaminergic tone, autonomic signaling, and EV-borne regulatory cargo may interact to influence symptom severity.

(3) Stress-triggered arrhythmias

Stress-triggered arrhythmias reflect sympathetic activation, autonomic imbalance, and myocardial vulnerability [4,18]. Circulating miRNAs are linked to cardiovascular remodeling and intercellular communication [13], and EV signaling is increasingly considered in inflammatory and cardiovascular contexts. We propose that gut-linked

Table 1
Converging pathogenic features of Parkinson's disease, irritable bowel syndrome, and stress-triggered arrhythmias, and an EV-based integrative layer.

Domain	Parkinson's disease	Irritable bowel syndrome	Stress-triggered arrhythmias	Shared substrate (established)	Proposed EV layer (revised; not exclusive)	Key references
Prodromal/Clinical overlap	GI dysfunction, constipation and dysmotility precede motor symptoms	Stress-exacerbated pain, altered bowel habits	Episodes precipitated by acute stress and sympathetic surges	Stress sensitivity, gut dysfunction and dysautonomia	Gut-linked EV cargo profiles may reflect/ participate in systemic vulnerability	[1,2,4,19,20]
Autonomic features	Dysautonomia, altered noradrenergic regulation	Heightened stress responsiveness; autonomic imbalance	Sympathetic hyperactivation lowers arrhythmic threshold	Autonomic pathways are primary coordinators	EVs may modulate autonomic targets indirectly via inflammatory/miRNA signals (hypothesis)	[3,4,18]
Pathological hallmarks	α-syn aggregation, dopaminergic loss, neuroinflammation	Barrier dysfunction, mucosal immune activation, visceral hypersensitivity	Electrical instability, remodeling	Inflammation and stress biology intersect across organs	EV-borne miRNAs/ proteins may sustain inflammatory remodeling across tissues	[12,13,16,17]
Links with stress	Stress accelerates vulnerability through oxidative and inflammatory mechanisms	Stress increases permeability and symptom severity	Stress surges trigger atrial/ventricular arrhythmias	Neuroendocrine stress responses affect all three	EVs may "package" regulatory signals (miRNAs/proteins) that outlast transient stress pulses	[4,16,17]
Candidate regulatory pathways potentially influenced by EV cargo (not validated gut-EV cargo lists)	EV-associated inflammatory regulators; α-syn species reported in EVs in PD contexts (source not necessarily gut)	EV-linked miRNA regulation of barrier/ immune pathways (plausible)	EV/miRNA regulation of remodeling and excitability (plausible)	Shared inflammatory/ miRNA pathways	Catecholamines in gut EVs: unproven sub-hypothesis; prioritize measurement over assumption	[5,12,13]

Table 2
Experimental approaches to test the "neuro-entero-cardiac bridge" hypothesis with explicit controls for EV heterogeneity, contamination, and causality.

Approach	Experimental model/design	Endpoints to assess	Critical controls (added)	Expected findings if hypothesis is valid	Key references
Cohort profiling	Compare circulating EV cargo in PD (prodromal + diagnosed), IBS, stress-arrhythmia phenotypes vs controls	EV-associated miRNAs/proteins; inflammatory markers; optional catecholamine assays	Standardized pre-analytics; EV-enrichment plus EV-depleted controls; replicate isolation methods	Distinct EV-cargo signatures correlate with symptom clusters/ comorbidity	[12,13,19,20]
Co-culture studies	Treat dopaminergic neurons, intestinal epithelial cells, cardiomyocytes with gut-linked EV fractions	Neuronal stress markers; barrier permeability; cytokines; electrophysiology proxies	EV-depleted conditioned media; detergent-disrupted EVs; matched protein/lipoprotein fractions	EV fractions induce cross-tissue regulatory changes more than soluble fractions	[8,12,13]
Stress-challenge models	Rodent chronic stress paradigms with phenotyping (GI, motor, ECG)	Gut permeability; neuroinflammatory markers; arrhythmia thresholds	Confirm EV modulation; parallel autonomic measurements; rule out nonspecific toxicity/off-target inhibitor effects	Stress shifts EV cargo; EV modulation attenuates sustained multi-organ vulnerability	[4,16–18]
Adoptive transfer (cautious)	Transfer purified gut-linked EV fractions from stressed to naïve animals	Behavioral, GI, ECG outcomes	Purity verification; dose–response; heat/detergent inactivation; EV-depleted controls	EV transfer reproduces components of vulnerability (partial phenotypes)	[8,14,15]
Multi-omics integration	EV proteomics/miRNA + clinical/ autonomic phenotyping + metabolite profiling	Systems-level correlations	Avoid over-interpretation; validate in independent cohorts	Integrated EV signatures improve risk stratification beyond single biomarkers	[7,10,12,13]

EV cargo could modulate arrhythmia susceptibility indirectly by influencing inflammation, autonomic responsiveness, and ion-channel regulatory networks via miRNA transfer. Candidate miRNAs often discussed in stress/inflammation contexts (e.g., miR-21, miR-34a) are presented as examples of plausible regulatory nodes, not as validated gut-EV cargo across all three conditions. Microbiota-derived metabolites, including TMAO-related pathways, may also contribute to arrhythmogenic vulnerability and should be integrated analytically with EV profiles rather than treated as competing explanations [6,7,11].

Evaluation of the hypothesis (falsifiable predictions)

Disease and stress-state EV signatures: Circulating EV cargo will differ across PD, IBS, and stress-arrhythmia phenotypes relative to controls, particularly in miRNA and inflammatory proteins. Associations should track clinical features (GI prodrome in PD; stress-exacerbated IBS; arrhythmia inducibility) [12,13,19,20].

Gut linkage: A measurable fraction of circulating EVs will be traceable to gut-associated cellular sources (epithelial/immune/ enteroendocrine/enteric) in relevant models, consistent with systemic EV communication during inflammatory states [8].

Functional effects are EV-dependent: In vitro effects on neuronal stress responses, epithelial permeability, or cardiomyocyte excitability will persist with purified EV fractions and diminish with EV disruption, and will not be reproduced by matched EV-depleted soluble fractions.

Catecholamine sub-hypothesis is testable and can fail: Targeted assays will either (a) detect catecholamines preferentially associated with well-characterized EV fractions under stress/disease conditions, or (b) show no enrichment beyond soluble pools thereby refuting catecholamine-EV transport as a meaningful component. Any detected EV-associated catecholamine signal should be interpreted against the background that synaptic/autonomic catecholamine signaling remains the dominant pathway [3,4,18].

Established pathways (vagus/autonomic signaling and microbiota metabolites, including TMAO-related mechanisms) should be measured in parallel to avoid attributing effects to EVs that are mediated by neural or soluble metabolic routes [3,6,7,11,18].

Consequences and implications

Biomarker implications

A conservative translational expectation is that circulating EV miRNA/protein profiles could stratify patients with (i) GI prodrome suggestive of PD risk [1,2,19], (ii) stress-responsive IBS phenotypes [16,17,20], and (iii) arrhythmia susceptibility during sympathetic surges [4,18]. This aligns with the broader concept of circulating miRNAs as biomarkers and extracellular communicators [13]. Parallel assessment of autonomic indices and microbiota-derived metabolites (including TMAO-related pathways) may further improve risk prediction [3,6,7,11,18].

Therapeutic implications

If EV-mediated regulatory signaling is validated, therapeutic directions could include attenuating pathological EV release/uptake pathways (while monitoring off-target effects), targeting specific EV cargo pathways (e.g., miRNA networks), and integrating EV-based strategies with established interventions addressing autonomic tone and stress-related gut physiology [3,4,16–18]. Claims of EV-catecholamine therapies should be deferred until catecholamine association is directly demonstrated and shown to be quantitatively meaningful.

Limitations and future directions

Catecholamine enrichment is unproven: We do not claim gut EVs are highly enriched with catecholamines in PD/IBS/arrhythmias. This is explicitly a sub-hypothesis requiring direct quantification, and any detected EV-associated catecholamines may be quantitatively minor compared with synaptic/autonomic signaling [3,4,18].

No claim of EV-catecholamine causation of PD: We do not assert EV-delivered catecholamines trigger α-syn aggregation; PD propagation and neurodegeneration are multifactorial and include vagal and microbiota-linked mechanisms [6,7,10,14,15].

Avoiding unvalidated cargo lists: We do not present dopamine/ norepinephrine or specific miRNAs as validated gut-EV cargo across all three conditions. Candidate miRNAs (e.g., miR-21, miR-34a) are illustrative regulatory nodes rather than confirmed gut-EV constituents [12,13].

Established gut–brain–heart pathways remain central: Autonomic (vagus/sympathetic) and microbiota-linked pathways including

TMAO-related mechanisms remain foundational. The EV model is positioned as an additional modulatory layer, not a primary coordinator [3,6,7,11,18].

Methodological rigor is essential: EV heterogeneity, co-isolation of lipoproteins/protein aggregates, and variability in isolation methods can confound functional claims. Proposed experiments therefore require EV-depleted controls, disruption/inactivation controls, and parallel measurement of soluble fractions to support causality.

Longitudinal causality needed: Prospective cohorts are required to determine whether EV signatures precede disease transitions or simply reflect established pathology [19,20]. Gut-on-chip and organoid systems can refine source attribution and mechanism.

Conclusion

We propose that stress-responsive gut-linked extracellular vesicles may contribute to shared vulnerability across PD, IBS, and stress-triggered arrhythmias by distributing regulatory cargo (particularly miRNAs and inflammatory mediators) that can sustain multi-organ remodeling. This hypothesis explicitly integrates rather than displaces established autonomic and microbiota-based gut–brain–heart mechanisms, including TMAO-related pathways. Importantly, catecholamine transport by gut EVs is not assumed; it is reframed as a falsifiable sub-hypothesis that may be quantitatively minor compared with synaptic/autonomic signaling. If validated, EV cargo profiles could provide integrated biomarkers and identify adjunctive therapeutic targets for patients at the intersection of gastrointestinal dysfunction, neurodegeneration risk, and arrhythmia susceptibility.

Consent statement/ethical approval

Not required.

Declaration of generative AI and AI-assisted technologies

The authors did not use generative AI or AI-assisted technologies in the writing, analysis, or preparation of this manuscript.

CRediT authorship contribution statement

Ugwu Okechukwu Paul-Chima: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Methodology, Conceptualization. **Mariam Basajja:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Methodology. **C. Ogenyi Fabian:** Writing – review & editing, Writing – original draft, Visualization, Validation. **N. Ugwu Chinyere:** Writing – review & editing, Writing – original draft, Visualization, Validation, Conceptualization. **Okon Michael Ben:** Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology. **Mundu M. Mustafa:** Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology.

Ethics approval and consent to participate

Not applicable.

Funding

This review did not receive any specific grant from funding agencies in the public, commercial, or not for profit sectors.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

The authors gratefully acknowledge Kampala International University for its support.

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