The Noxious Afferent

The Peripheral Stimuli by Which the Vagus Nerve Harms the Locus Coeruleus

A Short Catalogue of the Inflammatory, Metabolic, and Microbial Signals That, Relayed to the Coeruleus, Hold It in Chronic Overdrive — and the Single Dysregulated Gut-and-Metabolic Periphery From Which They All Arise

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A Short Communication companion to The Vagal Interface, The Coerulean Interface, and the mechanistic monograph The Vago-Coerulean Relay. It catalogues the peripheral stimuli that convert the vagal afferent signal into chronic locus coeruleus injury, and retains only a simplified description of the relay.

“The vagus is not the enemy; it is the messenger. The harm is in the message the modern periphery compels it to carry — and the remedy is to change the message at its source.”

— ONS Methodology Working Notes, 2026

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Abstract

The vagus nerve carries to the brainstem a continuous report of the peripheral interior, and the companion volumes of this series have argued that this report, relayed to the locus coeruleus, can drive that nucleus beyond its bioenergetic means. But not every vagal signal is harmful — most are the ordinary, adaptive traffic of interoception. This short communication asks a single, practical question: *which peripheral stimuli, carried by the vagus, actually harm the locus coeruleus?* The answer is that the harmful stimuli share a common form — they are chronic, inflammatory or metabolic, and they bias the relay toward sustained excitation rather than brief phasic response — and a common origin in the dysregulated gut and metabolic periphery. This communication catalogues them: bacterial endotoxin from the dysbiotic, barrier-compromised gut; the pro-inflammatory cytokines interleukin-1β, tumour necrosis factor, and interleukin-6; the loss of the protective short-chain fatty acid butyrate; the metabolic overload of hyperglycaemia, free fatty acids, and leptin resistance; hepatic and visceral inflammation; and the chronic pathogen burden of the oral and gut microbiomes. Each reaches the locus coeruleus through the same simplified relay — vagal afferent to the nucleus tractus solitarius, then through a dual medullary relay that is excitatory through one arm and inhibitory through the other — and each, by sustaining the excitatory arm and the corticotropin-releasing-factor stress bias, converts an adaptive interoceptive signal into a chronic overdrive that an already marginal nucleus cannot sustain. The communication's organising claim is that the harm is not in the vagus and not in any single signal but in the *chronicity and the inflammatory-metabolic quality* of what the modern dysregulated periphery asks the nucleus to keep responding to. The corollary is hopeful: every stimulus in the catalogue is modifiable.

Keywords: vagus nerve, locus coeruleus, endotoxin, lipopolysaccharide, interleukin-1β, butyrate, metabolic endotoxemia, leptin resistance, gut dysbiosis, corticotropin-releasing factor, neurodegeneration

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1. Introduction

The companion volumes of this series — *The Vagal Interface*, *The Coerulean Interface*, and the mechanistic monograph *The Vago-Coerulean Relay* — established that the afferent vagus modulates the locus coeruleus through a dual medullary relay, and that a chronic afferent load can drive the locus coeruleus beyond the bioenergetic ceiling that makes it the first nucleus to fail in Alzheimer's disease. Those works established the *pathway*. This short communication addresses the *input*: of all the signals the vagus carries, which ones harm the locus coeruleus, and what do they have in common?

The question matters because it is the actionable end of the framework. A pathway cannot be removed, but a stimulus can be reduced. If the harm the vagus does to the locus coeruleus is carried by a definable set of peripheral signals, and if those signals arise in the gut and the metabolic periphery, then the framework points to a programme of intervention that does not require reaching the brainstem at all — it requires changing what the periphery sends. This communication is deliberately brief and is organised around the catalogue of harmful stimuli rather than around theory; the theory is in the companion volumes, and is recapitulated here only as far as is needed to make the catalogue intelligible.

The central distinction throughout is between the *adaptive* and the *chronic* vagal signal. The afferent vagus evolved to report acute peripheral events — a meal, a transient infection, a momentary fall in blood pressure — and the locus coeruleus evolved to answer them with brief, phasic responses that resolve when the event

resolves. This acute interoceptive traffic is not harmful; it is the nucleus's normal work. Harm arises when the peripheral signal becomes *chronic* and *inflammatory or metabolic in character*, so that the locus coeruleus is asked to respond not for seconds but for years. The stimuli catalogued here are harmful precisely because the modern dysregulated periphery makes them continuous.

2. The Relay in Brief

The pathway by which any vagal stimulus reaches the locus coeruleus is reconstructed in detail in the companion monograph; here it is enough to state it simply. A vagal afferent fibre, sensing the peripheral state, releases glutamate onto the nucleus tractus solitarius (NTS) in the medulla — the obligatory first station through which all vagal traffic passes. From the NTS the signal reaches the locus coeruleus chiefly by an *indirect* route, relayed through a small set of medullary nuclei rather than by a single direct line. This relay has two arms: an excitatory arm, glutamatergic, that drives the locus coeruleus toward activation, and an inhibitory arm, GABAergic, that restrains it. The net effect of any vagal signal on the locus coeruleus is the balance these two arms strike.

Two features of this relay govern everything in the catalogue that follows. First, the excitatory arm couples to the brain's stress chemistry: sustained visceral and inflammatory drive engages corticotropin-releasing factor (CRF) input to the locus coeruleus, which shifts the nucleus into a high *tonic* firing mode — elevated baseline activity rather than brief phasic bursts. Second, the locus coeruleus answers this drive at a real metabolic cost, because, as the bioenergetic companion volume establishes, it is a nucleus that already operates near its energetic ceiling. A stimulus is harmful, then, when it chronically engages the excitatory arm and the CRF tonic bias — keeping the locus coeruleus in sustained high-tonic firing — because that is the state whose metabolic cost the nucleus cannot pay indefinitely. The relay is the same for adaptive and harmful signals; what differs is whether the signal is brief or chronic, and whether it is the ordinary traffic of interoception or the inflammatory-metabolic noise of a dysregulated periphery.

3. How a Chronic Afferent Signal Becomes Injury

Before the catalogue, the mechanism of harm in brief. A chronic afferent stimulus injures the locus coeruleus along three converging routes, all downstream of the sustained engagement of the excitatory relay arm.

The first is *excitotoxic overdrive*. Sustained glutamatergic drive through the excitatory relay holds the locus coeruleus in elevated firing, raising the calcium load and the metabolic demand of its neurons. The locus coeruleus neuron is unusually exposed to this cost because it is an autonomous pacemaker running a catecholaminergic chemistry that oxidises as it fires; sustained firing taxes the mitochondrial and NAD□ economy that supports it, and a nucleus already near its ceiling has no reserve to meet the additional demand.

The second is the *CRF tonic shift*. Chronic inflammatory and visceral stress, relayed centrally, engages the CRF input that biases the locus coeruleus toward high tonic firing — the stress signature. This is doubly costly: it raises baseline metabolic demand, and it degrades the nucleus's normal phasic responsiveness, so that the locus coeruleus does worse work at higher cost. The high-tonic state is the maladaptive operating point into which chronic noxious afferents push the nucleus.

The third is the *loss of the noradrenergic brake and the spiral that follows*. As the locus coeruleus degenerates under sustained overdrive, it releases less noradrenaline, and — as the Coerulean companion volume develops — noradrenaline is an endogenous brake on microglial inflammation. The withdrawal of the brake disinhibits microglia, raises the central inflammatory load, and feeds that load back onto the surviving locus coeruleus neurons, which the rising inflammation drives still harder. The chronic peripheral stimulus thus does not merely strain the locus coeruleus; it initiates a self-amplifying loop in which the nucleus's own decline accelerates its decline.

These three routes are the mechanism by which each stimulus in the catalogue does its harm. The catalogue itself is simply the list of the peripheral signals that engage them.

4. The Catalogue of Harmful Stimuli

4.1 Bacterial Endotoxin from the Dysbiotic Gut

The single most consequential harmful stimulus is bacterial lipopolysaccharide (LPS), the endotoxin of Gram-negative bacteria. In the healthy gut, LPS is contained behind an intact intestinal barrier; in dysbiosis and barrier compromise — the "leaky gut" of ageing, poor diet, and metabolic disease — LPS crosses into the circulation and the gut wall, producing the low-grade "metabolic endotoxemia" characterised in the metabolic-disease literature. LPS is a potent activator of the afferent vagus, both directly, through receptors of the innate immune system expressed on or near the afferent terminals and the vagal paraganglia, and indirectly, through the cytokines it provokes. Because dysbiosis is chronic, the LPS signal is chronic, and it engages the excitatory relay and the inflammatory drive continuously. Endotoxin is first in the catalogue because it is the stimulus that most directly converts a disordered gut into a sustained noxious afferent, and because it is the upstream cause of several of the cytokine signals that follow.

4.2 The Pro-Inflammatory Cytokines

The afferent vagus is the brain's principal neural sensor of peripheral inflammation, and the cytokines are its specific ligands. Interleukin-1β is the best characterised: vagal afferents respond to it, and the classical demonstration that subdiaphragmatic vagotomy blocks the brain's response to peripheral interleukin-1β established the afferent vagus as a necessary route for inflammatory signalling from below the diaphragm. Tumour necrosis factor and interleukin-6 act similarly. In acute infection this cytokine signalling is adaptive — it produces the sickness response that aids recovery and resolves with the infection. In the chronic low-grade inflammation of ageing — "inflammaging" — and in the persistent inflammation of metabolic and autoimmune disease, the cytokine signal does not resolve, and the afferent vagus reports it continuously to the relay. The pro-inflammatory cytokines are harmful to the locus coeruleus not because they are abnormal signals but because, in the chronically inflamed body, they never switch off.

4.3 The Loss of Butyrate: Harm by Omission

Not every harmful change is the addition of a noxious signal; some are the *loss* of a protective one. Butyrate, the short-chain fatty acid produced by beneficial gut bacteria from dietary fibre, is sensed by vagal afferents and is, in several ways, protective: it supports the integrity of the gut barrier (reducing the endotoxin leak of §4.1), it is anti-inflammatory, and — as the corpus's gut–brain axis work records — it underwrites an anti-amyloid antimicrobial checkpoint. A diet poor in fibre, or a dysbiotic microbiome depleted of butyrate-producing bacteria, removes this protective afferent tone, weakening the gut barrier and the anti-inflammatory set-point and thereby amplifying every other stimulus in the catalogue. The loss of butyrate is harmful to the locus coeruleus indirectly but powerfully: it is the removal of the brake on the gut, and its absence is permissive for the endotoxin and cytokine signals that directly overdrive the relay.

4.4 Metabolic Overload: Glucose, Fatty Acids, and Leptin

The afferent vagus is also a metabolic sensor, with hepatic and gastrointestinal afferents that report glucose, fatty acids, and the adipose hormone leptin. In metabolic health these signals are adaptive, reporting the nutritional state to coordinate appetite and metabolism. In metabolic syndrome, obesity, and type 2 diabetes — all established risk factors for cognitive decline in the corpus — they become chronic and excessive: persistent hyperglycaemia, elevated circulating free fatty acids, and the leptin resistance of obesity. A high-fat diet has been shown to inflame the vagal afferent ganglion itself and to render its afferents leptin-resistant and dysfunctional, so that metabolic overload both drives the relay and damages the sensor. The metabolic stimuli are harmful to the locus coeruleus because the dysmetabolic periphery, like the inflamed one, sends a signal that never resolves, and because the same dysmetabolism inflames the afferent pathway that carries it.

4.5 Hepatic and Visceral Inflammation

The liver is densely innervated by vagal afferents through the hepatic branch, and it is a principal site at which the metabolic and inflammatory periphery is integrated. Non-alcoholic fatty liver disease and the broader hepatic inflammation of metabolic syndrome therefore generate a substantial afferent signal, as does the chronic inflammation of the gut wall in inflammatory bowel disease and in subclinical intestinal inflammation. These visceral inflammatory states are harmful in the same way as the cytokine and endotoxin signals — by sustaining the inflammatory afferent drive — and they are noted separately because the liver and gut wall are large, chronically affected organs whose inflammation is a major and often unrecognised contributor to the total noxious afferent load.

4.6 The Chronic Pathogen Burden

Finally, chronic infection supplies a sustained noxious afferent. The periodontal and oral pathogens that the corpus records as Alzheimer risk factors, the gastric pathogen *Helicobacter pylori*, and the pathobionts of the dysbiotic gut all maintain a chronic local and systemic inflammatory state that the afferent vagus reports. The pathogen burden is harmful both directly, through the inflammation it sustains, and as a driver of the endotoxin and cytokine signals already catalogued. It is placed last not because it is least important but because its harm to the locus coeruleus runs largely through the inflammatory and endotoxin routes already described: a chronic infection is, from the locus coeruleus's point of view, simply another source of the unending inflammatory afferent that the catalogue's other entries also supply.

5. A Hierarchy of Harm, and Its Modifiability

The catalogue has a structure. Its entries are not independent; they form a hierarchy with the dysbiotic, barrier-compromised gut and the dysmetabolic periphery at its root. Gut dysbiosis and barrier failure produce the endotoxin (§4.1) and the loss of butyrate (§4.3); the endotoxin and the dysmetabolic state produce the cytokines (§4.2) and the hepatic and visceral inflammation (§4.5); and the chronic pathogen burden (§4.6) feeds the same inflammatory streams. The proximate harm to the locus coeruleus is the chronic engagement of the excitatory relay arm and the CRF tonic bias; the distal cause is a gut and a metabolism that the modern diet and the ageing body have pushed into a state of unremitting low-grade inflammation. The locus coeruleus is harmed, in the end, by a periphery that never stops asking it to respond.

This structure is the source of the framework's optimism. Every stimulus in the catalogue is modifiable, and they are modifiable at their shared root. Dietary fibre and a butyrate-supporting microbiome restore the gut barrier and lower the endotoxin and cytokine load; the reversal of metabolic syndrome lowers the glucose, fatty-acid, and leptin signals and reduces hepatic inflammation; the treatment of periodontal and gastric infection removes a chronic pathogen source. None of these interventions reaches the brainstem, and none needs to: they act on what the periphery sends, and by quieting the noxious afferent they lift the chronic overdrive from the locus coeruleus. The framework thus converts a set of well-known but loosely connected lifestyle risk factors for dementia into a single mechanistic statement — they are the peripheral sources of a chronic noxious vagal afferent that harms the nucleus that fails first — and in doing so it explains why their modification is protective and identifies the most upstream point at which the protection can be applied.

6. Conclusion

This short communication has catalogued the peripheral stimuli by which the vagus nerve harms the locus coeruleus and has argued that they share a common form and a common origin. Their form is chronicity: each is harmful not because it is an abnormal signal but because the dysregulated periphery makes it continuous, so that the locus coeruleus is held in the sustained high-tonic, CRF-biased firing whose metabolic cost it cannot pay. Their origin is the dysbiotic gut and the dysmetabolic body: bacterial endotoxin, the pro-inflammatory cytokines, the loss of protective butyrate, metabolic overload, hepatic and visceral inflammation, and the chronic pathogen burden are not six independent insults but the several faces of a single underlying state — a periphery in unremitting low-grade inflammation, reported without pause by the afferent vagus to a nucleus that cannot rest.

The mechanism is the one the companion volumes establish, recapitulated here only in brief: the noxious afferent reaches the locus coeruleus through the dual medullary relay, engages its excitatory arm and the stress chemistry, overdrives an already marginal nucleus, and, as that nucleus declines, releases the noradrenergic brake on microglia and opens the self-amplifying spiral. The contribution of this communication is to name the inputs to that mechanism and to show that they are few, related, and — above all — modifiable. The vagus is not the enemy; it is the messenger. The harm is in the message the modern periphery compels it to carry, and the remedy is to change the message at its source.

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