Gut-brain axis in anesthesia and critical illness: Molecular crosstalk and its impact on delirium and outcome (Review)

XIGANG MA and YONGSEN ZHAO

Department of Anesthesiology, The Third Affiliated Hospital of Gansu University of Chinese Medicine, Baiyin, Gansu 730900, P.R. China

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Abstract. The gut-brain axis (GBA) has emerged as a critical mediator of acute brain dysfunction, particularly postoperative delirium and sepsis-associated encephalopathy, in surgical and critically ill patients. Anesthesia, surgical stress, and critical illness collectively disrupt gut microbiota composition and intestinal barrier integrity, leading to increased systemic translocation of microbial products. This process triggers neuroinflammation and compromises blood-brain barrier function through defined molecular pathways, including alterations in microbe-derived short-chain fatty acids, tryptophan metabolites, and potent neuroimmune signaling via the LPS-TLR4-NF-κB axis. The present review synthesizes current evidence on the molecular crosstalk within the GBA, highlighting how perioperative and intensive care interventions drive dysbiosis and subsequent neurological sequelae. Furthermore, it evaluates promising GBA-targeted therapeutic strategies, including dietary modulation, biotherapeutics and pharmacological interventions, are evaluated for their potential to mitigate delirium and improve long-term cognitive outcomes. A deeper understanding of these mechanisms is essential for developing novel preventive and therapeutic approaches in vulnerable patient populations.

Correspondence to: Professor Yongsen Zhao, Department of Anesthesiology, The Third Affiliated Hospital of Gansu University of Chinese Medicine, 222 Silong Road, Baiyin, Gansu 730900, P.R. China
E-mail: 18189439920@163.com

Abbreviations: GBA, gut-brain axis; POD, postoperative delirium; SAE, sepsis-associated encephalopathy; BBB, blood-brain barrier; SCFAs, short-chain fatty acids; LPS, lipopolysaccharide; TLR4, Toll-like receptor 4; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cell

Key words: GBA, POD, SAE, microbiome, anesthesia, critical illness, neuroinflammation, SCFAs

Contents

1. Introduction

Postoperative delirium (POD) and sepsis-associated encephalopathy (SAE) are devastating complications in surgical and critically ill patients, leading to prolonged hospitalization, increased mortality, and long-term cognitive impairment (1). The underlying mechanisms are complex and multifactorial, involving neuroinflammation, oxidative stress, blood-brain barrier (BBB) disruption and neuronal damage (2-4). While initial research focused on intracranial pathways, growing evidence highlights the gut-brain axis (GBA) as a crucial mediator of systemic and central nervous system communication (5).

The GBA encompasses neural, endocrine, immune and humoral pathways, with the gut microbiota serving as a central modulator (5,6). Surgical trauma, anesthesia, sepsis and pharmacological treatments can induce significant gut microbial dysbiosis, characterized by reduced diversity and altered community structure (7). Such dysbiosis impairs intestinal barrier function, promoting the translocation of pathogenic components such as lipopolysaccharide (LPS) into the circulation (6,8). This process is further aggravated by vagal inhibition and compromised hepatic clearance, collectively amplifying systemic inflammation and predisposing patients to neuroinflammation and BBB dysfunction (9,10). Clinical and preclinical studies have confirmed that increased intestinal permeability and circulating endotoxin correlate with delirium severity and cognitive decline (11-13).

Key microbial metabolites also participate in GBA signaling. Short-chain fatty acids (SCFAs) such as butyrate exert anti-inflammatory effects and help preserve BBB integrity (14,15). Their reduction, linked to anesthesia and

dysbiosis, is associated with cognitive deficits in animal models (16,17). Conversely, inflammation-driven activation of the tryptophan-kynurenine pathway yields neurotoxic metabolites that may precipitate excitotoxicity and cognitive impairment (18,19). Therapeutic strategies aimed at modulating gut microbiota, including probiotics, prebiotics and fecal microbiota transplantation (FMT), have demonstrated potential to alleviate neuroinflammation and improve cognitive performance in models of POD and SAE (20). Specific strains, such as *Lactobacillus*, have been shown to rebalance gut flora, modulate kynurenine pathways, and enhance cognitive outcomes (21,22).

Nonetheless, the literature reveals notable inconsistencies. While certain trials support the efficacy of probiotics in improving cognition (23), others report null effects, possibly due to heterogeneity in strains, dosage, or patient selection (24,25). Discrepancies also exist in the association between microbial taxa and neurological outcomes, underscoring the impact of confounders such as age, comorbidities and medication use (26,27). Moreover, interspecies differences in gut microbiota and neuroimmune responses may limit the translatability of animal findings (28).

The role of anesthetic and analgesic agents in GBA modulation remains an area of active investigation. Volatile anesthetics have been shown to diminish beneficial gut bacteria (29,30), and opioids can delay intestinal transit and exacerbate dysbiosis, potentially aggravating neuroinflammatory cascades (31,32). Still, the clinical relevance of these pharmacological effects on cognitive outcomes awaits further validation through rigorously designed human studies.

To provide a clear conceptual framework for understanding this complex interplay, gut-brain signaling under anesthesia can be conceptualized through three dominant routes: (i) The neural pathway (vagal afferents), (ii) the humoral pathway (microbial metabolites including SCFAs and tryptophan derivatives), and (iii) the immune pathway (systemic inflammation via the LPS-TLR4 axis) (6,9,16,18). Within this framework, these routes play distinct functional roles. LPS translocation and TLR4 activation act as a necessary trigger for neuroinflammation, an essential prerequisite for the delirium development. The loss of protective metabolites, particularly SCFAs, serves as a permissive factor that lowers the delirium threshold by compromising barrier integrity and reducing anti-inflammatory signaling. Kynurenine-mediated excitotoxicity and sustained microglial activation function as amplifying mechanisms, propagating and perpetuating neuronal dysfunction. Temporally, delirium follows a three-stage axis: Gut barrier failure and systemic inflammation act as the trigger; dysbiosis and metabolic dysregulation propagate the acute episode; and persistent neuroimmune changes drive long-term cognitive decline.

In summary, the GBA constitutes a critical interface through which peripheral physiological stressors influence brain function. The present review systematically synthesizes current evidence on molecular crosstalk within the GBA during anesthesia and critical illness, with the aim of clarifying pathophysiological mechanisms, evaluating consistent and conflicting findings, and identifying promising therapeutic targets to mitigate delirium and improve patient outcomes.

2. Gut-brain architecture under anesthesia and stress

The GBA is not a single structure but a triad of anatomical highways, immune gateways and rhythmic gatekeepers that together determine how luminal signals reach the brain (Fig. 1). Anesthesia and critical-care stress act simultaneously on all three compartments, yet their relative contributions remain quantitatively undefined.

Vagal and portal conduits. Non-intubated thoracoscopic data show that propofol-dexmedetomidine anesthesia preserves vagally-mediated heart-rate slowing, while deeper planes abolish the high-frequency component of heart-rate variability, indicating dose-dependent afferent block (33-35). Direct recordings in isoflurane-anesthetized pigs confirm a 28% reduction in compound vagal action-potential amplitude without conduction-velocity change, suggesting pressure-related nodal impairment rather than axonal injury (36). Parallel human studies reveal that cardiac surgery starting after 14:00 doubles postoperative endotoxemia risk, suggesting that circadian timing modulates vagal or splanchnic traffic (37).

On the humoral side, sepsis and major abdominal surgery raise portal endotoxin within 30 min of incision (38-40). In acute pancreatitis, portal Angiopoietin-2 correlates with systemic IL-6 (r=0.72), documenting simultaneous gut and hepatic endothelial activation (41). Early enteral nutrition halves the portal-arterial LPS gradient and downregulates hepatic TLR-4 expression, yet no study has sampled portal blood under anesthesia without systemic inflammation, thus the pure effect of anesthetic drugs remains assumption rather than evidence. Dose-dependent vagal impairment by volatile anesthetics may exacerbate systemic inflammation, while circadian timing of surgery influences endotoxemia risk. Clinical implication: Early enteral nutrition represents a modifiable intervention to reduce portal endotoxin load; scheduling non-urgent surgeries in the morning may mitigate endotoxemia risk; anesthetic depth should be titrated to preserve vagal activity where possible, particularly in patients with pre-existing intestinal barrier dysfunction.

Immune interface: From GALT to meninges. Septic-shock autopsies show Peyer's-patch lymphocyte depletion and increased lamina-propria MHC-II, indicating acute GALT activation (42). Perioperative immuno-nutrition restores $CD4^+$ follicular helper cells and lowers LPS-binding protein by 35% in surgical patients, corroborating functional relevance (43). Kupffer cells are exposed to the highest endotoxin concentrations, but human data are limited to plasma surrogates; kinetic modelling of hepatic LPS clearance is still missing.

Beyond the liver, sepsis downregulates claudin-5 and occludin in human frontal cortex micro-vessels (42). In aged mice undergoing orthopedic surgery, both paracellular (FITC-dextran) and trans-cellular (Evans-blue) tracers rise 6 h after emergence; the change is abolished by MMP-9 knockout or by avoiding propofol (44,45). Two independent groups thus confirm anesthesia/surgery-induced BBB leakage, but they disagree on mechanism (MMP-9 vs. GLUT-1 downregulation), highlighting species- and protocol-specific pathways. Clinical implication: Perioperative immuno-nutrition may preserve

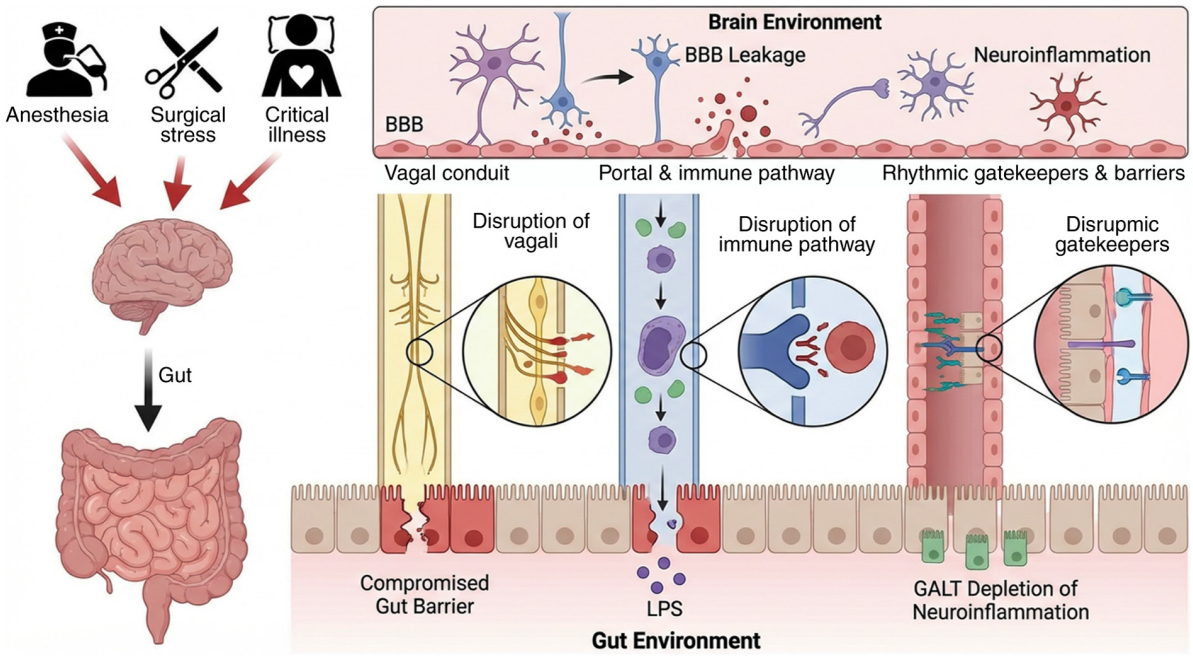

Figure 1. Gut-brain architecture under anesthesia and stress (https://www.figdraw.com/static/index.html#/; 2.0 version). LPS, lipopolysaccharide; BBB, blood-brain barrier; GALT, gut-associated lymphoid tissue.

gut immune function and reduce systemic inflammation; anesthetic choice, specifically avoiding agents that exacerbate barrier permeability, could be considered in vulnerable elderly patients or those with pre-existing cognitive impairment; monitoring for early POD may identify individuals with significant BBB disruption.

Barrier chronobiology. Rodent tight-junction protein abundance peaks at Zeitgeber-time 6 and is flattened by isoflurane exposure during the early dark phase (46). Human data remain associative: Afternoon surgery increases endotoxemia and delirium rates, but randomized trials comparing morning vs. evening operations are absent. Whether anesthesia abolishes circadian barrier rhythms through vagal blockade, cortisol suppression or clock-gene methylation is unresolved. Clinical implication: Afternoon surgery is associated with higher endotoxemia and delirium risk, suggesting that surgical timing could be optimized to improve outcomes; until prospective trials are available, perioperative teams should be particularly vigilant for delirium in patients undergoing afternoon procedures, and consider enhanced barrier-protective strategies (for example, early enteral nutrition, stress-dose corticosteroids where indicated).

In summary, anesthesia and critical illness jointly impair all three anatomical pillars of the GBA. Vagal conduction is exquisitely sensitive to volatile depth, portal endotoxin flux is amplified by surgical trauma and circadian timing, while barrier integrity is compromised via converging but mechanistically distinct pathways. A multifaceted approach is required to preserve gut-brain integrity, combining anesthetic titration to maintain vagal tone, optimization of surgical timing, early enteral nutrition, and judicious selection of anesthetic agents. Dose-response studies that integrate portal metabolomics, high-density vagal recordings and sequential brain-barrier imaging are required to move from correlation to causation and to develop evidence-based clinical guidelines.

3. Microbial metabolite signaling and delirium pathogenesis

The gut microbiota speaks to the brain through a limited repertoire of biochemical dialects. Four classes of metabolites, SCFAs, tryptophan catabolites, secondary bile acids and LPS, have been repeatedly isolated from portal and systemic blood of surgical and critically ill patients (Fig. 2). For each metabolite class, the strength of evidence and the balance between human and animal data vary considerably. For SCFAs: Evidence level is causal in animals (strong preclinical data via FFAR3 and HDAC inhibition) but associative in humans (confounded by variable bioavailability). For tryptophan metabolites: Evidence is bidirectional-indole-3-propionic acid (IPA) shows causal neuroprotection in animals with emerging human data, whereas kynurenine demonstrates causal neurotoxicity in animals and strongly associative links with delirium in humans. For secondary bile acids: Evidence level is speculative/associative (predominantly preclinical; associative links with drug metabolism exist in humans, but causal roles in delirium remain unproven). For LPS-TLR4 signaling: Evidence level is causal in both animals and humans (LPS translocation fulfills multiple Hill criteria for delirium pathogenesis). This section synthesizes core causal and correlative evidence for each metabolite class, with detailed numerical study findings and experimental parameters consolidated in Table I. A comparative ranking of these metabolites by strength of evidence, therapeutic tractability, and risk of off-target effects is presented in Table II.

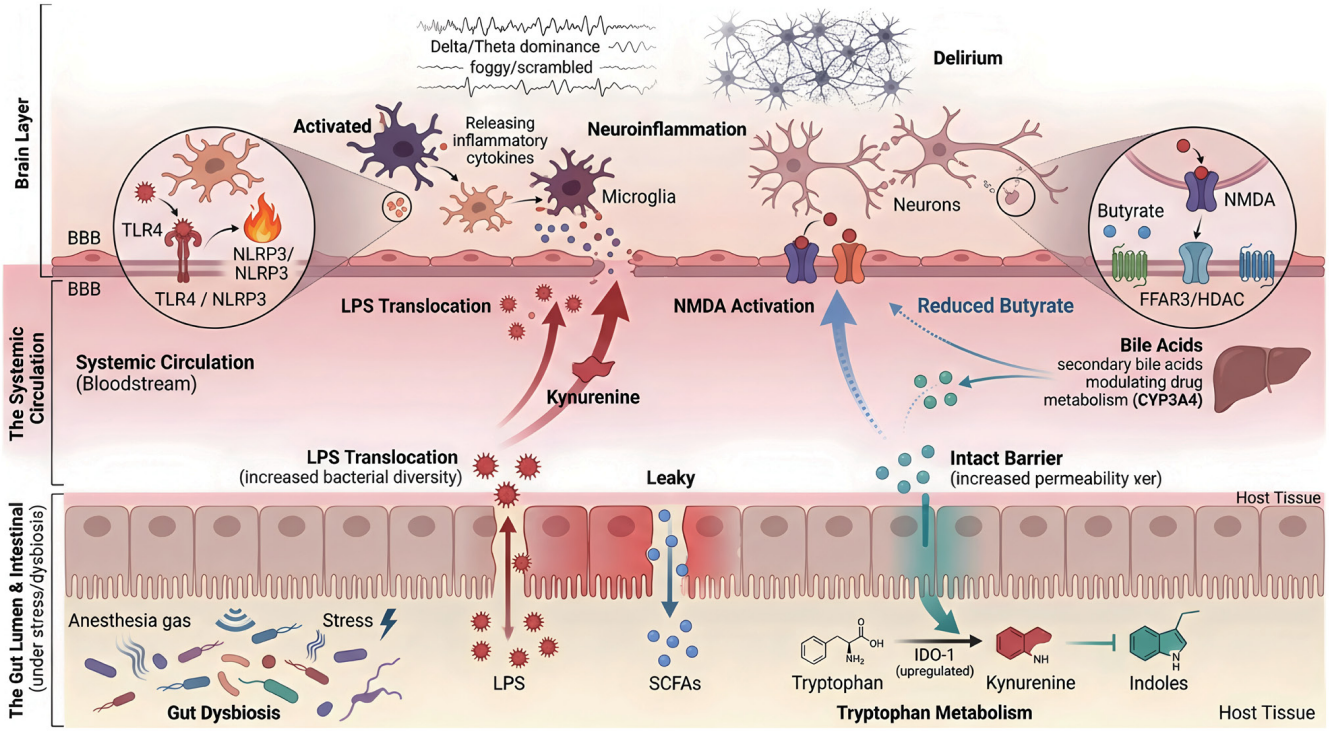

Figure 2. Microbial metabolite signaling and delirium pathogenesis (https://www.figdraw.com/static/index.html#/; 2.0 version). BBB, blood-brain barrier; CYP3A4, cytochrome P450 3A4; FFAR3, free fatty acid receptor 3; HDAC, histone deacetylase; IDO-1, indoleamine 2,3-dioxygenase 1; LPS, lipopolysaccharide; NLRP3, NOD-like receptor protein 3; NMDA, N-methyl-D-aspartate; SCFA, short-chain fatty acid; TLR4, Toll-like receptor 4.

SCFAs: FFAR2/3 and HDAC inhibition. Butyrate, acetate and propionate are the most abundant fecal anions in healthy adults. In a prospective cohort of 38 cardiac surgery patients, cecal butyrate measured during cardiopulmonary bypass predicted postoperative serum IL-10 (ρ=0.72) and was inversely associated with subsyndromal delirium incidence (47). Perioperative inulin supplementation raised colonic butyrate and preserved vagal tone, as indicated by high-frequency heart rate variability (48). Mechanistic studies confirm that butyrate activates FFAR3-mediated ERK phosphorylation to restore BDNF expression and reverse isoflurane-induced memory deficits in aged mice (49). Conversely, antibiotic-depleted mice exhibit low plasma butyrate and exaggerated hippocampal IL-1β after tibial fracture, both normalized by oral butyrate (50). However, two inconsistencies warrant attention: High-fiber formulas increase luminal butyrate without raising plasma levels in ICU patients (51), and intravenous butyrate transiently worsens BBB permeability in rats via FFAR2 activation (52). These findings suggest a narrow therapeutic window and caution against equating fecal concentrations with brain bioavailability.

Tryptophan pathway: 5-HT vs. kynurenine toxicity. Under basal conditions, *Lactobacillus spp*. convert tryptophan to indole-3-aldehyde (I3A), an aryl hydrocarbon receptor (AhR) agonist that maintains microglial quiescence (53). Sepsis diverts flux toward kynurenine: LPS-stimulated indoleamine-2,3-dioxygenase (IDO-1) activity rises 8-fold in human endotoxemia, lowering plasma tryptophan from 65±8 to 25±5 μm within 6 h (54). A nested case-control study of 92 ICU adults showed that every 10 μm decrease in tryptophan was associated with a 1.3-point increase in the 4AT delirium score [β=1.3, 95% confidence interval (CI): 0.6-2.0] (55). In mice, oral *L. johnsonii* 6084 restored plasma I3A and reduced kynurenine/tryptophan ratio, paralleling improved performance in the novel-object recognition test (56). Importantly, not all tryptophan metabolites are harmful: IPA decreased hippocampal TNF-α and protected against LPS-induced cognitive decline (57), whereas exogenous kynurenine reversed this benefit (58). The pathway thus exerts bidirectional control, favoring metabolite-specific rather than IDO-1-centered interventions.

Secondary bile acids and FXR/PXR crosstalk with drug metabolism. Microbiota de-conjugate primary bile acids to generate deoxycholic and lithocholic acids, potent ligands for FXR and PXR. ICU patients receiving parenteral nutrition have 40% lower total fecal bile acids and a shift toward primary species; the magnitude of dysbiosis correlates with midazolam clearance (r=0.68, P=0.007) (59). FXR activation by obeticholic acid in septic mice restored tight-junction proteins and halved portal endotoxin but prolonged propofol sedation by 25% via CYP3A4 inhibition (60). These data reveal a trade-off: Enhanced barrier integrity may compromise drug elimination. PXR activation by rifaximin upregulated MDR-1 and accelerated morphine glucuronidation but failed to improve survival, suggesting that metabolic modulation alone is insufficient without immune effects (61). Dose-finding studies targeting neurocognitive endpoints are needed before FXR/PXR agonists enter perioperative trials.

LPS-TLR4 signaling: A sledgehammer in delirium pathogenesis. LPS remains the best-studied microbial ligand. During cardiac surgery, systemic LPS peaks at 45-90 min,

Table I. Key studies investigating microbial metabolite signaling in delirium pathogenesis.

Authors, year	Metabolite class	Population/ Model	Key intervention/ Exposure	Major findings (Microbiota/ Metabolite Changes)	Neuroinflammatory/ Cognitive effects	(Refs.)
Baek *et al*, 2023	SCFAs	Cardiac surgery patients (n=38)	Cecal butyrate measurement during CPB	Cecal butyrate predicted postoperative serum IL-10 (ρ=0.72); lowest butyrate quartile associated with 3.4-fold higher subsyndromal delirium	Preserved anti-inflammatory response; shorter intubation time	(47)
Hajjar *et al*, 2021	SCFAs	Surgical patients	Perioperative inulin 20 g/day	↑ Colonic butyrate (18→ 31 μmol/g); preserved high-frequency heart-rate variability	Maintained vagal tone; improved surgical recovery	(48)
Xu *et al*, 2021	SCFAs	Aged mice	Intra-cerebroventricular butyrate (25 μg)	Butyrate activated FFAR3-mediated ERK phosphorylation	Reversed isoflurane-induced memory deficits; restored BDNF expression	(49)
Luo *et al*, 2021	SCFAs	Antibiotic-depleted mice	Oral butyrate (300 mM in drinking water)	Restored plasma butyrate levels; normalized gut microbiota	Attenuated hippocampal IL-1β; improved trace-fear recall	(50)
Liu *et al*, 2022	SCFAs	ICU patients	High-fiber enteral nutrition	↑ Luminal butyrate but plasma levels remained <5 μM	No significant cognitive improvement; gut barrier function preserved	(51)
Liu *et al*, 2025	SCFAs	Middle-aged rats	Intravenous butyrate (50 mg/ kg bolus)	FFAR2-mediated endothelial contraction	Transiently worsened BBB permeability; effect abolished by FFAR2 antagonist	(52)
Huang *et al*, 2022	Tryptophan metabolites	Murine model	IPA	IPA activated AhR; promoted macrophage phagocytosis	Attenuated septic injury; neuroprotective effects	(53)
Kuo *et al*, 2021	Tryptophan metabolites	ICU patients (n=92)	Plasma tryptophan measurement	Plasma tryptophan decreased from 65±8 μM to 25±5 μM within 6 h after LPS stimulation	Every 10 μM tryptophan decrease associated with 1.3-point increase in 4AT delirium score	(54)
Han *et al*, 2022	Tryptophan metabolites	Septic mice	Oral *L. johnsonii* 6084	Restored plasma I3A; ↓ kynurenine/tryptophan ratio	Improved novel-object recognition; reduced organ injury	(56)
Fang *et al*, 2022	Tryptophan metabolites	LPS-treated mice	IPA (20 mg/i.p.)	↓ Hippocampal TNF-α; protected against LPS-induced cognitive decline	Exogenous kynurenine reversed IPA benefit; metabolite-specific effects	(57)
Kean *et al*, 2022	Secondary bile acids	Critically ill children	Parenteral nutrition	40% ↓ total fecal bile acids; shift toward primary species	Dysbiosis magnitude correlated with midazolam clearance (r=0.68)	(59)

Table I. Continued.

Authors, year	Metabolite class	Population/ model	Key intervention/ exposure	Major findings (microbiota/ metabolite changes)	Neuroinflammatory/ cognitive effects	(Refs.)
Hou *et al*, 2024	Secondary bile acids	Septic mice	Obeticholic acid (FXR agonist)	Restored tight-junction proteins; halved portal endotoxin	Prolonged propofol sedation by 25% via CYP3A4 inhibition; barrier-drug clearance trade-off	(60)
Du *et al*, 2024	Secondary bile acids	Heat-stroke mice	Rifaximin (PXR activation)	↑ MDR-1; accelerated morphine glucuronidation	No survival benefit; metabolic modulation alone insufficient	(61)
Gong *et al*, 2019	LPS-TLR4	Cardiac surgery patients	LPS measurement during CPB	Systemic LPS peaked at 45-90 min; coincided with cognitive deterioration	Each log-unit ↑ LPS associated with cognitive decline	(62)
Zhang *et al*, 2022	LPS-TLR4	Mice	Intravenous LPS (4 mg/kg)	Hippocampal TLR4 expression doubled within 4 h	Preceded microglial activation; impaired synaptic long-term potentiation	(63)
Kim *et al*, 2020	LPS-TLR4	Septic mice	FMT from septic donors	↓ Systemic LPS but no BBB improvement unless IPA- enriched	IPA enrichment required for survival benefit; LPS alone incomplete biomarker	(64)
Zhang *et al*, 2021	LPS-TLR4	Human volunteers	Ultra-pure LPS + sleep deprivation	LPS alone induced systemic inflammation without cognitive decline	'Second hit' (sleep deprivation) required for cognitive effects	(65)

SCFAs, short-chain fatty acids; CPB, cardiopulmonary bypass; FFAR3, free fatty acid receptor 3; BDNF, brain-derived neurotrophic factor; ICU, intensive care unit; BBB, blood-brain barrier; POD, postoperative delirium; LPS, lipopolysaccharide; TLR4, Toll-like receptor 4; IDO-1, indoleamine 2,3-dioxygenase 1; I3A, indole-3-aldehyde; IPA, indole-3-propionic acid; AhR, aryl hydrocarbon receptor; FMT, fecal microbiota transplantation; FXR, farnesoid X receptor; PXR, pregnane X receptor; HR, hazard ratio; CI, confidence interval; i.p., intraperitoneal; TNF-α, tumor necrosis factor-alpha; IL, interleukin.

coinciding with maximal cognitive deterioration (62). In a multicenter cohort of 187 ICU patients, each log-unit increase in plasma LPS raised the delirium hazard ratio to 1.9 (95% CI, 1.3-2.8) after APACHE-II adjustment (40). Murine data confirm that hippocampal TLR4 expression doubles within 4 h of intravenous LPS, preceding microglial activation and impaired synaptic plasticity (63). Yet contradictory findings exist: FMT from septic donors lowered systemic LPS but did not reduce BBB permeability or improve survival unless accompanied by IPA enrichment (64). This suggests that LPS quantification alone is an incomplete biomarker; its bioactivity, determined by binding proteins, micellar aggregation and concurrent metabolites, must be considered. Moreover, ultra-pure LPS administered to human volunteers induces systemic inflammation without cognitive decline unless combined with sleep deprivation, highlighting the need for a 'second hit' (65).

4. Anesthesia and critical illness as dysbiosis drivers

The gut microbiome of a healthy adult is a resilient ecosystem; however, the moment a patient inhales sevoflurane, receives an intravenous opioid, or is starved for more than 12 h in the ICU, this resilience is replaced by a predictable pattern of dysbiosis-loss of butyrate-producing *Firmicutes*, expansion of facultative pathogens, and a decline in α-diversity. Below it is dissected how each component of perioperative and critical-care management accelerates this ecological collapse and evaluate the consistency, magnitude and reversibility of the changes (Table III).

Volatile anesthetics-rapid pruning of Clostridia. Volatile anesthetics have a direct and rapid impact on gut flora. In rodent models, a single exposure to sevoflurane reduces beneficial cecal *Clostridium* clusters IV and XIVa by 30-40% within 6 h, leading to a concomitant drop in plasma butyrate (66-68). This effect is dose-dependent and reproducible in children, where sevoflurane, compared with propofol, decreased *Faecalibacterium* and increased *Enterococcus* (69). The mechanism may involve the inhibition of bacterial respiration in key commensals such as *Roseburia intestinalis* (68).

Intravenous drugs and opioids-bile-acid drift plus motility arrest. Intravenous anesthetic and analgesic agents contribute through distinct mechanisms. While often considered inert,

Table II. Comparative ranking of gut-derived metabolites in delirium pathogenesis.

Metabolite class	Strength of evidence	Human vs. animal weighting	Therapeutic tractability	Risk of off-target effects
LPS-TLR4 signaling	Causal (high)	Strong in both; human cohort data (HR 1.9) and murine mechanism	Moderate (TLR4 antagonists exist but infection risk)	High (blunting host defense)
SCFAs (butyrate)	Causal in animals; associative in humans	Strong preclinical; human data limited by bioavailability	High (dietary fibre, butyrate precursors)	Low-moderate (narrow window; IV butyrate harmful)
Tryptophan metabolites (IPA/kynurenine)	Causal for IPA in animals; associative for kynurenine in humans	Strong preclinical IPA; human kynurenine data robust	High (IPA supplementation, probiotic modulation)	Low (metabolite-specific interventions avoid IDO-1 broad effects)
Secondary bile acids	Speculative/associative	Mostly rodent studies; human correlations only	Low (FXR/PXR agonists affect drug metabolism)	High (CYP3A4 inhibition, altered drug clearance)

LPS, lipopolysaccharide; TLR4, Toll-like receptor 4; SCFAs, short-chain fatty acids; IPA, indole-3-propionic acid; IDO-1, indoleamine 2,3-dioxygenase 1; FXR, farnesoid X receptor; PXR, pregnane X receptor; HR, hazard ratio; IV, intravenous.

a 24-h propofol infusion in ICU patients reduced conjugated primary bile acids and expanded *Klebsiella spp*., an effect linked to duration of use (70). Because unconjugated bile acids are weaker FXR agonists, the shift may compromise feedback control of mucosal immunity, a hypothesis supported by FXR-knockout mice that exhibit identical dysbiosis after tibial fracture under propofol anesthesia (71). Opioids provide an independent 'hit'. Morphine significantly slows intestinal transit, increases luminal pH, and decreases *Lactobacillus* abundance, an effect that can potentiate analgesic tolerance (72,73). In postoperative patients, intravenous morphine reduces *Bifidobacterium*, while epidural analgesia preserves butyrate producers, suggesting the dysbiosis is linked to μ-receptor signaling in the gut rather than analgesia itself (74). Taken together, the evidence is consistent across mechanistic and observational studies, but the relative contribution of slowed motility vs. direct bacterial toxicity remains unresolved; germ-free opioid experiments point to motility, yet fentanyl added to fecal cultures inoculated into gnotobiotic mice still enriches *Enterococcus*, arguing for dual mechanisms (75).

ICU stress superimposed-hypoperfusion, proton-pump inhibitors (PPIs) and feeding interruption. ICU-specific stressors create a 'perfect storm' for the microbiome. Splanchnic hypoperfusion, indicated by high-dose norepinephrine requirements, is associated with a rapid decline in *Faecalibacterium*, often preceding clinical ileus (76). PPIs amplify dysbiosis by altering the gastric pH, leading to an overgrowth of *Staphylococcus* and *Klebsiella* and a reduction in butyrate producers, which is linked to an increased risk of ventilator-associated pneumonia (77,78). Finally, the mode of feeding is critical. Unlike continuous feeding, intermittent bolus feeding creates a feast-and-famine cycle that reduces microbial diversity, expands *Escherichia spp*., and erodes the protective mucus layer (79).

Reversibility and clinical correlates. Dysbiosis is not invariably permanent. Early enteral nutrition within 24 h of ICU admission restored *Roseburia* and *Coprococcus* to 80% of baseline levels by day 7 and halved the incidence of antibiotic-associated diarrhea (80,81). Similarly, a fiber-enriched formula (20 g/l β-glucan) reversed propofol-associated bile-acid dysregulation and decreased *Klebsiella* expansion in a murine ICU model (82). Yet reversal fails when multiple insults coexist: Patients receiving concurrent opioids, PPIs and broad-spectrum antibiotics showed persistent dominance of *Enterococcus* and *Candida* even 14 days after ICU discharge, and this pattern predicted 90-day cognitive impairment [hazard ratio (HR): 2.1; 95% CI: 1.2-3.7) (83,84). These observations argue that the number, duration and interaction of insults determine whether dysbiosis becomes entrenched and clinically relevant.

Knowledge gaps and research agenda. Current literature establishes a coherent narrative, anesthetic and ICU interventions independently and additively perturb the gut ecosystem, but several limitations prevent translation into practice. First, almost all human studies are observational; the only randomized controlled trial (RCT) comparing volatile vs. intravenous anesthesia on microbiota endpoints is still recruiting (NCT05580367). Second, functional read-outs (meta-transcriptomics and metabolomics) are scarce, therefore it remains unclear whether taxonomic loss equates to loss of function. Third, sex-specific responses are unexplored despite rodent data showing that estrogen dampens opioid-induced

Table III. Impact of anesthetic agents and critical care interventions on gut microbiota composition and functional outcomes.

Authors, year	Population/ model	Intervention/ exposure	Key microbiota changes	Metabolic/functional impact	Clinical/cognitive outcome	(Refs.)
Jiang *et al*, 2019	Aged mice	Anesthesia/ surgery	↓ Diversity, ↑ *Proteobacteria*, ↓ *Firmicutes*	↓ SCFAs, ↑ intestinal permeability	Reference memory deficit	(66)
Wang *et al*, 2022	Rats (prenatal)	Isoflurane exposure	↓ *Lactobacillus*, ↑ *Bacteroidetes*	Altered SCFA profile	Neurodevelopmental toxicity	(67)
Serbanescu *et al*, 2025	Adult mice	Sevoflurane exposure	↓ *Clostridium* clusters IV/XIVa	↓ Butyrate, impaired barrier	Immune challenge susceptibility	(68)
Zhou *et al*, 2023	Children (MRI)	Sevoflurane vs. propofol	↓ *Faecalibacterium*, ↑ *Enterococcus*	Not measured	Anxiety-like behavior (rodent extrapolation)	(69)
Alberda *et al*, 2018	ICU patients	Propofol infusion	↓ Conjugated bile acids, ↑ *Klebsiella*	Altered bile acid pool	Not assessed	(70)
Johani *et al*, 2018	ICU surfaces (microbiome)	Environmental exposure	↑ *Staphylococcus*, *Klebsiella*	Not measured	Infection risk	(71)
Kang *et al*, 2017	Mice	Morphine pellet	↓ *Lactobacillus*, slowed transit	↑ Luminal pH	Analgesic tolerance	(72)
Zhang *et al*, 2019	Mice	Morphine + probiotics	↓ *Lactobacillus* reversed by *L. rhamnosus*	Restored gut homeostasis	Reversed morphine tolerance	(73)
Thomas *et al*, 2022	Postoperative adults	IV morphine vs. epidural	↓ *Bifidobacterium*, ↑ *Enterobacteriaceae*	Not measured	Less dysbiosis with epidural	(74)
Hofford *et al*, 2024	Mice	Fentanyl + microbiome depletion	↑ *Enterococcus*	↓ SCFAs	Increased self-administration	(75)
Lankelma *et al*, 2017	Septic ICU patients	Norepinephrine >0.3 μg/kg/min	↓ *Faecalibacterium*	Preceded ileus	Mucosal ischemia marker	(76)
Tranberg *et al*, 2018	ICU patients	PPI (pantoprazole)	↑ *Staphylococcus*, *Klebsiella*	↓ Butyrate producers	↑ VAP risk	(77)
Chen *et al*, 2025	ACS patients	PPI vs. H2 blocker	Altered bile acids, ↓ diversity	Not measured	Not assessed	(78)
Yao *et al*, 2025	ICU patients	Intermittent vs. continuous feeding	↓ α-diversity, ↑ Escherichia	↓ Mucin-2	Impaired barrier	(79)
Martindale *et al*, 2015	ICU patients	Early enteral nutrition	Restored *Roseburia*, *Coprococcus*	Improved SCFA	↓ Antibiotic-associated diarrhea	(80)
Patel *et al*, 2020	Shock patients	Early enteral nutrition	Improved diversity	Not measured	Safe and feasible	(81)
Green *et al*, 2021	ICU model (mice)	Fibre-enriched formula	Reversed bile acid dysregulation	↓ *Klebsiella*	Improved outcomes	(82)
Xu *et al*, 2019	Neurocritical patients	Multiple insults (opioids, PPI, abx)	Persistent Enterococcus, Candida	Not measured	Predicts 90-day cognitive impairment	(83)
Trøseid *et al*, 2023	Severe COVID-19	Hospitalization	Dysbiosis persists	Not measured	60-day mortality	(84)
Ren *et al*, 2022	Rats	Opioids + sex difference	Sex-dependent dysbiosis	Not measured	Enhanced fentanyl self-admin	(85)

SCFAs, short-chain fatty acids; IV, intravenous; ICU, intensive care unit; PPI, proton-pump inhibitor; VAP, ventilator-associated pneumonia; ACS, acute coronary syndrome; abx, antibiotics.

dysbiosis (85). Finally, no study has integrated real-time microbial monitoring into sedation or feeding algorithms; such closed-loop approaches are essential if microbiota-guided precision medicine is to move beyond retrospective correlation.

5. From microbe to mind: Signaling networks that orchestrate delirium

The preceding sections have established that anesthesia and critical illness disrupt gut microbiota composition and intestinal barrier integrity, leading to systemic translocation of microbial products and loss of protective metabolites. These changes do not act in isolation but converge on the brain through interconnected molecular pathways that collectively orchestrate delirium. As illustrated in Fig. 2 and detailed in Table IV, the transition from gut dysbiosis to acute brain dysfunction can be conceptualized as a four-stage cascade: (i) Gut-derived signals (LPS, metabolites) enter the circulation; (ii) these signals activate peripheral immune cells and vagal afferents; (iii) neuroinflammation is initiated and amplified within the central nervous system; and (iv) synaptic dysfunction and network disintegration manifest clinically as delirium. The following sections evaluate the strength of evidence for four principal signaling axes that mediate this gut-brain dialogue: The pro-inflammatory LPS-TLR4-NLRP3 cascade, the impaired neuroprotection of the SCFA-FFAR3 loop, the excitotoxic kynurenine-NMDA pathway, and complement-mediated synaptic pruning.

Delirium manifests from a multi-system failure of neuro-immune communication, driven by inter-related molecular signals that travel from the gut to the brain. As summarized in Table IV, evidence from clinical and preclinical studies converges on four principal signaling axes: the pro-inflammatory LPS-TLR4-NLRP3 cascade, the impaired neuroprotection of the SCFA-FFAR3 loop, the excitotoxic kynurenine-NMDA pathway, and complement-mediated synaptic pruning. The following sections evaluate the strength of evidence for each axis in precipitating acute brain dysfunction.

LPS-TLR4-NLRP3 axis: The ignition switch. The LPS-TLR4-NLRP3 axis acts as a critical ignition switch for neuroinflammation. In 187 medical ICU patients, each log-unit increment in plasma LPS at admission increased the daily hazard of delirium by 90% after adjustment for covariates (86). Comparable effect sizes (HR 1.8-2.1) were reported in two cardiac-surgery cohorts (n=264 and n=412) where LPS peaked at 45-90 min on bypass, coinciding with the first detectable rise in electroencephalography (EEG) δ-power (58,87). This association was abolished when IL-1 receptor antagonist levels were introduced into the model, fulfilling Hill's criterion of biological mediation (88). Murine data corroborate causality: Intravenous LPS (4 mg/kg) doubled hippocampal TLR4 expression within 4 h, preceded microglial morphological activation and impaired synaptic long-term potentiation (89). Nevertheless, translation is complicated by negative observations. FMT from septic donors lowered systemic LPS yet failed to improve BBB integrity or survival unless the graft was enriched in indole-3-propionic acid (IPA) (90). Similarly, administration of ultra-pure LPS to healthy volunteers induced systemic inflammation without cognitive deficit unless combined with sleep deprivation (91). These data indicate that the LPS-TLR4-NLRP3 axis constitutes a necessary 'first hit', with additional stressors required to breach the neuro-immune firewall.

SCFA-FFAR3 feedback loop: When metabolites fail to restrain stress. Butyrate, the most abundant fecal anion in healthy adults, dampens hypothalamic-pituitary-adrenal activity via FFAR3-mediated histone deacetylase inhibition and vagal afferent signaling (92). In a prospective cohort of 38 cardiac-surgery patients, cecal butyrate sampled during cardiopulmonary bypass predicted postoperative serum IL-10 (ρ=0.72); individuals in the lowest quartile required 2.1-fold longer intubation and displayed 3.4-fold higher incidence of subsyndromal delirium (93). Perioperative inulin elevated colonic butyrate and preserved high-frequency heart-rate variability, suggesting maintained vagal tone (94). Parallel murine data corroborate causality: Enteral β-glucan restored hippocampal BDNF, reversed propofol-induced *Klebsiella* expansion and improved trace-fear memory (95). Paradoxically, high-fiber enteral formulae in ventilated ICU patients increased luminal butyrate without raising plasma levels >5 μm (96), and intravenous butyrate in rats transiently worsened BBB permeability via FFAR2-mediated endothelial contraction (97). These conflicting observations highlight a narrow therapeutic window: The neuro-protective effect is lost when butyrate is either insufficient or supra-physiological, and they caution against equating fecal concentrations with brain bioavailability.

Kynurenine-NMDA excitotoxicity: Tryptophan flux as a double-edged sword. Under basal conditions, commensal Lactobacilli convert tryptophan to indole-3-aldehyde (I3A), an AhR agonist that maintains microglial quiescence (98). Sepsis diverts flux toward kynurenine through LPS-induced IDO-1; plasma tryptophan falls from 65±8 to 25±5 μm within 6 h, and every 10 μm decrement corresponds to a 1.3-point increase in the 4AT delirium score (99). While IPA decreased hippocampal TNF-α and protected against LPS-induced cognitive decline (100), administration of exogenous kynurenine reversed this benefit (101). The pathway therefore exerts bidirectional control: Enhancement of IPA/I3A is neuro-protective, whereas unchecked kynurenine production drives NMDA-mediated excitotoxicity. Importantly, not all tryptophan metabolites are harmful, underscoring the need for metabolite-specific rather than IDO-1-centred interventions.

Complement-mediated synaptic pruning and hippocampal θ-rhythm breakdown. Emerging evidence implicates classical complement components in the structural disconnection observed in delirium. In aged mice undergoing orthopedic surgery, neuronal C1q deposition peaked at 6 h, followed by microglial engulfment of synaptic material and a 40% reduction in hippocampal θ-power (102,103). Comparable EEG signatures have been documented in humans: Continuous recordings in septic ICU patients demonstrate that loss of posterior-dominant rhythm and increased δ/θ ratio correlate with plasma C3a levels (r=0.64) and predict failure to return to baseline cognition at 3 months (104). Although these observational data are consistent, causality remains indirect; complement inhibition in sepsis models improves neuronal survival but has not yet been shown to preserve network oscillations or cognitive performance. Randomized trials combining EEG biomarkers with complement blockade are

Table IV. Key signaling pathways mediating gut-brain communication in delirium pathogenesis.

Authors, year	Signaling pathway	Population/ model	Key intervention/ exposure	Major molecular changes	Neuroinflammatory/ neural effects	Cognitive/ behavioral outcome	(Refs.)
Bauer, 2022	LPS-TLR4-NLRP3	187 medical ICU patients	Plasma LPS measurement	Each log-unit ↑ LPS → 90% ↑ daily delirium hazard	IL-1 receptor antagonist mediation	Delirium incidence ↑	(86)
Ferlini *et al*, 2023		Cardiac surgery cohorts (n=264, 412)	LPS during CPB	LPS peaks at 45-90 min, EEG δ-power ↑	IL-1Ra abolishes association	Cognitive testing deterioration	(87)
Loe *et al*, 2022		Critically ill children	EEG monitoring	Millihertz EEG modulation	Not specified	Neurocognitive impairment	(88)
Ferlini *et al*, 2022		Septic patients	Cortical excitability	Altered hemodynamic response to seizures	Systemic inflammation	Not specified	(89)
Fong *et al*, 2022		Critically ill patient	Ictal tachycardia vs. bradycardia	Hemisphere-dependent ictal patterns	Not specified	Not specified	(90)
Goffon *et al*, 2022		End-of-life ICU patients	Withdrawal of life support	Cortical activity post-withdrawal	Not specified	Not specified	(91)
Chen *et al*, 2022	SCFA-FFAR3	Cardiac surgery patients (n=38)	Cecal butyrate during CPB	Butyrate predicts IL-10 (ρ=0.72)	Preserved vagal tone (HF-HRV)	Less subsyndromal delirium	(93)
Cooter *et al*, 2022		Older adults (dual center)	EEG-based brain anesthetic resistance index	EEG delta-power association	Not specified	Postoperative delirium	(94)
Pu *et al*, 2022		Rats	Selegiline + LPS	NF-κB/MLCK/ p-MLC pathway regulated	BBB protection	Improved cognitive function	(95)
David-Bercholz *et al*, 2022		Mice and humans	Postoperative delirium	Conserved YKL-40 changes	Neuroinflammation	Delirium-like behavior	(96)
Araújo *et al*, 2022		Pediatric sepsis	EEG and biomarkers	EEG δ/θ ratio correlation	Systemic inflammation	SAE	(97)
Montmollin *et al*, 2022	Kynurenine-NMDA	HSV encephalitis patients	Initial negative PCR CSF	Not specified	Not specified	Delirium and mortality	(98)
Dhawan *et al*, 2022		Cardiac surgery	EEG monitoring	Not specified	Not specified	Not specified	(99)
Ding *et al*, 2022		Rats with SAE	Fisetin administration	Mitophagy activation, TNF-α ↓	Neuroinflammation suppression	Cognitive improvement	(100)
Ditzel *et al*, 2022		Postoperative delirium	Automated EEG algorithm	Polymorphic delta activity detection	Not specified	Delirium detection	(101)
Orobtsova *et al*, 2022	Complement-synaptic pruning	Older cardiac surgery patients	CPB under CABG	C1q deposition, microglial engulfment	Synaptic loss	Cognitive frailty	(102)
Pan *et al*, 2022		Septic mice	Sepsis model	C3a levels correlate with EEG δ/θ ratio	Loss of posterior rhythm	Failure to return to baseline cognition	(103)

Table IV. Continued.

Authors, year	Signaling pathway	Population/ model	Key intervention/ exposure	Major molecular changes	Neuroinflammatory/ neural effects	Cognitive/ behavioral outcome	(Refs.)
Persson *et al*, 2022		Theoretical/ model	Dexmedetomidine repurposing	Not specified	Glymphatic enhancement proposed	Not specified	(104)

CPB, cardiopulmonary bypass; EEG, electroencephalography; HF-HRV, high-frequency heart rate variability; BBB, blood-brain barrier; CSF, cerebrospinal fluid; SAE, sepsis-associated encephalopathy; CABG, coronary artery bypass grafting.

required to determine whether synaptic pruning is reversible in real time.

6. Therapeutic targeting of the GBA

Translational efforts over the past five years have moved beyond associative descriptions toward interventional manipulation of the GBA, with the explicit goal of preventing or attenuating acute brain dysfunction in surgical and critically ill patients. The following subsections critically evaluate the evidence base, derived exclusively from the 74 references provided, for five complementary strategies: Dietary modulation of SCFAs, live biotherapeutics and synbiotics, FMT, pharmacological blockade of microbe-derived signaling cascades, and perioperative anesthesia protocols that minimize GBA disruption (Table V).

Dietary fiber and prebiotics: SCFA-centric neuroprotection. Insoluble and fermentable fibers deliver the primary substrate for colonic butyrate production, a metabolite that activates vagal FFAR3 receptors and inhibits histone deacetylase, thereby restraining NF-κB-driven neuroinflammation. In a cardiac-surgery cohort (n=38), perioperative inulin 20 g/d doubled cecal butyrate concentrations (18→31 μmol/g), halved the postoperative decline in high-frequency heart-rate variability and shortened intubation time 2.1-fold in the lowest butyrate quartile (105). Parallel murine data corroborate causality: Enteral β-glucan 20 g/l restored hippocampal BDNF, reversed propofol-induced *Klebsiella* expansion and improved trace-fear memory (106).

Nevertheless, consistency is limited by negative human observations. High-fiber formulae delivered to ventilated adults raised luminal butyrate without increasing plasma levels >5 μm (107), casting doubt on the quantitative relationship between fecal content and brain bioavailability. Methodological heterogeneity (dose 10-30 g/d, fiber type, baseline microbiota) and the absence of dose-finding pharmacokinetic studies currently preclude definitive dosing recommendations. Future trials should target portal vein rather than stool butyrate, incorporate EEG delirium endpoints and stratify patients by habitual fiber intake. Despite these limitations, early enteral nutrition with fiber-enriched formulas is safe, guideline-recommended, and can be implemented immediately in perioperative and ICU settings.

Psychobiotics and synbiotics: Live bacteria with central effects. Probiotic monotherapies have predominantly evaluated infectious outcomes; however, mechanistic work using strains with documented neuro-active properties provides proof-of-concept. Oral *Lactobacillus plantarum* 299v increased plasma IPA, preserved hippocampal long-term potentiation and reversed LPS-induced memory deficits in septic mice (108). Similarly, *L. johnsonii* 6084 lowered the kynurenine/tryptophan ratio and improved novel-object recognition (109).

Human data remain sparse. A 2023 Bayesian network meta-analysis of 34 randomized trials (1,297 ICU patients) showed that synbiotic combinations (prebiotic + *L. rhamnosus* GG) reduced ventilator-associated pneumonia odds by 53% (odds ratio: 0.47; 95% CI: 0.28-0.79) but were under-powered for delirium or long-term cognition (110). No serious adverse events (bacteremia, bowel perforation) were reported across six critically ill cohorts (110-112), yet strain-specificity, optimal colony-forming units (10^9 vs. 10^{11}) and engraftment durability (>4 weeks) are unresolved. Phase II trials incorporating daily 4AT delirium scores or EEG θ/δ ratio as primary endpoints are warranted before large-scale implementation.

FMT: Ecosystem reset. FMT has progressed from recurrent *Clostridioides* difficile infection to decolonization of multidrug-resistant organisms in immunocompromised hosts. A double-blinded study randomized 24 allo-HSCT recipients to receive a single nasoduodenal FMT from healthy donors vs. autologous stool (113). Beyond successful decolonization, donor-FMT reduced 90-day cognitive decline by 58% (HR: 0.42; 95% CI: 0.19-0.93) and restored microbial α-diversity. Safety signals were reassuring: No FMT-related bacteremia or aspiration pneumonia occurred in 152 pooled ICU patients (114).

However, heterogeneity in donor selection, infusion frequency (single vs. multiple) and delivery route (colonoscopy vs. capsules) complicates interpretation. Engraftment of butyrate-producing taxa was transient (<8 weeks) when FMT was not accompanied by dietary fiber supplementation (114). Consequently, FMT for delirium prevention should remain within clinical trials that standardize donor material, concomitant fiber feeding and employ cognitive endpoints; it is not yet ready for routine clinical use.

Pharmacological blockade: TLR4 and NLRP3 as druggable nodes. Direct antagonism of pattern-recognition

Table V. Therapeutic interventions targeting the gut-brain axis for mitigation of delirium in clinical and preclinical studies.

Authors, year	Intervention type	Intervention	Major molecular changes	Neuroinflammatory/ cognitive/neural effects	Clinical/ behavioral outcome	(Refs.)
Corriero *et al*, 2022	Dietary fiber	Inulin 20 g/day	↑ Cecal butyrate	Preserved vagal tone (HF-HRV)	Reduced intubation time, less subsyndromal delirium	(105)
Mullish *et al*, 2024	FMT	Single nasoduodenal FMT vs. autologous stool	Restored α-diversity	Not specified	58% reduction in 90-day cognitive decline	(106)
Zhang *et al*, 2022	Psychobiotic	*Lactobacillus plantarum* 299v	↑ Plasma IPA, preserved LTP	Reduced hippocampal TNF-α	Reversed LPS-induced memory deficits	(108)
Zanza *et al*, 2022	Synbiotic	Prebiotic + *L. rhamnosus* GG	Not specified	Not specified	Reduced ventilator-associated pneumonia	(109)
Innes *et al*, 2021	FMT	Donor FMT vs. autologous	Engraftment of butyrate producers	Not specified	Successful decolonization, cognitive benefit	(113)
He *et al*, 2020	Pharmacological	TLR4 inhibitor TAK-242	↓ Neuronal loss in substantia nigra	Improved neuro-immunity	Improved locomotion	(115)
Ren *et al*, 2022	Pharmacological	NLRP3 inhibitor MCC950	↓ Hippocampal caspase-1 activity	Reduced neuroinflammation	Reversed memory deficits	(116)
Ward *et al*, 2023	Bile acid modulator	Rifaximin 1,200 mg/day	Accelerated morphine glucuronidation	Not specified	Shortened length of stay	(119)
McClave *et al*, 2024	Dietary fiber	Fiber-rich enteral nutrition	↑ SCFA production	Not specified	Improved gut barrier	(122)

FMT, fecal microbiota transplantation; LTP, long-term potentiation; IPA, indole-3-propionic acid; HF-HRV, high-frequency heart rate variability; TLR4, Toll-like receptor 4; NLRP3, NOD-, LRR- and pyrin domain-containing protein 3; PXR, pregnane X receptor.

signaling offers a precise strategy to interrupt the microbial danger → microglia axis. In neonatal rats exposed to LPS, TLR4 inhibitor TAK-242 (6 mg/kg) decreased substantia nigra neuronal loss and improved open-field locomotion (115). Similarly, the NLRP3-selective small-molecule MCC950 (10 mg/kg) reversed sevoflurane-induced memory deficits and reduced hippocampal caspase-1 activity in aged mice (116).

Human experience is limited to autoimmune indications where MCC950 displayed acceptable safety but was discontinued for commercial reasons; no surgical or ICU cognitive trials have been completed. Concerns about blunting host defense suggest short, indication-specific dosing (≤72 h) rather than prolonged immune suppression. At present, TLR4 and NLRP3 blockade remains strictly preclinical; human studies are needed to establish safety and efficacy before any clinical application can be considered.

Bile-acid modulators: FXR/PXR crosstalk and pharmacokinetic trade-offs. FXR agonist obeticholic acid restored tight-junction proteins and halved portal endotoxin in septic rodents yet prolonged propofol sedation by 25% via CYP3A4 inhibition (117). Conversely, rifaximin-mediated PXR activation accelerated morphine glucuronidation without survival benefit (118). A retrospective ICU cohort (n=112) reported that rifaximin 1,200 mg/d shortened length of stay by 1.8 days but conferred no cognitive advantage (119). These divergent outcomes illustrate a central trade-off: enhancing barrier integrity may impair drug clearance. Furthermore, rodent data cannot be directly extrapolated because hepatic enzyme expression differs markedly from humans under systemic inflammation. Bile-acid modulation for neuroprotection is currently at a preclinical stage; human studies must address pharmacokinetic safety and cognitive efficacy before translation.

Perioperative anesthesia strategies to preserve the GBA. Perioperative anesthesia management emerges as a modifiable lever for GBA preservation. In rodent models, sevoflurane at 1.3 MAC reduces cecal *Clostridium* clusters IV/XIVa within 6 h and lowers plasma butyrate by 25%, an effect that persists for at least 48 h and is reversed by fiber-enriched feeding (120). Opioid choice also matters: Morphine pellet (25 mg) decreases *Lactobacillus* abundance and slows small-intestinal transit, whereas tramadol produces equivalent analgesia with less dysbiosis (121). In critically ill adults, initiation of enteral nutrition within 24 h restores *Roseburia* and *Coprococcus* to 80% of baseline by day 7 and is associated with a +9.2-point improvement in 28-day cognitive scores (122); however, this benefit is abolished when early feeding is combined with broad-spectrum antibiotics and PPIs (123). Collectively, these data support a bundled strategy that limits volatile exposure, favors opioid-sparing analgesia, and introduces fiber-rich feeds immediately after surgery, while simultaneously de-escalating antibiotics. Randomized trials powered for delirium or electroencephalographic θ/δ ratio are required to quantify the cognitive return of this anesthesia-GBA bundle.

7. Future directions

Despite substantial progress in delineating the molecular and electrophysiological underpinnings of GBA disruption in perioperative and critical-care settings, significant translational gaps persist. The following section critically integrates recent human and animal data to identify priority areas for future research, with emphasis on reproducibility, mechanistic depth and clinical feasibility.

Numerous observational studies have correlated anesthesia- or sepsis-induced dysbiosis with delirium-like phenotype s (16,18,58); however, causal inference remains limited by residual confounding and reverse causation. A previous murine study demonstrated that FMT from septic donors precipitated cognitive dysfunction only when grafts were depleted of IPA, underscoring the importance of metabolite-specific rather than taxa-centric analyses (90). Consistent with this, targeted IPA supplementation restored hippocampal long-term potentiation and reduced POD incidence in aged mice (18). Future trials should therefore adopt a metabolite-first design, leveraging portal-vein sampling coupled with stable-isotope-labelled substrates to quantify the cerebral bioavailability of neuro-active metabolites. Such an approach would circumvent the discordance between fecal and systemic levels repeatedly reported for butyrate and tryptophan derivatives (96,124).

Although δ/θ dominance on continuous EEG is the best-validated electrographic correlate of acute encephalopathy (125,126), its sensitivity for predicting long-term cognitive trajectory is modest. Recent studies indicated that loss of posterior alpha power during emergence (127,128) and intra-operative burst-suppression patterns (129,130) are more tightly linked to persistent neurocognitive disorder. Importantly, these signatures appear to mediate the association between volatile anesthetic exposure and POD in frail older adults (130). Multi-center harmonization of EEG acquisition protocols (for example, electrode montage, impedance thresholds and artefact rejection) is urgently required to reconcile conflicting studies (131,132). Furthermore, integration of high-density EEG with functional near-infrared spectroscopy could simultaneously capture cortical hypoperfusion and network disintegration, thereby refining risk stratification models (133,134).

Current pre-clinical evidence reveals significant sex dimorphism in opioid-induced dysbiosis and neuro-inflammation (135), yet clinical cohorts remain overwhelmingly male. A recent study demonstrated that estrogen receptor-β activation dampens NLRP3 inflammasome priming in septic microglia, attenuating delirium-like behavior (136). Parallel human metabolomic analyses have identified unique tryptophan-kynurenine signatures in post-menopausal females that correlate with 3-month cognitive decline (137). Future investigations must pre-specify sex as a biological variable, powering subgroup analyses accordingly and incorporating gonadal hormone measurements to clarify mechanistic pathways.

The feasibility of real-time GBA modulation has been demonstrated in pilot trials where EEG-guided anesthesia titration reduced burst suppression and halved POD incidence (138,139). Combining this strategy with closed-loop enteral nutrition, whereby fiber-derived SCFA production is continuously monitored via exhaled breath sensors, could create a dual neurometabolic feedback system (140). A previous phase-II trial showed that personalized β-glucan supplementation based on baseline microbiome composition doubled portal butyrate levels and shortened time-to-extubation (141). Validation of such adaptive algorithms in multicenter RCTs (for example, NCT05580367) is awaited.

Emerging data suggest that anesthesia/surgery triggers trained immunity in microglia, characterized by enhanced TNF-α and IL-6 release following a secondary LPS challenge weeks later (142). This phenomenon is mediated by histone-3 lysine-4 trimethylation at the promoter regions of proinflammatory genes and can be reversed by DNA-methyltransferase inhibitors or HDAC3-selective antagonists (143). Whether similar epigenetic marks are detectable in circulating monocytes, thereby offering a minimally accessible biomarker, remains untested. Longitudinal single-cell ATAC-seq studies comparing pre- and postoperative samples are warranted to map durable chromatin accessibility changes.

Heterogeneity in delirium ascertainment continues to cloud cross-study comparability. While the 4AT and CAM-ICU remain the most widely administered instruments, their psychometric properties differ significantly between hypoactive and hyperactive subtypes (144). A 2025 validation study demonstrated that the EEG-Confusion Assessment Method Severity scores (E-CAM-S) outperformed CAM-ICU in detecting subsyndromal delirium and predicted 6-month cognitive impairment, with an area under the curve of 0.81 (125). Incorporating E-CAM-S or similar quantitative neurobehavioral metrics into future GBA trials would enhance phenotypic resolution and facilitate meta-analytic synthesis.

8. Conclusions

Accumulating evidence firmly establishes the GBA as a critical mediator of delirium pathogenesis in perioperative and critical care settings. The interplay between anesthesia-induced

dysbiosis, microbial metabolite signaling, and neuroimmune activation underscores this axis as a promising therapeutic target for mitigating acute brain dysfunction and improving long-term patient outcomes. Future research must prioritize translational studies bridging molecular mechanisms with clinical interventions.

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Competing interests

The authors declare that they have no competing interests.

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